A MICROFABRICATED DIELECTRIC AFFINITY SENSOR FOR CONTINUOUS GLUCOSE MONITORING

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ABSTRACT

We present a microfabricated affinity sensor using permittivity measurement for continuous glucose monitoring (CGM). This device is based on a perforated electrode separated from a bottom electrode on a substrate by a solution of a synthetic glucose-sensitive polymer. Glucose permeates through the perforated electrode and binds with the polymer, leading to a change in the polymer solution permittivity, which can be measured via the sensor capacitance. We characterize the frequency-dependent glucose response of the sensor capacitance, and assess the time response and the drift of the device. This glucose sensor has potential use in implantable, long-term, and continuous glucose monitoring.

KEYWORDS: Permittivity, Dielectric, Glucose Sensor, Microelectromechanical Systems

INTRODUCTION

Continuous glucose monitoring (CGM) has been commonly realized by subcutaneously implanted enzymatic electrochemical detection, in which glucose is irreversibly consumed, causing a change in the equilibrium glucose concentration. In addition, electroactive chemical generation and hydrogen peroxide production may cause erosion of the sensor electrodes and deactivation of the functional enzymes, causing the decay of device accuracy, reliability, and longevity over time [1]. In contrast, affinity binding is a promising alternative to electrochemical detection. Boronic-acid based synthetic polymers, as glucose-specific receptors, have demonstrated excellent stability and controllable specificity in glucose detection. Emerging affinity devices using boronic-acid based polymers have been realized by measuring fluorescence intensity [2], color shift of photonic crystals [3], hydrogel swelling [4], and viscosity [5]. However, the applicability of these methods to fully implanted operations is complicated by issues such as the need for optical access or mechanical moving parts. We have previously demonstrated a proof-of-concept microelectromechanical systems (MEMS) device that determined glucose concentration from capacitive permittivity measurement [6]. However, this sensor can only measure polymer solutions premixed with glucose at various concentrations, limiting the device’s practical application in CGM. To address this issue, we present a novel dielectric glucose sensor with a perforated electrode. This perforated electrode is embedded in a diaphragm separated from an electrode on the substrate by the polymer solution. Environmental glucose diffuses through the semi-permeable membrane and binds with the polymer, causing a change in the permittivity of the polymer solution, which can then be detected via changes in the capacitance between the two electrodes. Results from in-vitro characterization of this sensor have demonstrated that this dielectric affinity glucose sensor can be practically useful in a fully implantable sensor for long-term CGM.

THEORY

The MEMS dielectric affinity glucose sensor is based on a perforated diaphragm that is situated inside a microchamber and supported by several anti-stiction posts, which prevent the diaphragm from collapsing while providing additional resistance to environmental disturbances (e.g., shock, vibration) (Figure 1). The microchamber is filled with the solution of poly(N-hydroxyethyl acrylamide)-ran-3-acrylamidophenylboronic acid (PHEAA-ran-PAAPBA), a synthetic glucose-specific polymer, and is sealed by a semipermeable membrane to prevent the polymer from escaping while allowing glucose to permeate to the solution. An AC electric field (E-field) is imposed on a perforated electrode embedded in the diaphragm and an electrode on the substrate below. These electrodes are separated by the polymer solution. Glucose binds reversibly to the phenylboronic acid moieties in PHEAA-ran-PAAPBA to form strong cyclic boronate ester bonds, resulting in a change in the polymer polarization behavior and hence the permittivity of the polymer solution. Thus, measuring the sensor capacitance allows determination of glucose concentration.

EXPERIMENTAL

The fabrication of the device (Figure 2) started with deposition and patterning of a gold layer to form the bottom electrode (1mm×1mm×100nm) and a resistive temperature sensor on a silicon oxide coated silicon substrate, which were then passivated by a parylene layer (1 μm in thickness). Following the spin-coating and patterning of a sacrificial photoresist layer (3 μm in thickness), another parylene layer (1.5 μm in thickness) was deposited. A gold layer was further deposited and patterned to form the top perforated electrode (1mm×1mm×100nm) subsequently passivated by a parylene layer (3 μm in thickness) and an SU-8 layer (20 μm in thickness), resulting in nine anti-stiction posts. A thick SU-8 layer 80 μm in thickness was finally spin-coated and patterned to form a microchamber as well as an inlet and an outlet for polymer solution handling.
two successively coated SU-8 layers also acted as a mask to pattern the lower parylene layers by reactive ion etching to expose the sacrificial photoresist layer and form a diaphragm with the holes for the glucose diffusion. The diaphragm was finally released by removing the sacrificial layer using photoresist stripper. A semi-permeable membrane was then glued onto the microchamber using an epoxy. The sensor was encapsulated into an acrylic test cell with a total volume of approximately 1 mL.

