A CAPACITIVELY BASED MEMS AFFINITY GLUCOSE SENSOR

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ABSTRACT

This paper presents a capacitively based MEMS affinity sensor for continuous glucose monitoring applications. This sensor consists of a vibrating Parylene diaphragm, which is remotely driven by a magnetic field and situated inside a microchamber. A solution of poly(acrylamide-ran-3-acrylamidophenylboronic acid) (PAA-*ran*-PAAPBA), a biocompatible glucose-sensitive polymer, fills the microchamber, which is separated from its surroundings by a semi-permeable membrane. As glucose concentration is varied, viscosity changes induced by glucose/polymer binding cause a detectable change in the Parylene diaphragm vibration which can be measured capacitively. The response time of the sensor to glucose concentration changes is approximately 3 minutes which can be further improved with optimized device designs. The device has been tested at physiologically relevant glucose concentrations ranging from 27 to 324 mg/dL, showing excellent reversibility and stability.

KEYWORDS

Biosensing, capacitive sensing, continuous glucose monitoring, affinity binding

INTRODUCTION

Continuous glucose monitoring (CGM) is desirable for diabetes patients to manage their daily physiological glucose levels, as it reduces the risk of complications caused by abnormal conditions such as hypoglycemia or hyperglycemia. CGM is generally achieved by non-invasive or minimally invasive detection of glucose. Currently, subcutaneously implanted enzymatic electrochemical detection is the prevailing CGM technique, due to its high sensitivity and specificity. A number of commercially available devices are available based on this method, such as the Medtronic MiniMed Paradigm [1], Freestyle Navigator [2], and Dexcom Seven [3]. However, the irreversible glucose consumption and by-products during electrochemical reactions affect the accuracy of glucose detection. Furthermore, the glucose consumption rate is susceptible to biofouling on the sensor surface that would affect the diffusion rate, and thus the device sensitivity. As a result, electrochemical CGM sensors generally exhibit large drifts over time and require frequent calibration [4].

Miniaturized sensors, based on MEMS technology, allow low-cost non-invasive or minimally-invasive glucose monitoring based on electrochemical, impedance, electrophoretic, thermal, optical and colorimetric detection methods. We have previously reported a MEMS glucose sensor that measured the viscosity change of a glucose solution after the binding of glucose with a novel glucose-sensitive polymer [5]. The sensor was based on a magnetically actuated cantilever whose vibration was detected optically, represented our initial effort towards an implantable CGM sensor. Building on that work, this paper presents a MEMS CGM sensor which allows capacitive measurement of glucose-induced viscosity changes. This sensor consists of a freestanding Parylene diaphragm with embedded permalloy actuation strips and gold capacitive sensing electrodes, and demonstrates the feasibility for stable and potentially implantable CGM.

DEVICE DESIGN AND FABRICATION

The device consists of a magnetically driven, vibrating Parylene diaphragm situated inside a microchamber that is further sealed by a cellulose acetate (CA) semi-permeable membrane (Fig. 1). The diaphragm is deposited with a gold electrode and further electroplated with permalloy strips. A bottom gold electrode is separated from the vibrating diaphragm by a sealed air chamber. A remotely applied AC electromagnetic field generates a time-dependent torque on the magnetized permalloy strips, causing the diaphragm to vibrate. A biocompatible glucose-sensitive polymer solution (PAA-*ran*-PAAPBA) fills the microchamber for affinity glucose binding and detection. As glucose molecules permeate through the CA membrane, binding with the polymer leads to increased viscosity and hence viscous damping on the diaphragm vibration, producing a measureable capacitance change across the electrodes.

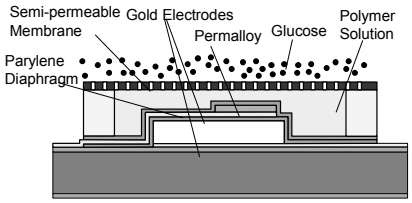

Fig. 1. Schematic of the MEMS capacitive glucose sensor.

