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ORIGINAL ARTICLES

Aluminum Gallium Nitride (GaN)/GaN High Electron Mobility Transistor-Based Sensors for Glucose Detection in Exhaled Breath Condensate

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Abstract

Background:

Immobilized aluminum gallium nitride (AlGaN)/GaN high electron mobility transistors (HEMTs) have shown great potential in the areas of pH, chloride ion, and glucose detection in exhaled breath condensate (EBC). HEMT sensors can be integrated into a wireless data transmission system that allows for remote monitoring. This technology offers the possibility of using AlGaN/GaN HEMTs for extended investigations of airway pathology of detecting glucose in EBC without the need for clinical visits.

Methods:

HEMT structures, consisting of a 3-μm-thick undoped GaN buffer, 30-Å-thick $Al_{0.3}Ga_{0.7}N$ spacer, and 220-Å-thick silicon-doped $Al_{0.3}Ga_{0.7}N$ cap layer, were used for fabricating the HEMT sensors. The gate area of the pH, chloride ion, and glucose detection was immobilized with scandium oxide (Sc_2O_3), silver chloride (AgCl) thin film, and zinc oxide (ZnO) nanorods, respectively.

Results:

The Sc_2O_3-gated sensor could detect the pH of solutions ranging from 3 to 10 with a resolution of ~0.1 pH. A chloride ion detection limit of 10^{-8} *M* was achievedt with a HEMT sensor immobilized with the AgCl thin film. The drain–source current of the ZnO nanorod-gated AlGaN/GaN HEMT sensor immobilized with glucose oxidase showed a rapid response of less than 5 seconds when the sensor was exposed to the target glucose in a buffer with a pH value of 7.4. The sensor could detect a wide range of concentrations from 0.5 n*M* to 125 μ*M*.

continued →

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Abbreviations: (Ag) silver, (AgCl) silver chloride, (AlGaN) aluminum gallium nitride, (Ar) argon, (Au) gold, (DI) deionized, (EBC) exhaled breath condensate, (GO_X) glucose oxidase enzyme, (HCl) hydrogen chloride, (HEMTs) high electron mobility transistors, (ICP) inductively coupled plasma, (MBE) molecule beam epitaxy, (PBS) phosphate-buffered saline, (Pt) platinum, (RF) radio frequency, (Sc_2O_3) scandium oxide, (SiNx) silicon nitride, (Ti) titanium, (ZnO) zinc oxide

Keywords: AlGaN/GaN, chloride ion, glucose, HEMT, noninvasive detection, pH, sensor

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Abstract cont.

Conclusion:

There is great promise for using HEMT-based sensors to enhance the detection sensitivity for glucose detection in EBC. Depending on the immobilized material, HEMT-based sensors can be used for sensingt different materials. These electronic detection approaches with rapid response and good repeatability show potential for the investigation of airway pathology. The devices can also be integrated into a wireless data transmission system for remote monitoring applications. This sensor technology could use the exhaled breath condensate to measure the glucose concentration for diabetic applications.

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Introduction

Diabetes is a leading cause of death and disability, with more than 135 million people afflicted worldwide. Projections suggest that the number will rise to 300 million by the year 2025. All current consumer tests for glucose require lancing the skin to draw blood for testing. The pain and inconvenience of drawing blood for testing limit frequent monitoring of sugar levels, increase the probability of death and disability, and put a very severe burden on an already overburdened hospital system.

Thus, it is extremely desirable to develop and test a noninvasive, low-cost, handheld, and wireless-capable sensor for glucose sensing. Among alternative body fluids, testing glucose using the exhaled breath condensate (EBC) is the most attractive approach. This breath-based technology, which allows for point-of-need testing with quick and accurate results, has the potential to open many new opportunities in the medical, home, law enforcement, and industrial diagnostic markets.[1–12] It has also been reported that the glucose level in the breath shows a correlation with blood glucose,[13] and solution conductivity has been used to estimate the dilution effect of the collected breath condensate. However, the error bars (standard deviation) on the breath glucose axis exhibited far too much variability. While the glucose in EBC may be an exciting prospect for glucose detection, glucose can be roughly two orders of magnitude lower in EBC compared to blood; thus, the accuracy, sensitivity, and robustness of the sensors for breath need to be better than that of conventional blood-based glucose monitors.

