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A Biocompatible Affinity MEMS Sensor for Continuous Monitoring of Glucose

Xian Huang[1], Siqi Li[2], Jerome Schultz[3], Qian Wang[2], Qiao Lin[1*]

[1]*Mechanical Engineering Department, Columbia University, New York, NY, USA*
[2]*Chemistry and Biochemistry Department, University of South Carolina, Columbia, SC, USA*
[3]*Bioengineering Department, University of California, Riverside, CA, USA*

Abstract — **In this paper, we present two designs for developing a biocompatible affinity MEMS glucose sensor. Based on these designs, two devices were fabricated and characterized. These devices, consisting of a micro- cantilever or membrane situated inside microchambers, are driven by a remote magnetic field and separated from the sensing environment by a semi-permeable membrane. A change in viscosity induced by the binding of poly(acrylamide-*ran*-3-acrylamidophenylboronic acid) (PAA-*ran*-PAAPBA) copolymer with glucose is determined by the damped vibration of the cantilever or the membrane in the devices. The cantilever-based sensor has been used to measure physiologically relevant glucose concentrations from 0 to 324 mg/dL with a response time of approximately 3 minutes. This response time was further improved to 1.5 minutes using the membrane-based sensor.**

Keywords —***Glucose sensor, Copolymer, Vibration, MEMS***

I. INTRODUCTION

Continuous glucose monitoring system (CGMS) is highly desirable for diabetes management. CGMS is generally achieved through subcutaneously implanted enzymatic electrochemical sensors, which have been commercially realized with the MiniMed Paradigm, Freestyle Navigator CGMS, and DexCom STS CGMS. These products detect glucose by enzyme-catalyzed reactions. Although electrochemical glucose detection possesses high sensitivity and excellent selectivity to the glucose, it also incurs significant drawbacks, such as irreversible glucose consumption and drift from hydrogen peroxide production. Therefore, electrochemical CGMS require frequent calibration to mitigate instabilities over time, making long-term operation difficult [1].

Miniaturized MEMS sensors provide low-cost non-invasive or minimally-invasive glucose measurement based on various methods such as, electrochemistry [2], glucose binding protein [3], hydrogel swelling [4], and synthetic glucose-responsive polymers [5]. We previously developed a MEMS glucose sensor [3] using a SU-8 microcantilever and a glucose binding protein concanavalin A (Con A). Due to the immunogenicity and cytotoxicity of Con A [6], this glucose sensing system was incompatible for implantable applications. In addition, due to material limitations of SU-8 and osmotic pressure imbalances, this device showed limited mechanical reliability, poor reversibility, and significant drift. Here, we present two devices incorporating a vibrational cantilever or membrane for affinity glucose sensing and demonstrate preliminary results in characterizing them. These devices utilize parylene construction and a biocompatible synthetic copolymer, poly(3-acrylamidophenylboronic acid) (PAAPBA), for glucose detection avoiding the immunogenicity and cytotoxicity of the sensing solution while maintaining excellent mechanical reliability and measuring reversibility. The cantilever-based design is our initial effort towards developing an implantable glucose sensor, while the membrane-based device aims at replacing the optical cantilever vibration measurement with a more practical electronic method. These devices demonstrate the feasibility for stable and potentially implantable MEMS-based continuous glucose monitoring.

II. DEVICE DESIGN AND OPRATIONA PRINCIPLE

A. Sensor Designs

The cantilever-based glucose sensor consists of a microcantilever situated inside a microchamber (Fig. 1a and Fig. 2a). The cantilever is fabricated from parylene and anchored to the substrate at one end, while suspending over an etched silicon cavity at its free end. A permalloy thin film is electroplated onto the cantilever, and subsequently covered with an additional parylene layer. A PDMS microchamber is attached to the substrate and sealed from the top with a cellulose acetate (CA) semi-permeable membrane. The environmental glucose can permeate through the semi-permeable membrane and bind with the PAAPBA copolymer inside the microchamber. The crosslinking between the glucose and the polymer increases the viscosity of the fluid in the microchamber as well as the damping of the cantilever vibration, causing a decrease in cantilever vibration amplitude and a shift in vibration phase which can be measured using an optical lever technique.