The polymer PAA-*ran*-PAAPBA contains phenylboronic acid moieties which reversibly form strong ester bonds with glucose, resulting in the crosslinking of the polymer and an increase in the viscosity of the polymer

solution. Details of this polymer are described elsewhere [6].

Device fabrication started with depositing the bottom gold electrode (400×400×0.1 μm) onto a SiO_2 coated wafer (Fig. 2a), followed with the sacrificial photoresist layer (5 μm) and Parylene layer (3 μm) deposition and patterning (Fig. 2b). A second gold layer was subsequently deposited and patterned to form the top electrode (350×350×0.1μm) (Fig. 2c) followed with permalloy strips (35×200×2 μm) (Fig. 2d) electroplating (Fig. 2e) and an additional Parylene passivating layer (3 μm) (Fig. 2f). The sacrificial photoresist layer beneath the Parylene layer was finally removed by acetone (80 °C) to release the diaphragm, forming a suspended diaphragm over an air cavity (Fig. 3a). After wafer dicing and electrode wiring, a chip was bonded to a polycarbonate sheet in which a hole was drilled to form a microchamber (approximate 10 μL in dimensions), which was in turn bonded to a semi-permeable membrane using an epoxy adhesive. Another polycarbonate sheet, in which a test cell (volume: 300 μL) was fabricated along with inlet and outlet channels for introduction of glucose solutions, was finally adhesive bonded to the CA membrane. The device was driven by a solenoid and electronically monitored using the scheme shown in Figs. 3b, 4.

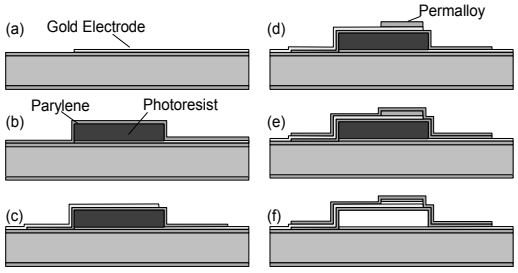

Fig. 2. Fabrication process: (a) Bottom gold electrode deposition; (b) Sacrificial layer patterning and Parylene deposition; (c) Top gold electrode deposition; (d) Permalloy electroplating; (e) Additional Parylene layer deposition; (f) Sacrificial layer removal and diaphragm releasing.

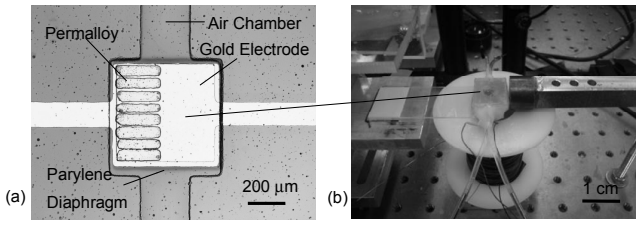

Fig. 3. Images of (a) the device and (b) the experimental setup.

MATERIALS AND EXPERIMENTAL SETUP

Chemicals and reagents used in the experiments include PAA-*ran*-PAAPBA (synthesized using a previously described method [6]) and D-(+)-glucose (Sigma-Aldrich). Phosphate buffered saline (PBS), pH 7.4, was prepared from potassium phosphate (20 mM), NaCl (150 mM) and NaN_3 (0.05%). PAA-*ran*-PAAPBA (284 mg, with 5% of PAAPBA in the polymer) was dissolved in PBS (6 mL) to obtain the sensing solution. Glucose stock solution (1 M) was prepared by dissolving glucose (1.8 g) in PBS to 10mL. A series of glucose solutions (27 mg/dL, 54 mg/dL, 108 mg/dL, 162 mg/dL, 216 mg/dL, and 324 mg/dL) were prepared by further diluting the stock solution with PBS.

