

ORIGINAL ARTICLE

Sensitive silica-alumina modified capacitive non-Faradaic glucose sensor for gestational diabetes

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Lizhen Chen and Wenyang Xie contributed equally in this study.

Abstract

A highly sensitive silica-alumina (Si-Al)-modified capacitive non-Faradaic glucose biosensor was introduced to monitor gestational diabetes. Glucose oxidase (GOx) was attached to the Si-Al electrode surface as the probe through amine-modification followed by glutaraldehyde premixed GOx as aldehyde-amine chemistry. This Si-Al (~50 nm) modified electrode surface has increased the current flow upon binding of GOx with glucose. Capacitance values were increased by increasing the glucose concentrations. A mean capacitance value was plotted and the detection limit was found as 0.03 mg/mL with the regression coefficient value, $R^2 = 0.9782$ [$y = 0.8391x + 1.338$] on the linear range between 0.03 and 1 mg/mL. Further, a biofouling experiment with fructose and galactose did not increase the capacitance, indicating the specific glucose detection. This Si-Al-modified capacitance sensor detects a lower level of glucose presence and helps in monitoring gestational diabetes.

KEYWORDS

biomarker, capacitive non-Faradaic sensor, gestational diabetes, glucose oxidase

Abbreviations: Si-Al, Silica-Alumina; GOx, Glucose oxidase; APTES, 3-Aminopropyltriethoxysilane; nm, Nanometer; μm , micrometer; Å, Angstrom; UV, Ultraviolet; mg, milligram; mL, microliter; KOH, Potassium hydroxide; BSA, Bovine Serum Albumin; LOD, Limit of detection; GLU, Glutaraldehyde; HIV, Human Immunodeficiency Virus; ELISA, Enzyme-linked Immunosorbent Assay; R², Regression Co-efficient

1 | INTRODUCTION

Gestational diabetes is a condition with an abnormally high glucose level during the pregnancy, which raises the risk of getting type-2 diabetes to the mother and the baby at later stages of life.¹ In addition, gestational diabetes

causes various health issues to mother and fetus, which includes macrosomia (baby is larger than normal) and hypoglycemia to a baby after birth (lower blood sugar), lower serum calcium and magnesium levels for mothers.² At the same time, controlled diabetes solves all these issues caused by high blood sugar level. So that accurate and continuous monitoring of the glucose level is mandatory for a healthy pregnancy.³ An efficient and accurate sensing method is necessary to monitor and manage gestational diabetes. On the other hand, a higher level of the human population has been affected by diabetes and lead to several subsequent problems. Without undergoing proper control and treatment, diabetes causes a lot of serious health issues, including heart disease and stroke. So that, an effective glucose sensor is necessary for all, especially those who are watching their blood glucose level. Hence, a reliable, low-cost, and sensitive nanomaterial-based glucose biosensor is introduced here to identify the glucose using glucose oxidase (GOx) as the probe.

An electrochemical biosensor with GOx is the preferred device to identify the glucose level due to its selectivity, simplicity, and sensitivity.^{4–7} At the same time, the main challenge is the immobilization of enzyme on the sensing electrode surface. The low efficiency of GOx immobilization on an electrode disrupts the glucose identification and also affects the performance. To overcome these issues, various researchers have applied the nanomaterials for efficient probe immobilization. Nanomaterials can easily attach with a probe/target by immobilizing on the sensing surfaces through the chemical linker or by electrostatic interaction.^{8,9} Different nanomaterials, such as gold, graphene, silica, iron, and silver, are common in use for surface functionalization.^{10–12} This probe conjugated nanomaterials to give a more stable form of biomolecules and increase the number of biomolecular attachments on the sensing electrode surface.¹³ In addition, the nanomaterial-conjugated electrode surface increases the current flow upon the interaction of biomolecules.¹⁴ Among other metals, silica and aluminum are the well-established materials for the recognizing biological interaction with a high signal transduction. The unique electrical property of silica-alumina (Si-Al) nanocomposites provides a wide range of opportunities to construct various biosensors for recognizing different biomolecules.^{15,16} In particular, the excellent conductivity, high-surface area, biocompatibility, and high density yield extensive application of Si-Al for constructing a piezoelectric and electrochemical biosensor.¹⁷ In the current research, (3-Aminopropyl)triethoxysilane (APTES) modified Si-Al was seeded on the electrode surface and then GOx premixed glutaraldehyde was attached on APTES-Si-Al to identify the glucose level by a capacitive biosensor.