One the other hand, the membrane-based glucose sensor is based on a vibrational parylene membrane (Fig. 1b and Fig. 2b). Two parallel gold electrodes are separately deposited on the parylene membrane and a SiO_2 coated Si substrate. Several permalloy thin film strips are electroplated onto the top electrode, and covered with an additional passivating parylene layer. The interaction of the copolymer and the glucose molecules leads to increased vibrational damping of the parylene membrane, thus producing a measureable capacitance change across the metal electrodes.

B. Sensing Principle

The vibrational structures on the devices can be actuated by an electromagnetic field produced by a solenoid. This electromagnetic field generates a torque on the magnetized

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Contact author: Dr Qiao Lin, **qlin@columbia.edu.*

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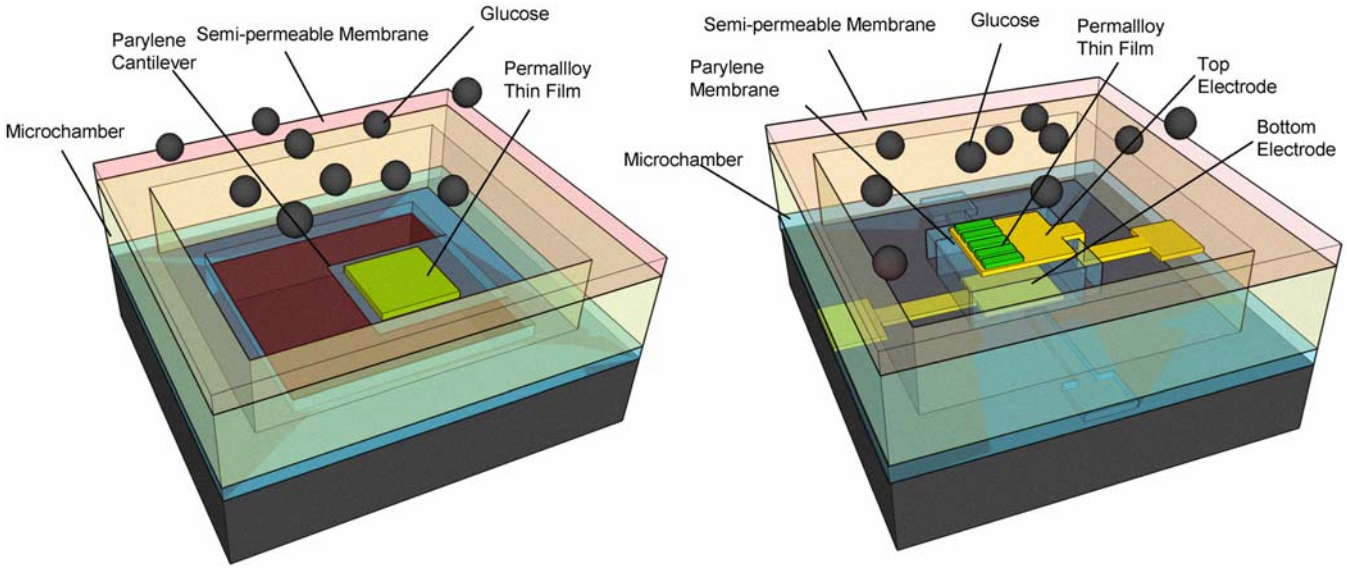

Fig. 1. Schematics of (a) the cantilever-based and (b) membrane-based MEMS viscometric glucose sensors.

permalloy film, causing the deflection of its supporting structure. Therefore, an AC voltage actuated solenoid generates a time-dependent electromagnetic field and produces a time-dependent torque to the vibrational structure, leading to the vibrations of the cantilever or the membrane. These vibrations can be detected by an optical lever technique or an electrical capacitance measurement, respectively.