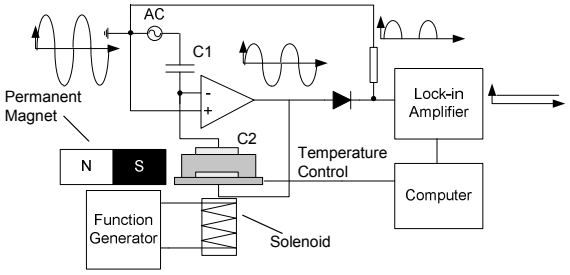

Fig. 4. Experimental setup for characterization of the MEMS glucose sensor.

The diaphragm vibration was driven by a solenoid which under a 5 V_{rms} driving voltage generated an electromagnet field perpendicular to the diaphragm surface (Fig. 4). A permanent magnet was placed parallel to the diaphragm surface to magnetize the permalloy strips. Diaphragm vibration was detected by measuring the capacitance changes between the two gold electrodes through a signal measurement circuit. This circuit changed a 0.5 V_{pp} input AC voltage into a positive half-wave whose amplitude was proportional to the ratio of the standard capacitor C1 and the sensor capacitance C2. A lock-in amplifier captured the change in the output voltage and sent it to a computer for voltage-capacitance conversion. All experiments with this device were conducted at 37 °C with closed-loop temperature control by placing the device on an ultra-thin Kapton heater and using a K-type thermocouple for temperature measurement.

RESULTS AND DISCUSSION

To characterize the device, we first measured the frequency dependent capacitance changes at a glucose concentration of 108 mg/dL. The measurements were performed over an excitation frequency range from 400 to 2000 Hz with an increment of 100 Hz. As can be seen from Fig. 5, the capacitance of the device increased at frequencies between 400 Hz and 1500 Hz, indicating an increase in diaphragm vibration amplitude. The capacitance reached a peak (2500 pF) at approximately 1500 Hz, showing an apparent resonance of the diaphragm vibration. The diaphragm vibration then attenuated with increasing frequency, which corresponded to the decrease in the capacitance. The average error in the capacitance measurements was within 1%, which was better than our

pervious cantilever-based sensor based on optical measurements. The frequency response curve of the capacitance changes did not correspond to that of a simple mass-spring-damper system. This might have been caused by frequency-dependent parameters in the system, for example, the electromagnetic field varied from 0.85 kA/m at 100 Hz to 0.1 kA/m at 2000 Hz. This issue will be addressed in our future work.

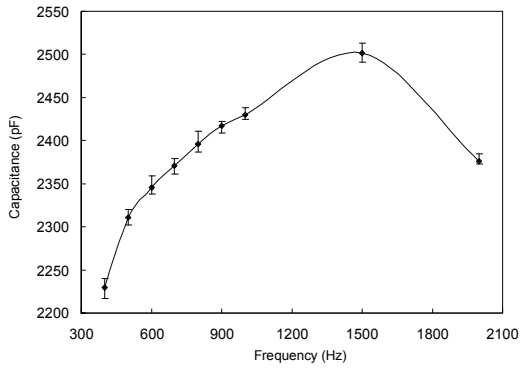

Fig. 5. Frequency response of device capacitance at 108 mg/dL glucose concentration.

The time response of the sensor to changes in glucose concentration was characterized using the time constant, which was physically defined as the time for the sensor to reach 63% of its final value when experiencing a glucose concentration change. In order to experimentally determine this value, the chamber of the device was initially filled with glucose-free polymer solution, while the test cell was filled with PBS buffer. Glucose solution (108 mg/dL) was then introduced into the test cell. The capacitance of the sensor which was proportional to the amplitude of the diaphragm vibration was obtained over time at 600 Hz (Fig. 6). It can be seen that the capacitance decreased gradually with time, corresponding to a steady increase in the damping on the diaphragm vibration due to the viscosity increase induced by glucose-polymer binding. The capacitance finally saturated to a constant level (at approximately 2346 pF), reflecting that the diaphragm vibration had reached steady state and the process of glucose permeation and binding had reached equilibrium. The time constant was determined to be approximately 3.0 minutes. This is appropriate for CGM applications, considering 5-15 minutes of response times for commercially available systems.