Aluminum gallium nitride (AlGaN)/GaN high electron mobility transistors (HEMTs) have shown promise for biosensing applications,[14–27] as they include a high electron sheet carrier concentration channel induced by piezoelectric polarization of the strained AlGaN layer and spontaneous polarization. Positive countercharges at the HEMT surface layer are induced by the two-dimensional electron gas located at the AlGaN/GaN interface. Any slight changes in the ambient can affect the surface charge of the HEMT, thus changing the electron concentration in the channel at the AlGaN/GaN interface. The typical detection time for the AlGaN/GaN HEMT-based sensor is in the 5- to 20-second range. Additionally, because of the wide energy band gap, the AlGaN/GaN material system is extremely chemically stable. The detection is real time (a few seconds), and the technology can be interfaced easily with wireless electronics. With proper surface immobilizations, AlGaN/GaN HEMT sensors have been used for different sensing applications, such as gas sensing for detecting hydrogen, carbon monoxide, carbon dioxide, and ammonium, as well as liquid sensing for detecting protein, pH value of a solution, lactic acid, breast cancer in saliva, DNA, kidney injury molecules, prostate cancer, glucose, chloride ion, and mercury ion.[14–27]

For glucose detection, the AlGaN/GaN gate area is immobilized with an oxidase enzyme through zinc oxide (ZnO) nanorods. The glucose oxidase enzyme (GO_x) is used commonly in biosensors to detect levels of glucose for diabetes patients. By keeping track of the number of electrons passed through the enzyme, the concentration of glucose can be measured. Because of the importance and difficulty of glucose immobilization, numerous studies have focused on the techniques of immobilization of glucose with carbon nanotubes, ZnO nanomaterials, and gold particles.[28,29] ZnO-based

nanomaterials are especially interesting due to their nontoxic properties, low cost of fabrication, and favorable electrostatic interaction between ZnO and GO_x.

The activity of GO_x is highly dependent on the pH value of the solution,[30] and the glucose concentration in the EBC can also be diluted by condensing water vapor in the air during EBC collection. Although the pH value of a typical healthy person is between 7 and 8, the pH value in the EBC can vary significantly depending on the health condition of each individual, e.g., the pH value for patients with acute asthma has been reported as low as 5.23 ± 0.21 (n = 22) as compared to 7.65 ± 0.20 (n = 19) for control subjects.[31] Depending on the dew point and the relative humidity of the ambient, the water vapor can be condensed during EBC collection and dilute the glucose concentration in the EBC. Therefore, in order to realize the AlGaN/GaN HEMT glucose sensor for EBC-based glucose detection, it is essential to determine the pH value of the glucose solution and the dilution effect in the condensed EBC at the same time for an accurate glucose concentration determination.

This article reports on the device fabrication of integrating AlGaN/GaN HEMTs based on pH, glucose, and chloride ion sensors on a single chip. Epitaxial AlGaN/GaN layer structure, HEMT fabrication, and the sequence for immobilizing the gate area of the HEMT for sensing pH, chloride ion, and glucose are also discussed.

Methods

Material Growth and Device Fabrication

The HEMT structure consists of a 3-μm-thick undoped GaN buffer, 30-Å-thick $Al_{0.3}Ga_{0.7}N$ spacer, and 220-Å-thick silicon-doped $Al_{0.3}Ga_{0.7}N$ cap layer. Epilayers are grown by molecule beam epitaxy (MBE) or metal organic chemical vapor deposition on thick GaN buffers on sapphire or silicon substrates.

Individual HEMT mesa isolation was performed with inductively coupled plasma (ICP) etching with Cl_2/argon (Ar)-based discharges at –90-volt dc self-bias, ICP power of 300 watts at 2 MHz, and a process pressure of 5 mTorr. Ohmic contacts (50 × 50 μm^2) separated with 50-μm gaps consist of e-beam deposited titanium (Ti)/Al/platinum (Pt)/gold (Au) patterned by liftoff and annealed at 850°C, 45 seconds under flowing N_2. A contact resistivity of 2–5 × 10^{-6} Ω-cm^2 was achieved. E-beam deposited Ti/Al/Pt/Au-based metallization was used for the metal interconnection. The layout and microscope image of the multifunctional sensor chip, as well as a zoom-in view of the sensor active areas, are shown in **Figure 1**. The inner sensor chip is the chloride ion sensor, which has an extra electrode connecting to the gate for anodizing the silver (Ag) into silver chloride (AgCl). The middle sensor is the pH sensor, and the outer sensor is the glucose sensor.