The microsensor was characterized using a previously reported experimental setup [6] (Figure 3). Briefly, the temperature of the polymer solution was maintained at 37 °C via closed-loop control by a Peltier heater (Melcor, CP14), whose voltage is controlled according to feedback from the integrated temperature sensor. The device was coupled to a capacitance/voltage transformation circuit driven by a sinusoidal input from a function generator (Agilent, 33220A). All experiments were conducted at frequencies below 100 kHz as allowed by a lock-in amplifier (Stanford Research Systems, SR830), which measured the amplitude and phase shift of the output voltage from the circuit. The equivalent capacitance \( C_x \) that is directly related to the polymer permittivity was determined from the output voltages of the circuit when alternatively coupling the microsensor and a reference capacitance \( C \) into the circuit. The device was first characterized by obtaining the frequency-dependent capacitance at a selected glucose concentration. The device time response to a glucose concentration change was then assessed to demonstrate the potential application of the device in CGM. Finally, the device stability was obtained over an extended measuring period of approximately 4 hours to evaluate the suitability of the device for long-term, stable CGM applications.

RESULTS AND DISCUSSION

The frequency responses of device to the E-field with a frequency from 0.5 to 100 kHz was first obtained with a glucose-free PHEAA-ran-PAAPBA solution (Figure 4). The device frequency response, which was given in terms of the sensor capacitance, underwent a rapid decline from 366 to 34 pF at frequencies lower than 10 kHz, and then gradually increased to 48 pF at 100 kHz. The abnormal decrease of the sensor capacitance at low frequencies could be attributed to the effects of interfacial polarization which typically occur at the interface of two different media. The device capacitance changes after the binding between PHEAA-ran-PAAPBA and glucose were also obtained at selected glucose concentrations from 50 to 200 mg/dL (Figure 5). The sensor capacitance decreased with increasing glucose concentration after 10 kHz. In contrast, at frequencies between 0.5 and 10 kHz, the sensor capacitance increased with glucose concentrations. These frequency-dependent sensor response suggests that we can measure glucose-induced permittivity change through capacitance at a fixed excitation frequency. At our measurement frequencies (lower than 100 kHz) a number of polarization mechanisms might contribute to the glucose-dependent capacitance change of the device, such as electronic polarization, ionic polarization, orientational polarization, and interfacial polarization. The binding between the polymer and glucose may change the polarization behaviors of ions (e.g., Na⁺, K⁺, and H3O⁺), and dipoles (e.g., AAPBA, HEAA, and H2O) in the polymer solution, leading to the change in the permittivity of the polymer solution as well as the change in the sensor capacitance. Although the underlying cause of the crossover of sensor ca-

![Figure 1: Dielectric glucose sensor: (a) Schematic design and (b) device micrograph.](image1)

![Figure 2: Fabrication process: (a) Gold layer deposition and patterning to form bottom gold electrode, and passivation of gold electrode by Parylene; (b) Sacrificial photoresist layer deposition and patterning; (c) Parylene deposition and gold layer deposition and patterning to form the top perforated electrode; (d) Parylene passivation layer deposition; (e) SU-8 deposition and patterning to form the diaphragm and the microchamber; (f) SU-8 patterning, sacrificial layer removal, and semi-permeable membrane bonding.](image2)

![Figure 3: Experimental setup and a capacitance/voltage transformation circuit for sensor capacitance measurement.](image3)
capacitance at a frequency of approximately 5 kHz requires further investigation, it could be possibly related to the glucose-induced changes in the interfacial polarization.

We next measured the time response of the sensor capacitance in response to a glucose concentration change (Figure 6). For example, the glucose concentration was initially allowed to be equilibrated at 50 mg/dL in the test cell and sensor chamber. Next, the solution in the test cell was replaced with another glucose solution at 100 mg/dL. We observed that the sensor capacitance decreased with time, corresponding to the decrease in polymer solution permittivity. The capacitance finally saturated to a constant level, reflecting that the process of glucose permeation and binding had reached a dynamic equilibrium. The time constant of this process was determined to be approximately 4.6 min, and can be further improved by shortening the distance between the semi-permeable membrane and the electrode. Finally, we investigated the drift of the sensor output by exposing the sensor to 100 mg/dL glucose solution over a period about 4 hours (Figure 7). We can observe that the sensor capacitance is steady at 32.65 pF with almost no drift. These results demonstrate the excellent stability of our sensor, which is ideal for long-term CGM.

CONCLUSION

We have presented an affinity glucose sensor that is based on capacitance measurements of glucose-induced permittivity changes of a glucose-sensitive polymer PHEAA-ran-PAAPBA. This CGM sensor features a perforated electrode that allows the permeation of glucose. Sensor frequency response has demonstrated that the frequency-dependent sensor capacitance changes at varied glucose concentrations. In addition, the time constant and the drift of the sensor have been investigated. The results show that our sensor possesses acceptable time response and excellent stability, which is preferable for long-term, reliable CGM.

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REFERENCES


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