The polymer sensing solution consists of a synthesized PAA-ran-PAAPBA copolymer and provides a stable and biocompatible glucose sensitive system [7]. The boronic acid moiety in the PAAPBA segment is well known for its reversible and strong binding with glucose, which causes the crosslinking of the copolymer and an increase in viscosity (Fig. 3). The biocompatible poly(acrylamide) (PAA) segment was used to improve the solubility of PAAPBA, and provides an additional neighbor stabilizing effect to enhance the binding between boronic acid and carbohydrates.

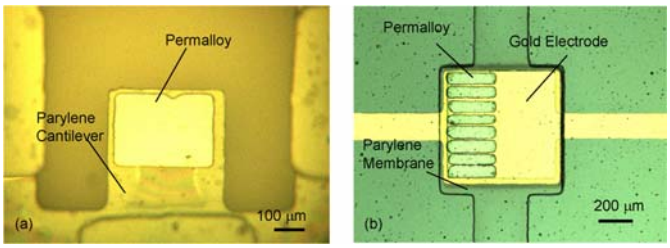

Fig. 2. Images of the (a) cantilever-based and (b) membrane-based MEMS viscometric glucose sensors.

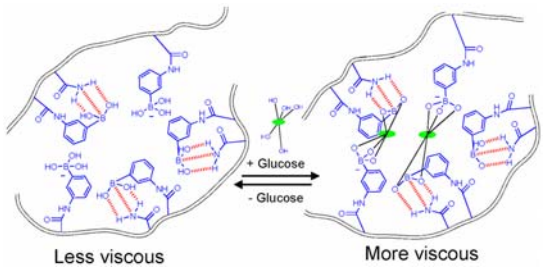

Fig. 3. The sensing principle of the biocompatible glucose-sensitive copolymer PAA-ran-PAAPBA.

III. Materials and Experimental Setups

A. *Materials.*

A 1 M stock glucose solution was obtained by dissolving glucose (1.8 g) in 10 mL of Phosphate Buffered Saline (PBS). A series of glucose concentrations (54 mg/dL, 108 mg/dL, 162 mg/dL, 216 mg/dL, and 324 mg/dL) were prepared by further aliquoting the glucose stock. PAA-*ran*-PAAPBA copolymer solution with 1.9%, 2.3%, 4.3%, 5%, and 7.3% of PAAPBA composition was prepared using a previously described method [7].

B. *Experimental setup.*

The cantilever vibration was measured using an optical lever [3]. The cantilever was driven by a home-made solenoid (2000 turns of a 200 μm diameter copper wire on a 2.5 cm diameter plastic core), which under a driving voltage of 5 V_{rms}, produced a magnetic field strength of about 700 A/m perpendicular to the cantilever surface. A permanent magnet with a field intensity of 500 kA/m was placed parallel to the cantilever surface to magnetize the permalloy film. The vibration of the cantilever was detected by the optical-lever. All experiments were conducted at 37 °C.

This experimental setup was then slightly modified to accommodate the capacitance measurement for the membrane-based sensor. Similarly, the sensor was driven by the combinative effect of a home-made solenoid (3000 turns of a 200 μm diameter copper wire on a 3 cm diameter plastic core) generating a 800 A/m electromagnetic field intensity and a permanent magnet with a magnetic field intensity of 500 kA/m. A 4 V_{rms} voltage was applied to the capacitive sensor which was serially connected to a 5 pF standard capacitor. By monitoring the differences in the voltage between the standard capacitor and the sensor with a lock-in amplifier, changes in capacitance can be obtained.