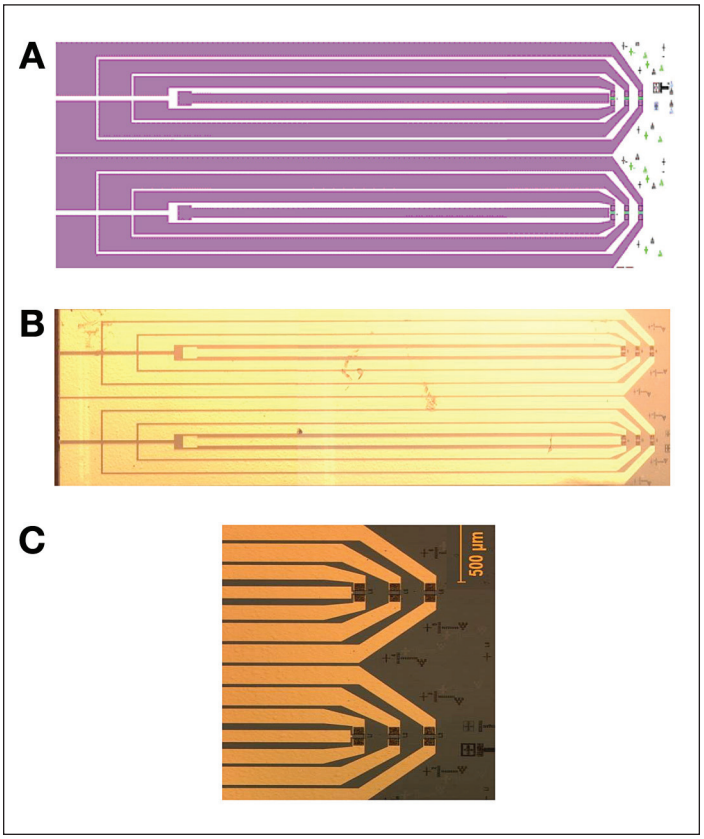

Figure 1. **(A)** The layout and **(B)** microscope image of the multifunctional sensor chip, as well as **(C)** a zoom-in view of sensor active areas. The inner sensor chip is the chloride ion sensor, which has an extra electrode connecting to the gate for anodizing the Ag into AgCl. The middle sensor is the pH sensor, and the outer sensor is the glucose sensor.

Sensor Immobilizations

Scandium oxide Deposition for pH Sensing. Because there is a thermal treatment at 300°C during the scandium oxide (Sc_2O_3) deposition process, this high temperature treatment would degrade the AgCl thin film of the chloride sensor and ZnO nanorods for the glucose sensor. Thus, immobilization of the pH sensor needs to be performed first. A 400-nm dielectric layer, silicon nitride (SiNx), deposited with a plasma-enhanced chemical vapor deposition system was employed to passivate the high mobility transistor wafer. Sc_2O_3 (100 Å) was deposited as a gate dielectric through a contact window of the SiNx layer to the gate area of the specific AlGaN/

GaN HEMT for pH sensing, and the contact window was open with tetrafluoromethance/oxygen (CF_4/O_2) plasma etching. Before Sc_2O_3 deposition, the wafer was exposed to ozone for 25 minutes. It was then heated *in situ* at 300°C cleaning for 10 minutes inside the growth chamber. A 10-nm Sc_2O_3 film was deposited by radio frequency (RF) plasma-activated MBE at 100°C using elemental scandium evaporated from a standard effusion all at 1130°C and O_2 derived from an Oxford RF plasma source.[32] Because Sc_2O_3 was deposited over the entire wafer, the Sc_2O_3 beyond the gate area of the pH sensor was removed with ICP etching with Cl_2/Ar-based discharges. A schematic device cross-sectional view of the pH sensor is illustrated in **Figure 2A**.

Anodize Ag Thin Film into AgCl for Chloride Ion Sensing. After immobilization of the gate area for the pH sensor, the AgCl thin film was prepared for chloride ion sensing. The AgCl thin film was fabricated by anodizing an Ag thin film in a hydrogen chloride (HCl) solution. First, a Ti (10 nm)/Ag (100 nm) thin film was deposited as the gate electrode metal of the chloride ion sensor with an e-beam evaporator. An AZ-1818 positive photoresist was used to open a window on the Ti/Ag for AgCl potentiostatic anodization. The selective area Ag was anodized in 0.1 *N* HCl solution stirred continuously at 25°C with a constant bias voltage of 1 volt for 5 seconds, and only part of the Ag thin film was anodized into AgCl. A schematic device cross-sectional view of the Ag/AgCl-gated HEMT chloride ion sensor is shown in **Figure 2B**.

ZnO Nanorod Growth for Glucose Sensing. The glucose sensor was achieved with selective-area ZnO nanorod growth on the gate area of the glucose sensing HEMT. By incorporating the nanorods on the HEMT gate sensing area, the total sensing area and sensitivity could increase significantly. ZnO nanocrystals, prepared with the Pacholski method,[33] were coated on the gate area of the glucose sensor. The ZnO nanorods were subsequently grown in a solution of 20 m*M* zinc acetate hexahydrate [$Zn(NO_3)_2{\cdot}6H_2O$] and 20 m*M* hexamethylene triamine ($C_6H_{12}N_4$). Subsequently, the sample was removed from solution, rinsed thoroughly with acetone, followed by deionized water to remove any residual salts, and air dried at room temperature. A schematic device cross-sectional view of the Ag/AgCl-gated HEMT chloride ion sensor is shown in **Figure 2C**.