Highlights

- A highly sensitive silica-alumina modified capacitive non-Faradaic glucose biosensor was introduced to monitor gestational diabetes through aldehyde-amine chemistry.
- Glucose oxidase was interacted with increasing glucose concentrations and detected at 0.03 mg/mL.
- A biofouling experiment with fructose and galactose did not increase the capacitance, indicating the specific glucose detection.

The capacitive biosensor is an affinity sensor, which works by registering the binding between the target and probe attached sensing electrode surface. Capacitive sensors are suitable for various substrates and highly reliable for wireless sensors and operate at low cost.^{18,19} The capacitive biosensor can measure the changes in the dielectric layer at the electrode interface when a target molecule interacts with an immobilized capture molecule on the electrode surface.²⁰ The capacitance between the electrode and the electrolyte is given by the following equation:

$$C = (2n\epsilon_0\epsilon A)/d,$$

where ϵ is a dielectric constant, ϵ_0 is the permittivity of the free space, A is the surface area of the plates, d is an insulating layer thickness and n is the number of repetitive fingers.^{21,22} Previously, capacitive sensors were successfully utilized for detecting heavy metals, proteins, nucleotides, and organic molecules.^{20,23–26} Apart from that non-Faradaic capacitive measurement reduces the protein denaturing caused by metallization and improves the detection performance.^{27,28} In this work, the non-Faradaic capacitance sensor was used to identify the glucose on the GOx-modified electrode surface. To overcome the current issues, this study shows that the non-Faradaic capacitive glucose sensor has several advantages for high-performance such as optimized finger and gap regions, right surface chemical, cheaper, easier to use, higher sensitivity, selectivity, and to be operated by both alternate and direct currents. Surface chemical functionalization is one of the crucial parts to immobilize the probe (GOx) at higher numbers.^{29–31} Herein, the coupling of APTES and Glu has played a major role in enhancing the number of GOx attachment and demonstrated the high performance.



2 | CHEMICALS AND METHODS

2.1 | Biomolecules and reagents

Coal fly ash was received from a thermal power plant (India). Sodium hydroxide, sulfuric acid, GOx, glucose, glutaraldehyde, and bovine serum albumin (BSA) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Whatman filter paper was ordered from Thermo Fisher Scientific (Waltham, MA, USA). APTES was ordered from Merck (Branchburg, NJ, USA).

2.2 | Synthesis of Si-Al composite

The Si-Al composite was prepared from coal fly ash as described by Ramanathan et al.³² The following steps are involved in this process: (1) Fly ash was dissolved in 2 M of 1 L sodium hydroxide and heated at 100°C for 5 h to dissolve sodium aluminosilicate from the fly ash; (2) sodium aluminosilicate was filtered and separated by Whatman filter paper; (3) extracted sodium aluminosilicate was placed on the stirring hot plate at 50°C and 2 M of H₂SO₄ was added slowly until it reaches the condition to form a gel (at pH 7); (4) the gel was separated by centrifugation and washed by distilled water, and then dried at 90°C to get the Si-Al composites.

2.3 | Electrode surface fabrication

The electrode surface was fabricated as described previously using the traditional wet etching procedure. Initially, AutoCAD software was used to design the desired electrode surface with the gap size (10 μm), length (7500 μm), electrode size (10 μm), thickness (40 nm), width (4100 μm), and the finger length (4000 μm). The following procedures were used to prepare the desired electrode: (1) The silica wafer was washed with piranha solution; (2) thermal oxidation (2800 Å) was carried out to form the silicon dioxide layer; (3) aluminum with the thickness of 45 nm was deposited by using a thermal evaporator; (4) a positive photoresist was coated with a spin-coater and soft baked at 90°C for 1 min; (5) UV light was used to transform the pattern on the electrode; (6) uncovered portion was removed by RD-6 developer and hard-baked at 90°C for 2 min; (7) An electrode was dipped in an aluminum etching solution to remove the desired aluminum; (8) the final electrode was washed with acetone and distilled water.