IV. EXPRRIMENT RESULTS AND DISCUSSIONS

A. *Glucose Sensitive Copolymer*

To investigate the binding ability of our copolymer with the glucose molecules, we synthesized a series of copolymer solutions with varying PAAPBA composition (1.9% to 7.3%). An Ubbelohde viscometer (CANNON® Instrument Company) was used to measure the viscosity change in the copolymer solution after its interaction with glucose molecules. As shown in Fig. 4, polymer 1 and 4 with about 2% PAAPBA had similar responses to glucose concentration from 0 to 918 mg/dL, while polymer 1 showed a higher viscosity due to an increased PAAPBA percentage. Comparably, copolymer solutions with a PAAPBA moiety larger than 4.3% exhibited a dramatic change in viscosity with increasing glucose concentration, indicating significantly enhanced sensitivity to viscosity with higher PAAPBA content. The control polymer 3 (using N-phenylacrylamide (NPAA) instead of N-3-acrylamidophenylboronic acid (AAPBA) as the monomer) had no boronic acid group in the polymer. It was highly inert to the glucose concentration change, indicating that AAPBA was indeed the glucose-reactive component in the copolymer. Since a higher PAAPBA percentage would significantly increase the viscosity of the solution and the damping to the cantilever vibration, a 1.9% PAAPBA copolymer solution was more preferable in the following MEMS device experiments to minimize the damping of the cantilever vibration and ensure large cantilever response.

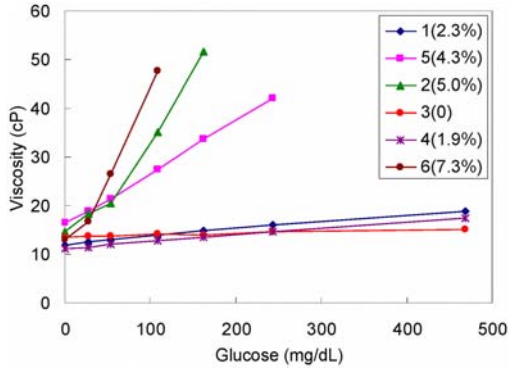

Fig. 4. Viscosity responses of polymers of different molecular weight and PAAPBA percentage.

The reversibility of this copolymer, indicating the stability of this copolymer over time, was measured using the Ubbelohde viscometer. A 4.7% copolymer solution, retained inside a semi-permeable dialysis tubing, was repeatedly immersed into a PBS buffer and 450 mg/dL glucose solution. The blank copolymer solution showed a viscosity of 6.4 cP. In the glucose solution, the viscosity increased to 20.4 cP. After dialysis against PBS buffer, its viscosity significantly dropped to 5.4 cP (Fig. 5), indicating that removal of glucose dissociated the crosslinking network and lowered the viscosity of the copolymer solution. The viscosity after copolymer/glucose binding was slightly different over time, which can be attributed to the loss of polymer on the dialysis device.

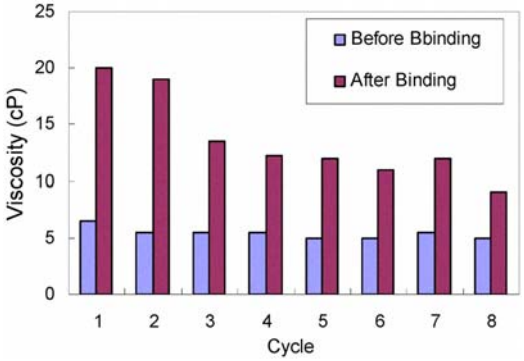

Fig. 5. Reversibility of the copolymer (4.7%) to glucose concentration changes.

B. *Physical Characteristics of Prototype Sensors*

The electromagnetic fields, used to actuated the sensors, were generated by two manually wound solenoids. These solenoids displayed frequency-dependent characteristics equivalent to inductances, leading to the changes in electromagnetic field intensity and the corresponding electromagnetic force applied to the vibrating cantilever and membrane. Thus, it is important to know the attenuation of the electromagnetic field over frequency for calibrating the measured result of the cantilever amplitude and membrane capacitance. As shown in Fig. 6, Solenoid 1 and Solenoid 2 were for the cantilever-based sensor and the membrane-based sensor, respectively. Both solenoids with initial magnetic field intensities at approximately 800 A/m were actuated by a 5 V_{rms} AC voltage. With increasing actuating frequency, the electromagnetic field intensity decreased correspondingly. This can be interpreted as the increasing obstruction from the inductances of the solenoids due to the rising frequency. The electromagnetic field intensities dropped to nearly 0 A/m at 2500 Hz for both solenoids, which provided the upper working frequency of our devices.