Exhaled Breath Condensate Collection. To take advantage of the quick response (less than ~5 seconds) of the HEMT sensor, a real-time EBC collector is needed.[34–36]

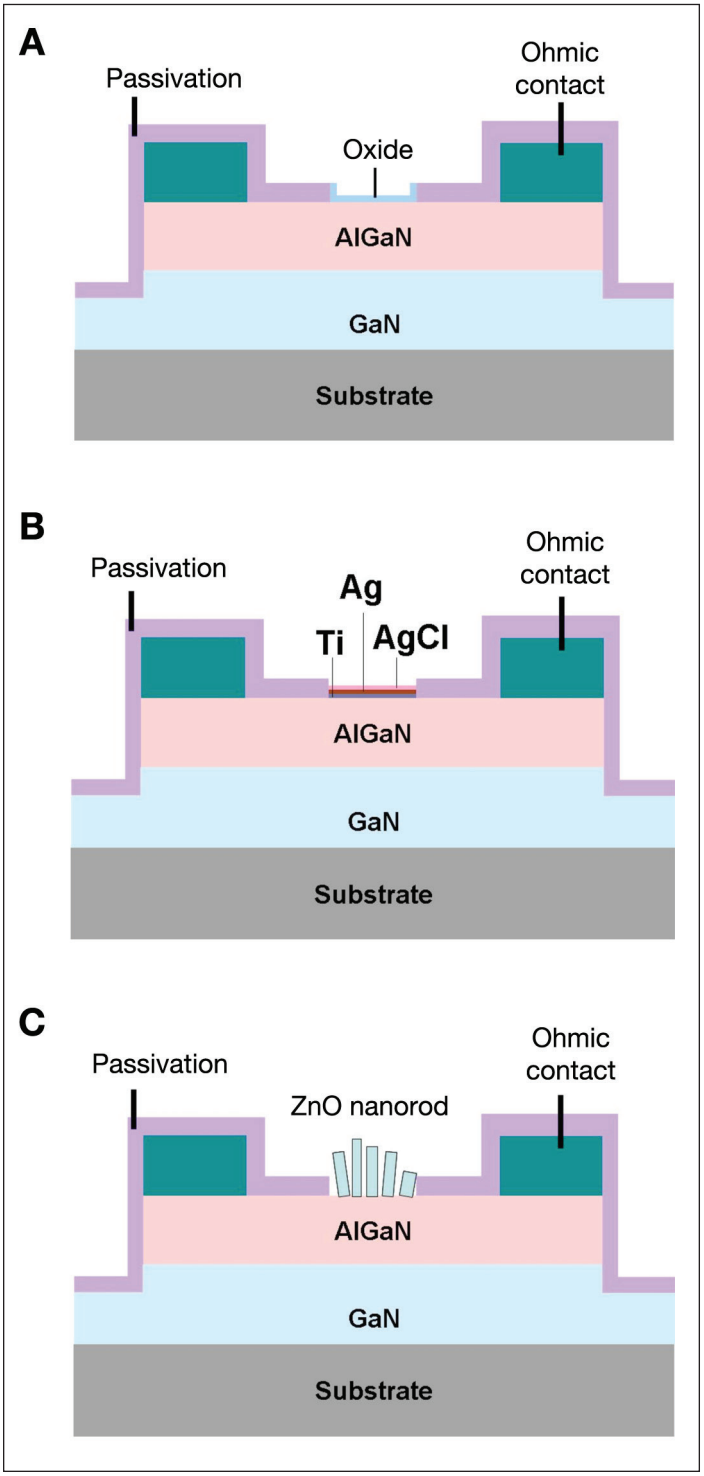

Figure 2. (A) A schematic device cross-sectional view of the Sc_2O_3-gated HEMT pH sensor. **(B)** A schematic device cross-sectional view of the Ag/AgCl-gated HEMT chloride ion sensor. **(C)** A schematic device cross-sectional view of the ZnO nanorod-gated HEMT chloride ion sensor.

The amount of the EBC required to cover the HEMT sensing area is very small. Each tidal breath contains around 3 µl of the EBC. The contact angle of the EBC on Sc_2O_3 has been measured to be less than 45°, and it

is reasonable to assume a perfect half-sphere of EBC droplet formed to cover the 10 × 50-μm^2 gate area for sensing. The volume of a half-sphere with a diameter of 50 μm is around 3 × 10^{-11} liters. Therefore, one hundred thousand 50-μm-diameter droplets of EBC can be formed from each tidal breath.