2.4 | Preparation of APTES-modified Si-Al

Si-Al was modified by APTES to attach the surface of the sensing electrode. For that, 1 mg/mL of synthesized Si-Al was dissolved in 1% of APTES (diluted in ethanol) and then was kept for 1 h, then placed under the shaking condition for 3 h. After that, the unbound APTES was washed out by 30% ethanol and separated by centrifugation. The modified Si-Al was kept in a refrigerator for further immobilization process.

2.5 | GOx-modified sensor surface preparation

GOx was immobilized on the electrode surface through Si-Al composites. The following steps were involved in this process: (a) A sensing electrode was treated with 1% of KOH for 15 min; (b) APTES-Si-Al was added and rested for 3 h; (c) premixed glutaraldehyde-GOx (1% of glutaraldehyde was mixed with GOx for 1 h) was allowed to interact with APTES; (d) excess APTES surfaces were covered with 2% of BSA. In between each step, the surface was washed with PBS buffer and the current capacitance changes were recorded after each immobilization step.

2.6 | Glucose determination on the GOx-modified electrode surface

Glucose was determined on the GOx attached electrode surface. After the surface was covered with BSA, the capacitance response was noted at this point. And then, glucose with 0.5 mg/mL was added to the GOx surface and interacted for 15 min. The capacitance response was noted at this point; the difference was considered as the binding of glucose with the GOx. Further to identify the limit of glucose detection, the glucose concentration from 0.03 until 0.25 mg/mL was diluted and dropped individually on the GOx-immobilized surface. The capacitance with responses was noted for each concentration of glucose. The differences were plotted in an excel sheet to calculate the regression value (R^2) for identifying the linearity with the detection limit of glucose. The limit of detection (LOD) was calculated with the lowest concentration of an analyte against the background signal ($S/N = 3:1$), in other means, $\text{LOD} = \text{standard deviation of the baseline} + 3\sigma$. The sensitivity of the device was determined by measuring the apparent difference between the two lowest concentrations tested.

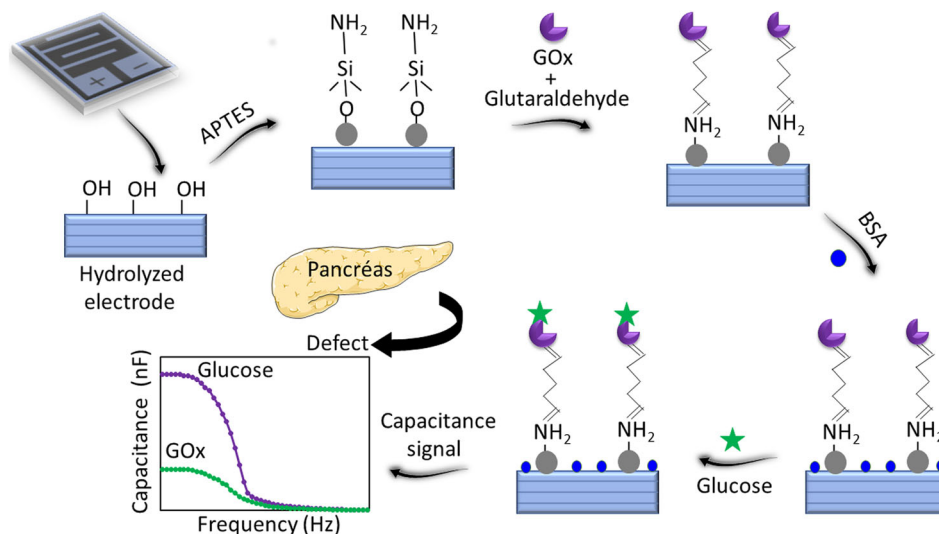


FIG 1 Schematic illustration of capacitance sensor for glucose detection. Measured on GOx-modified electrode surface. APTES-modified Si-Al was attached on OH-treated electrode surface and then GLU-mixed GOx was added to react with APTES. This GOx-modified electrode was used to identify the glucose

2.7 | Biofouling effect on the GOx-modified surface: Surface selectivity

To identify the biofouling effect on the sensing electrode, instead of glucose, a similar concentration at 0.5 mg/mL of fructose and galactose was dropped on the GOx modified surface. The current capacitance changes were recorded. These current changes were compared with the genuine interaction between glucose and GOx.