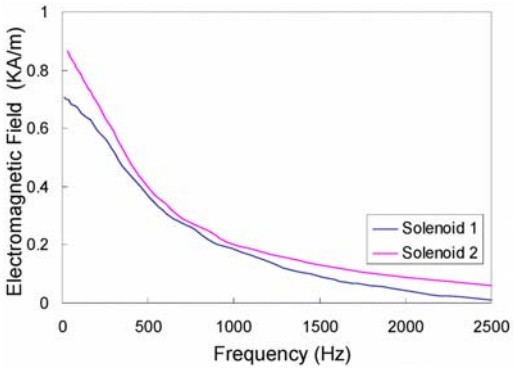

Fig. 6. Frequency dependent electromagnetic field intensity.

The fundamental measuring function of the cantilever-based and the membrane-based glucose sensors were then characterized by obtaining the time constant of its response to glucose. This parameter, reflecting the time for the sensor to complete one measurement cycle, is an important index for CGMS. The microchambers of the devices were initially filled with PBS buffer, and were then exposed to 108 mg/dL glucose solutions. The cantilever vibration amplitude, at a fixed frequency (28 Hz), and the electrode capacitance change (at

600 Hz) were obtained over time (Fig. 7). For the cantilever-based sensor, a gradual decrease in solution viscosity inside the test cell was observed, indicating the permeation of glucose molecules through the membrane and the binding with copolymer inside the microchamber. Amplitude response leveled as glucose concentration between the microchamber and test cell equilibrated. The time constant, which represented the time consumption for glucose permeation into the chamber and equilibrium binding with the copolymer, was then determined to be 3 minutes, which has been further improved to 1.5 minutes for membrane-based sensor. This improvement was due to the decrease in the microchamber height from 1 mm to 0.5 mm, which significantly reduces the distance and time for the glucose to diffuse through the membrane to the sensing area. Moreover, the 1.5 minute time response was adequate for CGM applications [8], compared with a 5-15 minute detection period for current commercial CGM products.

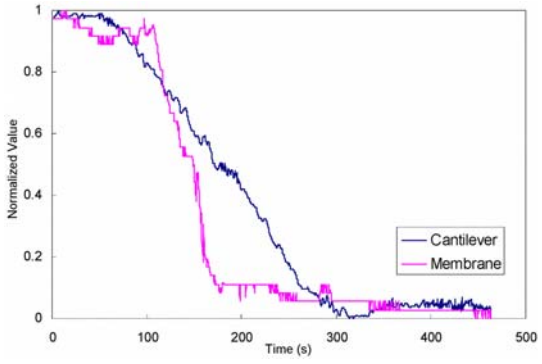

Fig. 7. The normalized time response of the cantilever-based sensor at 28 Hz and the membrane-based sensor at 600 Hz.

C. *Glucose Measurements by Cantilever-Based Design with Optical Detection*

To model the measurement of physiological glucose concentration in interstitial fluid (ISF), harmonic cantilever vibrations were measured at varying glucose concentrations (27 mg/dL, 54 mg/dL, 108 mg/dL, 216 mg/dL, and 324 mg/dL). We present some preliminary results here. The glucose solutions were initially filled within the test cell and permeated into the microchamber through the semi-permeable membrane. These experiments compared the signal changes in vibration amplitude and phase spectrum for each glucose solution, reflecting the sensor response to various glucose solutions. As the glucose concentration increased from 27 to 324 mg/dL, the vibration amplitude decreased accordingly with an observed total reduction of nearly 70%. This was accompanied by a shift of vibration resonance frequency from 27.54 to 26.77 Hz which indicated a significant increase in vibrational damping and the viscosity of the polymer solution. Moreover, there was a significant change in the phase shift for the cantilever vibration (Fig. 8). At 15 Hz, the phase shift increased from 4° at 27 mg/dL to 30 ° at 324 mg/dL. The results of harmonic vibration measurements demonstrated the capability of measuring different glucose solutions by recording either the phase shift or vibration amplitude at a fixed frequency where different glucose solutions were most distinguished.