To condense the entire 3 μl of water vapor, only ~7 joules of energy is needed to be removed for each tidal breath, which could be achieved easily with a thermal electric module, a Peltier device, as shown in **Figure 3A**. The AlGaN/GaN HEMT sensor is mounted directly on top of the Peltier unit (TB-8-0.45-1.3 HT 232, Kryotherm), as shown in **Figure 3B**, which could be cooled to precise temperatures by applying known voltages and currents to the unit. During our measurements, the hotter plate of the Peltier unit was kept at 21°C, and the colder plate was kept at 7°C by applying a bias of 0.7 volt at 0.2 A. The effect of the temperature on the amount of condensate collected was not studied in the work. The condensation temperature may have some effect on the pH value determination, which will be addressed in future work. The sensor took less than 2 seconds to reach thermal equilibrium with the Peltier unit. This allowed the exhaled breath to immediately condense on the gate region of the HEMT sensor.

Results

Figure 4 shows a highly dense array of 20- to 30-nm diameter and 2-μm-tall ZnO nanorods grown on the 10 × 50-μm^2 gate area. The total area of the ZnO was increased significantly with the ZnO nanorods. The ZnO nanorod matrix provided a microenvironment for immobilizing negatively charged GO_x while retaining its bioactivity and passed charges produced during the GO_x and glucose interaction to the AlGaN/GaN HEMT.

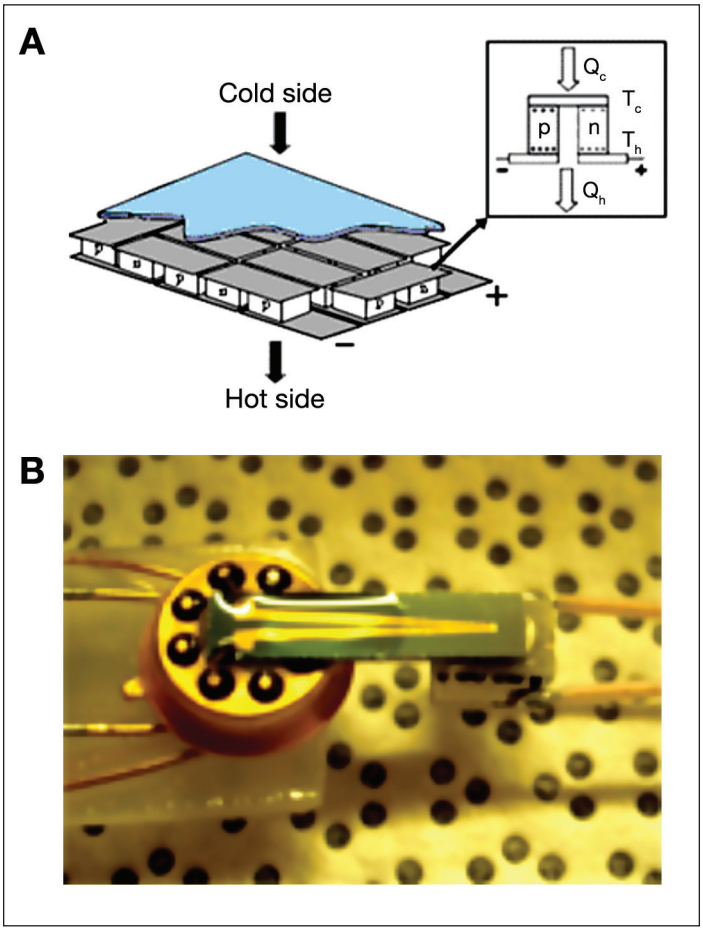

Figure 3. (A) A schematic thermal electric module. **(B)** An AlGaN/GaN HEMT sensor chip mounted on top of a Peltier unit (TB-8-0.45-1.3 HT 232, Kryotherm).