All capacitive measurements were carried out at room temperature with a constant power supply. All experiments were performed in triplicate and averaged to confirm the reproducibility under the maintained wet-condition during the measurements. The devices prepared with the same batch were used for the optimization and reproduction of experiments. Unless otherwise stated between each surface modification or interaction, a thorough washing was done using 10 reaction volumes of 10 mM PBS (pH 7.4). The sensing area of the device used could accommodate from 10 until 100 μL of the reaction solution.

3 | RESULTS AND DISCUSSION

Figure 1 shows the schematic illustration of the capacitance sensor for glucose determination on the GOx-modified electrode surface. As shown in Figure 1, APTES-modified Si-Al was immobilized on the KOH-treated electrode surface and then glutaraldehyde (GLU)-GOx was allowed to react with APTES on Si-Al. The primary advantage of Si-Al is high nonfouling compared to other met-

als. Another great advantage is Si-Al can be prepared from a cheap source, for example, fly ash. Here premixed GOx with GLU prior to adding on the sensor substrate, which increases the number of GOx interactions with GLU. Previously, the anti-HIV p24 antibody was mixed with GLU and then attached on the APTES-immobilized ELISA polystyrene surface improves the detection of p24 protein and reached the lower detection limit.³³ This strategy increases the number of GOx immobilization on the sensing electrode, which leads to the lower detection of glucose. After GOx modification, the excess APTES area was blocked by BSA to avoid nonspecific binding. This GOx-modified electrode surface was used to identify the glucose.

3.1 | Electrode functionalization

The captured GOx molecular immobilization process was confirmed by changing the capacitance on the electrode surface. Figure 2(A) shows the capacitance changes after each biomolecular immobilization. As shown in the figure, the OH-tethered electrode surface shows the capacitance value as 1.13×10^7 nF at 1 Hz, after adding APTES-Si-Al conjugates it increased to 1.19×10^7 nF. This increment confirms the binding of APTES on the OH-modified electrode surface. Further, when the GLU-GOx mix was added, the capacitance value was increased to 1.19×10^7 nF, which happened due to the interaction of aldehyde in GLU with the amine on APTES. GLU has the aldehyde group at both ends, one end reacts amine of APTES on the sensing surface, and the other end reacts the amine with GOx. Finally,

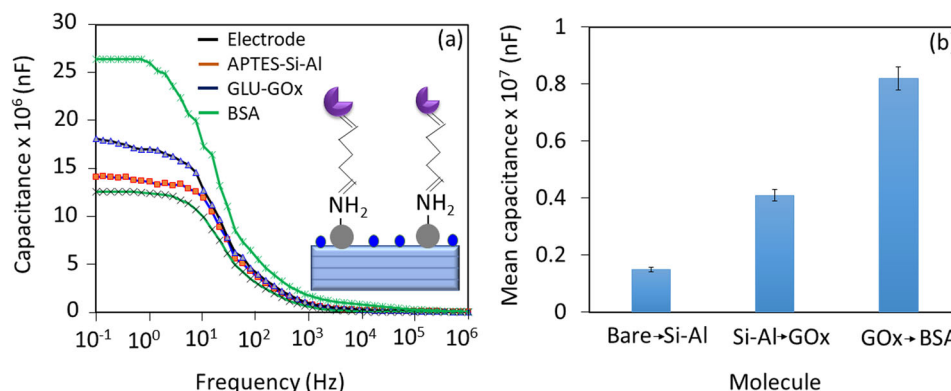


FIG 2 Capture molecule of the GOx immobilization process. (A) capacitance changes after each immobilization of biomolecules. The increment in capacitance after each immobilization step confirms the modified GOx surface. Figure inset is the diagrammatic representation. (B) Capacitance value difference for each biomolecular immobilization. The difference after adding GOx confirms the binding of GOx on the sensing electrode surface