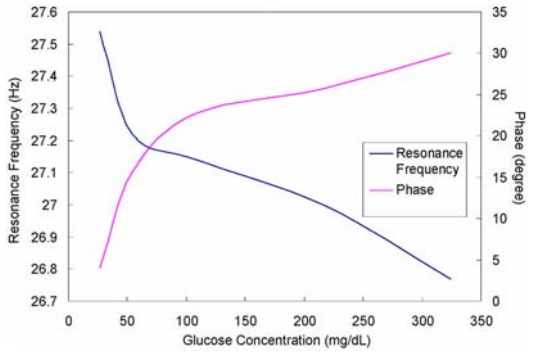

Fig. 8. Change in resonance frequency and phase shift at physiologically relevant glucose concentrations measured by cantilever-based sensor.

Measurement of time-dependent glucose variations simulated a typical change of glucose concentration in interstitial fluid to obtain the reversibility and the stability of the cantilever-based sensor. The reversibility of the device represents the potential of our device for long-term glucose monitoring without repeated calibration. In this experiment, 54 mg/dL and 324 mg/dL glucose solutions were adopted to mimic the glucose level before and after intake of food. 108 mg/dL glucose solution represented a stable daily glucose level. In addition, two intermediate glucose concentrations (162 mg/dL and 216 mg/dL) were also measured (Fig. 9). The measured vibration amplitude at 28 Hz alternated from 43 μV at 54 mg/dL to 20 μV at 324 mg/dL, and maintained 37 μV at the stable state. For glucose solutions with the same concentration, the cantilever vibration amplitude was almost the same. These results reflected an excellent reversibility of our device, indicating its ability for long-term continuous monitoring of glucose in subcutaneous tissue without frequent laborious recalibration. We also assessed the drift in the device by continuously measuring 108 mg/dL glucose solution over time after the glucose history measurement. We observed a consistent vibration amplitude (37 μV) and found that there was virtually no drift of this measured signal over a measurement period of about 8 hours. Compared with our previous system [3], this result indicated a significant improvement and highlighted the excellent stability of the current device.

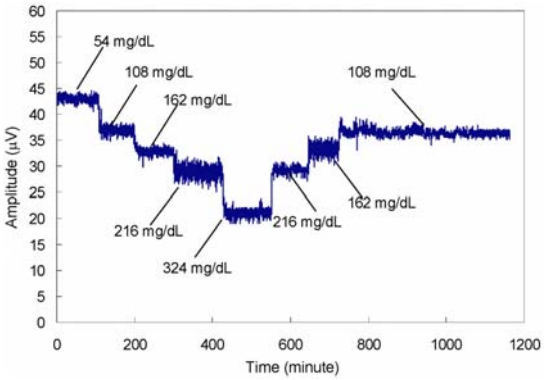

Fig. 9. Measurement of Time-dependent glucose variations and drift of the cantilever-based sensor. (The noise shown reflects environmental disturbances to the optical setup.)

D. *Glucose Measurements by Cantilever-Based Design with Optical Detection*

To characterize the viscosity response of the membrane-based sensor, capacitance changes in PBS buffer were measured in 108 and 162 mg/dL glucose solution in the test cell with 1.9% PAAPBA solution in the microchamber. As the viscosity of the fluid increased, the capacitance of the device decreased, indicating an increasing damping to the membrane vibration (Fig. 10). For example, the sensor had a larger capacitance (320 pF) when only PBS buffer was present in the test cell at 600 Hz as compared to that of 108 mg/dL and 162 mg/dL glucose solutions (319 and 317 pF respectively). The decrease in capacitance with glucose concentration was attributed to the increasing damping which limited the displacement of the vibrational membrane from its static equilibrium position, leading to an enlarged distance between the top and bottom electrodes in the sensor.