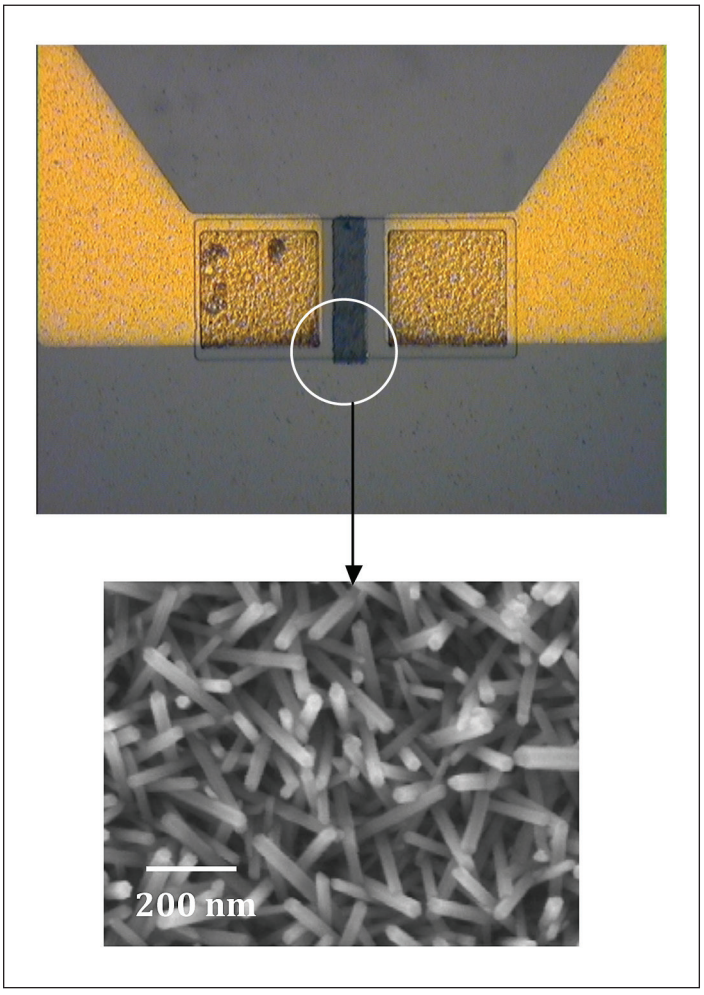

Figure 4. A highly dense array of 20- to 30-nm diameter and 2-μm-tall ZnO nanorods grown on the 10 × 50-μm^2 gate area of a HEMT sensor.

Figure 5A shows real-time glucose detection using the drain current change in the HEMT sensor with a constant bias of 250 mV and the amount of drain current change (**Figure 5B**) in different concentrations of glucose dissolved in the phosphate-buffered saline (PBS) buffer solution. No current change could be seen with the addition of buffer solution at around 200 seconds, showing the specificity and stability of the device. In sharp contrast, the current change showed a rapid response of less than 5 seconds when target glucose was added to the surface. So far, glucose detection using the Au nanoparticle, ZnO nanorod and nanocomb, or carbon nanotube material with GO_x immobilization is based on electrochemical measurement.[28,29] Because there is a reference electrode required in the solution, the volume of sample cannot be minimized easily. The current density was measured when a fixed potential was applied between the nanomaterials and the reference electrode. This was first-order detection, and the range of detection limit of these sensors was 0.5–70 μ*M*. Glucose sensing was measured through the drain current of HEMT with a change of the charges on the ZnO nanorods, and the detection signal was amplified through the HEMT. Although the response of the HEMT-based sensor was similar to that of an electrochemical-based sensor, a much lower detection limit of 0.5 n*M* was achieved for the HEMT-based sensor as a consequence of this amplification effect. Because there was no reference electrode required for the HEMT-based sensor, the amount of sample only depends on the gate dimensions and can be minimized. The sensors do not respond to glucose unless the enzyme is present, as shown in **Figure 5**.[21]

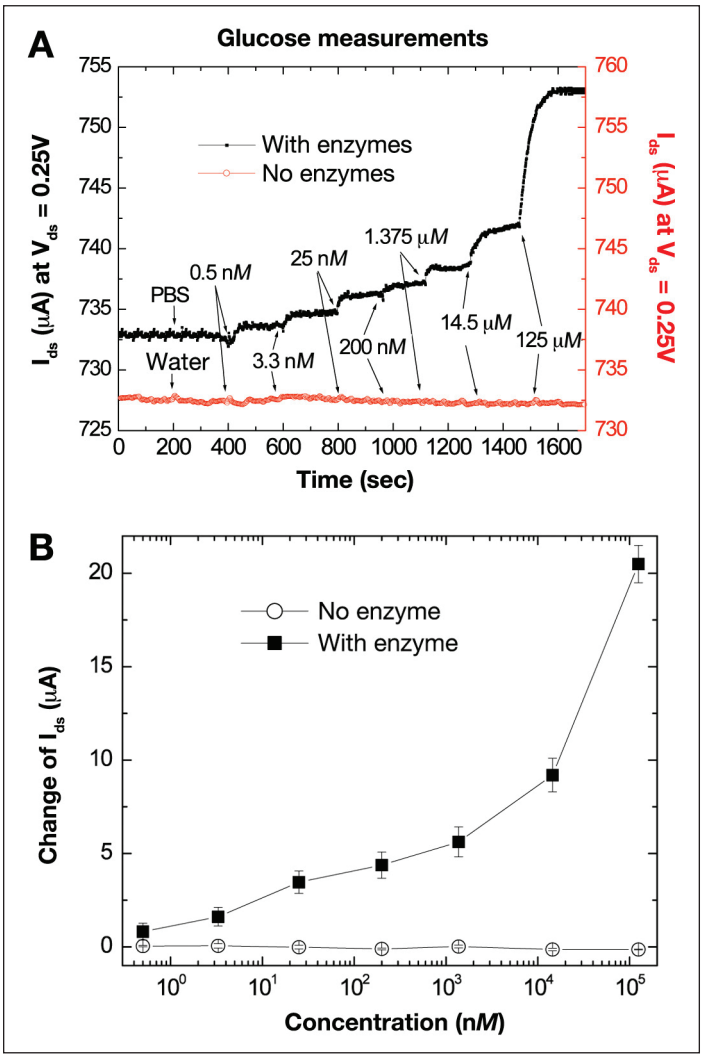

Figure 5. **(A)** Real-time glucose detection using drain current (I) change in the HEMT sensor with a constant bias of 250 mV. **(B)** Amount of drain current change in different concentrations of glucose dissolved in a PBS buffer solution.