To investigate the sensor response to various glucose concentrations, the steady state diaphragm vibration was then measured at various, physiologically relevant glucose concentrations at selected frequencies between 400 and 1500 Hz. The device exhibited a gradual decrease in capacitance with glucose concentration (Fig. 7) at each measured frequency. Specifically, at 600 Hz, the capacitance varied from about 2450 pF to 2250 pF while the glucose concentration changed from 27 mg/dL to 324 mg/dL. These observations indicated a significant increase in vibrational damping, which was consistent with increased viscosity of the polymer solution at higher glucose concentrations. In addition, the trend in each curve suggests that it was practicable to determine the glucose concentration by concentrating on the capacitance change at one fixed frequency, where the capacitance differences between glucose concentrations can be distinguished.

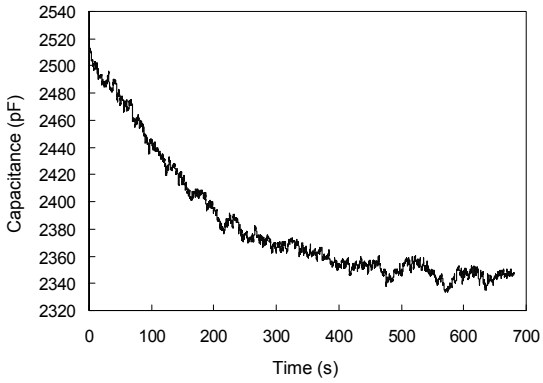

Fig. 6. Time history of the device capacitance at 600 Hz upon exposing the device to a 108 mg/dL glucose solution.

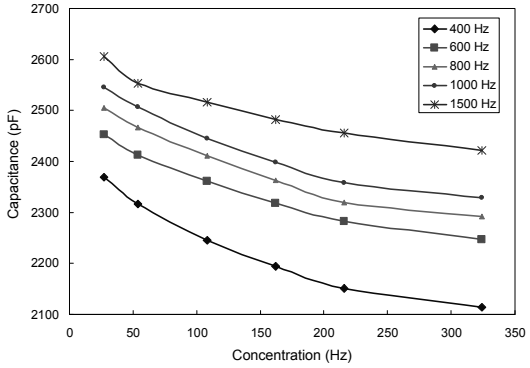

Fig. 7. The sensor response to the glucose solutions at physiologically relevant concentrations.

Measurements of a time-dependent sequence of glucose variations were made to simulate possible glucose concentrations in the interstitial fluid, and also to evaluate the reversibility and stability of this capacitive glucose sensor. In these measurements, glucose concentrations of 27 mg/dL and 54 mg/dL represented the glucose levels before intake of food or during a potentially hypoglycemic state, and 216 mg/dL and 324 mg/dL were used to simulate glucose levels after intake of food or a potentially hyperglycemic state. In addition, glucose concentrations of 108 mg/dL and 162 mg/dL represented normal daily

glucose levels. As shown in Fig. 8, when the glucose concentration varied from 27 to 324 mg/dL, the measured capacitance at 600 Hz decreased from approximately 2450 pF to 2250 pF. The sensor capacitance returned to approximately 2457 pF lasting response to the last 27 mg/dL glucose sample. Also, the average capacitance at 108 mg/dL over the two periods, approximately defined by the intervals of [110, 150] and [500, 550] minutes, were respectively 2361 pF and 2363 pF, which agree within 0.1%. This indicated an excellent reversibility of our sensor in response to glucose concentration variations. Moreover, with a capacitance measurement resolution of about 10 pF, it is estimated that the glucose concentration could be resolved with a relative error of less than 11%. This is considered clinically acceptable [7], and can be improved by more sensitive capacitive sensor designs (e.g., with a reduced separation between the electrodes). The device was also exposed to 27 mg/dL glucose solution over an extended period to assess the drift in the device response. For the [600, 1000] minute period, the capacitance of the sensor was steady at 2457 pF with a standard deviation of 4.75 pF and 0.08 pF/hour drift rate. Compared with our previously device which used optical detection, this electrical measuring method allows improved stability desirable for long-term continuous glucose monitoring.