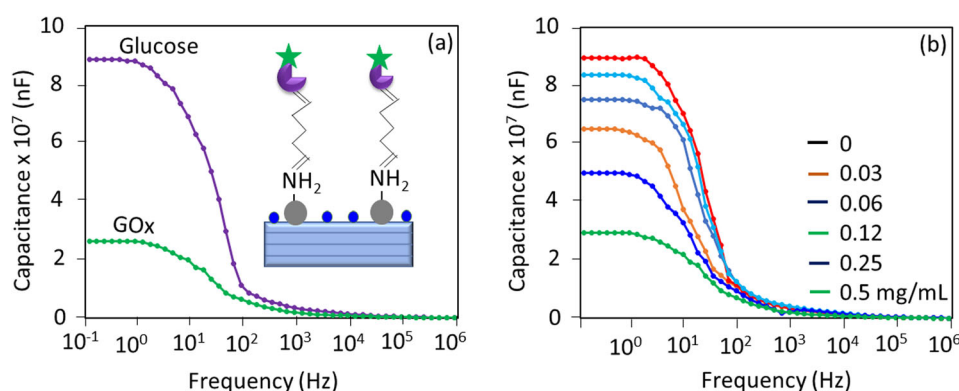


FIG 3 Glucose determination on the Si-Al-GOx modified electrode. (A) 1 mg/mL of glucose was dropped on the GOx-modified surface. The capacitance value was increased drastically confirms the binding of GOx with glucose. Figure inset is the diagrammatic representation. (B) Titration of glucose from 0.03 to 0.5 mg/mL on the GOx-modified electrode surface. A clear increment in capacitance was noted for each glucose concentration

the blocking agent “BSA” was added, and the capacitance value was increased to 1.73×10^7 nF. It was clearly noted that the increment in capacitance after each immobilization step, in particular, GLU-GOx confirms the attachment of the capture molecule on the electrode surface and is used to identify the glucose molecule as the target (Figure 2B).

3.2 | Glucose determination on the Si-Al-modified electrode surface

The glucose concentration was determined on the Si-Al-modified electrode. At first, a higher concentration of 1 mg/mL of glucose was added on the GOx surface, the capacitance value was increased from 2.64×10^7 to 8.86×10^7 nF (Figure 3A). This clear increment in capaci-

tance changes has confirmed the interaction of glucose to the immobilized GOx. Further, glucose was diluted from 0.03 to 0.25 mg/mL on the GOx-modified electrode surface. As shown in the figure, when 0.03 mg/mL of glucose was added, the capacitance value was increased from 2.64×10^7 to 4.49×10^7 nF, which confirms the detection of 0.03 mg/mL glucose (Figure 3B). Increasing the glucose concentration to 0.06, 0.12, 0.25, and 0.5 mg/mL, the capacitance values were changed to 5.85×10^7 , 6.76×10^7 , 7.53×10^7 , and 8.85×10^7 nF, respectively. It was noticed that with increasing the glucose concentration, the capacitance value also gradually increased (Figure 4A). The mean value of capacitance for each glucose concentration was plotted in an excel sheet and calculated the R^2 (regression coefficient) as 0.9782, and the detection limit of glucose was found as 0.03 mg/mL (Figure 4B).