Discussion

Although measuring the glucose in the EBC is potentially a noninvasive and convenient method for monitoring patients with diabetes, the activity of the immobilized GO_x is highly dependent on the pH value of the solution. The GO_x activity can be reduced to 80% for a pH value of 5 to 6. If the pH value of the glucose solution is larger than 8, the activity drops off very quickly.[30] **Figure 6** shows time-dependent source–drain current signals with a constant drain bias of 500 mV for glucose detection in deionized (DI) water and PBS buffer solution. Fifty microliters of PBS solution was placed on the

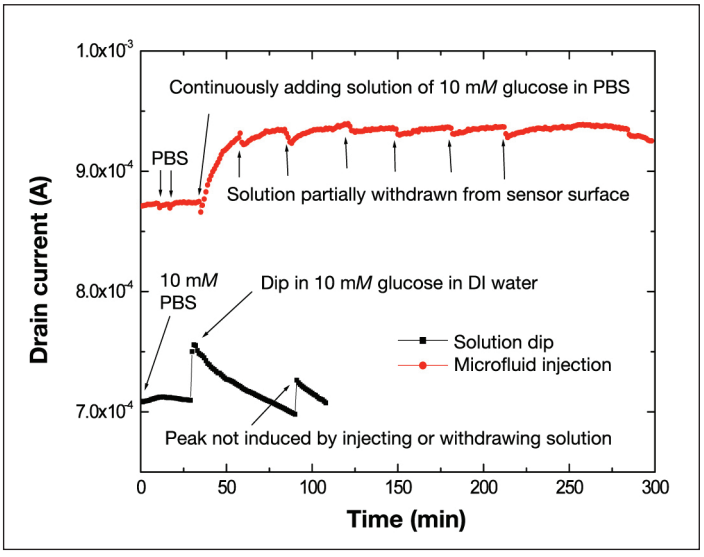

Figure 6. Time-dependent source–drain current signals with a constant drain bias of 500 mV for glucose detection in DI water and PBS buffer solution.

glucose sensor and no current change was seen with the addition of buffer solution at 20 and 30 minutes. This stability is important to exclude possible noise from the mechanical change of the buffer solution. In sharp contrast, the current change showed a rapid response in less than 20 seconds when the sensor was dipped into 100 ml of a 10 m*M* glucose solution using DI water as the solvent. This sudden drain current increase indicated that GO_x reacted immediately with glucose, and oxygen was produced as a by-production of this reaction. However, the drain current gradually decreased. This was due to the oxygen produced in the reaction between GO_x and glucose solution and changing the pH value adjacent to the gate area. Because there was no agitation in the glucose solution, the solution around the gate area became more basic and the activity of GO_x decreased as a consequence of the high pH value environment from 60 to 85 minutes. Because of the lower activity of GO_x in the high pH value condition, the amount of oxygen produced from the reaction between GO_x and glucose decreased as well during the period of 60–85 minutes. Once the hydroxide (OH^-)ions produced from the reaction between oxygen and water diffused away the gate area, the pH value decreased. Thus, around 85 minutes, the pH value of the glucose solution around the gate area decreased enough to allow the activity of GO_x to resume and then the drain current of the glucose sensor showed another sudden increase. The same process happened again, and the drain current of the glucose detection decreased gradually for a second time.

However, when the glucose sensor was used in a pH-controlled environment, the drain current stayed fairly constant, as shown in **Figure 6**.[14,18–20] In this experiment, 50 µl of PBS solution was introduced on the glucose sensor to establish the baseline of the sensor as in the previous experiment. Then, glucose with a 10 n*M* concentration prepared in PBS solution was introduced to the gate area of the glucose sensor through a microinjector. There was no glucose in the 50-µl PBS solution, and the PBS solution was added at 20 and 30 minutes. It took time for the glucose solution to diffuse to the gate area of the sensor through the blank PBS, and the drain current increased gradually corresponding to the glucose diffusion process. Because fresh glucose was continuously provided to the sensor surface and the pH value of the glucose was controlled, once the concentration of the glucose reached equilibrium at the gate of the glucose sensor, the drain current of the glucose remained constant, except in the presence of glucose solution, which was taken out from time to time using a micropipette. Small oscillations of the drain current were observed, which could be eliminated using a microfluidic device for this experiment.