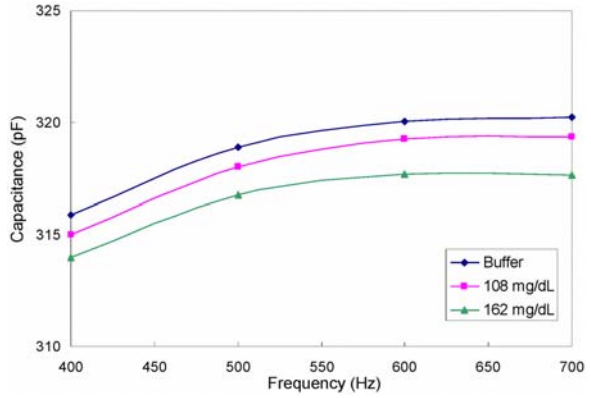

Fig. 10. The viscosity-dependent capacitance changes in different fluids of the membrane-based sensor.

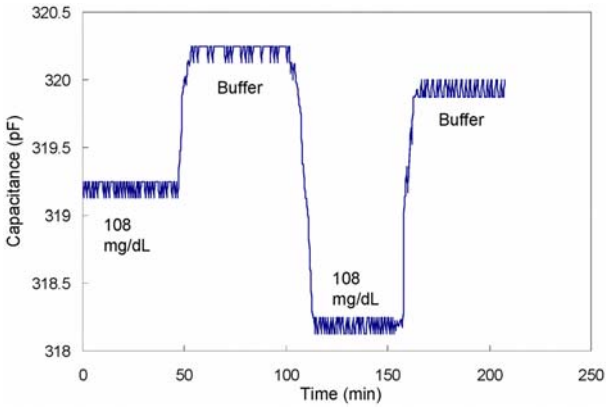

Fig. 11. Reversibility of the membrane-based sensor to glucose concentration changes.

Finally, we also observed the reversibility of the membrane-based sensor with respect to glucose concentration changes to test its long-term stability. By alternately introducing 108 mg/dL glucose solution and PBS buffer (Fig. 11), the measured capacitance at 600 Hz repeatedly cycled between 319 and 320 pF with a variation about 1pF which can be contributed to the drift of the device and the error in the volume of samples introduced to the test cell. This result reflected a good stability of the device, while the reversibility can be further improved by diminishing the drift of the sensor and carefully introducing sample volumes in each measuring cycle.

V. CONCLUSIONS

In this paper, two designs to develop an implantable MEMS viscometer utilizing a novel biocompatible glucose-responsive copolymer and vibrational microstructures are presented. The first design, consisting of a magnetically driven parylene microcantilever coated with a permalloy thin film, was located in a PDMS microfluidic chamber. The sensing fluid, consisting of PAAPBA copolymer, exchanged glucose with the fluid outside the device through a CA semi-permeable membrane. Glucose concentration can be determined by detecting viscosity changes induced by the binding of glucose to PAAPBA, which affected the vibration characteristics of the cantilever. The dynamic characteristics of the device were characterized with the cantilever vibration in PBS buffer and 108 mg/dL glucose solution at 28Hz. The time response of this device was found to be 3 minutes, which was better than previously reported glucose sensors. In addition, the device response to physiologically relevant glucose concentrations (27 mg/dL to 324 mg/dL) was obtained. Moreover, the device exhibited excellent reversibility and negligible drift during extended experimental time (~8 hours).

The other design replaces the microcantilever with a parylene membrane. Two gold electrodes were deposited on the membrane and a SiO2 coated substrate respectively, transducing the membrane vibration to the change in capacitance between the two electrodes. The time response of this sensor was determined to be 1.5 minutes, which was achieved by further diminishing the height of the microchamber. In addition, the device response to various viscosities and its reversibility were also investigated. Since the vibration of membrane-based sensor can be detected by electrical methods, which is easier to be integrated into a small device than the optical-lever system employed in the cantilever-based sensor. This device shows its potential to be subcutaneously implantable. However, the characterization of the new device is still under investigation, and will be pursued in future work.

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