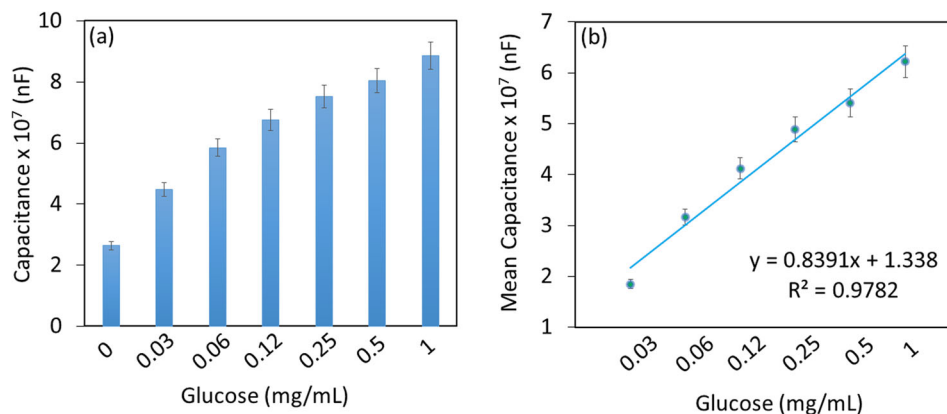


FIG 4 Capacitance value for different glucose concentration interactions GOx. (A) With increasing the glucose concentration, capacitance values were also gradually increased. (B) Mean value of capacitance for each concentration. Plotted in an excel sheet and calculated the R^2 value as 0.9782, and the detection limit of glucose was found to be 0.03 mg/mL

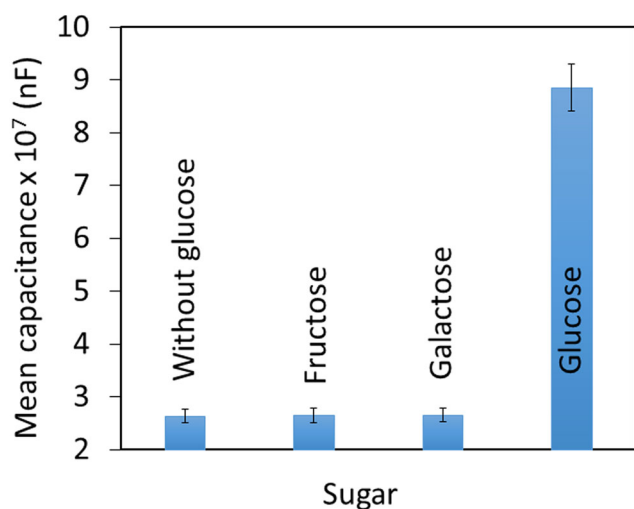


FIG 5 Biofouling effect on the sensing electrode surface. Control experiments were conducted with galactose and fructose interaction on the immobilized GOx. The capacitance value did not increase, while it increased with glucose as the target

3.3 | Biofouling effect on the GOx-modified surface

Biofouling plays a major role in determining the signal-to-noise ratio. Unnecessary binding of other biomolecules on the sensing surfaces leads to false positive result. In particular, APTES in the sensing electrode attracts biomolecules nonspecifically through the electrostatic interaction. It was proved that APTES-modified silica surface shows higher nonspecific binding with streptavidin-conjugated gold nanoparticles, and it was blocked by polyethylene glycol-based polymers.^{34,35} Here we used BSA to cover the excess APTES molecule. Apart from that, the method used

here is the premixture of GLU and GOx and covers most of the APTES molecule, which reduces the biofouling. To identify the biofouling effect on the sensing electrode, control experiments were conducted with other related sugars such as the galactose/fructose interaction on the immobilized GOx. As shown in Figure 5, after adding the control sugars, the capacitance value did not increase, while it shows the increment with glucose. This experiment confirms that the sensing electrode surface only recognizes the glucose molecule as the target. Considering the life-time storage of the bare device was noticed to be for several months when stored under the maintained desiccator. The same device has turned its surface stability upon attaching the probe and was noticed to be lost ~33% of activity after a month.

4 | CONCLUSION

The Si-Al-modified glucose sensor was prepared to monitor gestational diabetes during the period of pregnancy. Si-Al was attached to the electrode surface through the amine linker. Glutaraldehyde-mixed GOx increases the immobilization of GOx on the Si-Al-modified electrode surface. On this surface, glucose was monitored by the capacitance sensor. With increasing the glucose concentration, the capacitance values were gradually increased. The detection limit was calculated with a mean difference of each glucose concentration, and it was 0.03 mg/mL. Further, the sensing electrode surface did not show any biofouling effect, which was confirmed with the interactions of other sugars namely, fructose and galactose. The sensing electrode surface is demonstrated here to identify the lower level of glucose and helps in monitoring the condition with gestational diabetes.



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