The HEMT sensor immobilized with the Sc_2O_3 thin film has been demonstrated with excellent response to the pH value of the solution.[14,18-20] **Figure 7** shows the drain current of the HEMT immobilized with the Sc_2O_3 at a bias of 0.25 volt as a function of time from HEMTs with Sc_2O_3 in the gate region exposed for 150 seconds to a series of solutions whose pH varied from 3 to 10. The current increased significantly upon exposure to the liquids as the pH decreased. The change in current was 37 µA/pH. The HEMTs showed stable operation with a resolution of ~0.1 pH over the entire pH range, showing the remarkable sensitivity of the HEMT to relatively small changes in the concentration of the liquid.

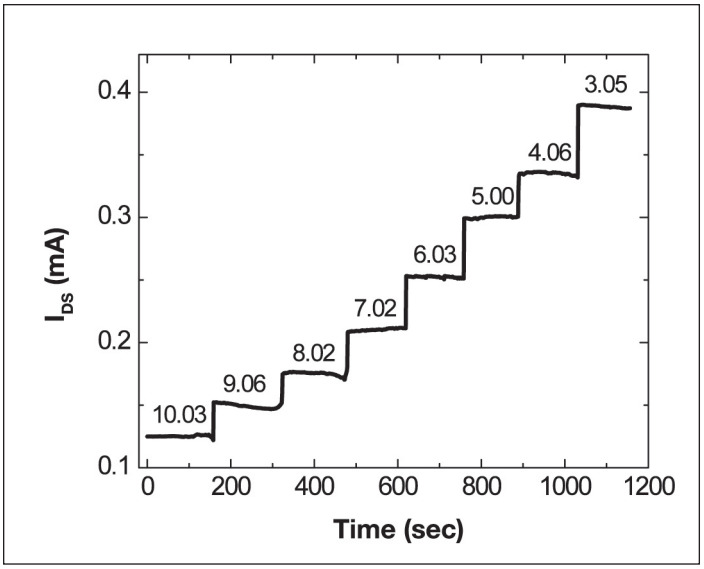

Figure 7. Drain current (IDS) of a Sc_2O_3 immobilized as a function of time.

Because EBC contains primarily water droplets, the biomarker concentration in the EBC is dependent on the degree of dilution in the sample. High respiration during exercise or different tidal breath patterns may alter airway surface liquid osmolarity, and the airway lining fluid component of the EBC can be highly diluted by condensing vapor phase water. The concentrations of electrolytes in the EBC can be measured and then compared with those in blood plasma to estimate the dilution factor of the biomarkers in airway lining fluid. It has been reported that no change of chloride ion concentration was identified in the EBC samples. The HEMT sensor immobilized with the AgCl thin film has also demonstrated an excellent response to chloride

ion concentrations.[25,26] As illustrated in **Figure 8**, the sensor showed rapid responses with the chloride ion concentrations in the exposed solutions. This encouraging result shows the possibility of using chloride ion concentrations to calibrate the dilution factor during the measurement of biomarkers in EBC.

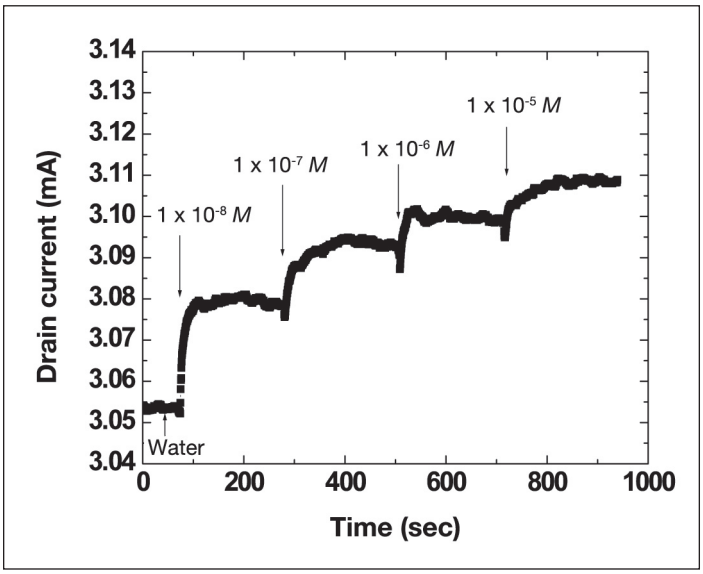

Figure 8. Drain current of an AgCl thin film-immobilized HEMT sensor as a function of time when exposed to different chloride ion concentrations.

Conclusions

There is great promise for using HEMT-based sensors to enhance the detection sensitivity for glucose detection in the EBC. Depending on the immobilized material, HEMT-based sensors can be used for sensing different materials. These electronic detection approaches with rapid response and good repeatability show potential for the investigation of airway pathology. The high surface area of nanowires provides an ideal approach for enzymatic detection of biochemically important substances. The devices can also be integrated into a wireless data transmission system for remote monitoring applications.

Acknowledgments:

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