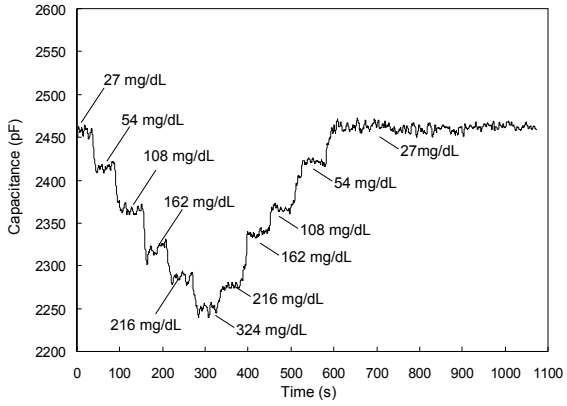

Fig. 8. Capacitance change in time-dependent glucose variations. The glucose was measured in sequence simulating possible glucose concentrations in interstitial fluid.

CONCLUSION

In this paper, a capacitively based MEMS affinity glucose sensor that uses a biocompatible glucose-responsive polymer has been presented. The sensor consists of a diaphragm which is situated inside a microchamber and is driven magnetically. The microchamber is filled with a PAA-*ran*-PAAPBA polymer solution, which specifically recognizes glucose by affinity binding. A cellulose acetate semi-permeable membrane sealed the chamber, preventing the polymer from escaping but allowing the environmental glucose to permeate through. The crosslinking of the polymer due to its binding to glucose changes the viscosity of the polymer solution and the damping on the diaphragm vibration. Thus, by capacitively measuring the viscously damped diaphragm vibration, the glucose concentration can be determined. Experimental results have shown that the sensor responded to glucose concentration variations at a time constant of about 3.0 minutes. The steady state diaphragm vibration measured showed that the sensor experienced a decrease in the capacitance of about 200 pF when glucose concentration varied from 27 mg/dL to 324 mg/dL. Finally, time-dependent glucose concentration variations were measured to simulate the glucose levels in the interstitial fluid. The measured data indicated that the device was highly reversible and stable, with virtually no drift in an extended measuring period of about 8 hours. These results have demonstrated the potential of our device to be used as a subcutaneously implanted sensor for continuous glucose monitoring.

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REFERENCES

[1] www.minimed.com
[2] www.freestylenavigator.com
[3] www.dexcom.com
[4] J. C. Pickup, F. Hussain, N. D. Evans, and N. Sachedina, "In Vivo Glucose Monitoring: The Clinical Reality and The Promise," *Biosensors and Bioelectronics*, vol. 20, pp. 1897-1902 2004.
[5] X. Huang, S. Li, J. Schultz, Q. Wang, and Q. Lin, "A MEMS Sensor for Continuous Monitoring of Glucose in Subcutaneous Tissue," *Proc. IEEE Int. Conf. Micro Electro Mechanical Systems (MEMS '09)*, Sorrento, Italy, 2009, pp. 352-355.
[6] S. Li, X. Huang, E. N. Davis, Q. Lin, and Q. Wang, "Development of Novel Glucose Sensing Fluids with Potential Application to Microelectromechanical Systems-based Continuous Glucose Monitoring," *Journal of Diabetes Science and Technology*, vol. 2, pp. 1066-1074, 2008.
[7] W. L. Clarke, D. Cox, L. A. Gonder-Frederick, W. Carter, and S. L. Pohl, "Evaluating clinical accuracy of systems for self-monitoring of blood glucose.," *Diabetes Care*, vol. 10, pp. 622-628, 1897.

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