A MEMS SENSOR FOR CONTINUOUS MONITORING OF GLUCOSE IN SUBCUTANEOUS TISSUE

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ABSTRACT

We present a MEMS sensor for continuous glucose monitoring for diabetes management. The device consists of a microcantilever, which is driven by remote magnetic field and situated in a microchamber separated from the sensing environment by a semi-permeable membrane. As glucose concentration varies, viscosity changes induced by glucose/copolymer binding in a poly(acrylamide-*ran*-3-acrylamidophenylboronic acid) (PAA-*ran*-PAAPBA) copolymer solution produce a measurable change in cantilever vibration. The device has been used to measure physiologically relevant glucose concentrations from 0 to 324 mg/dL. The response time of the sensor to glucose concentration changes was 3 minutes and can be further improved with optimized device designs.

INTRODUCTION

Continuous glucose monitoring system (CGM) is highly desirable for diabetes treatment. This is commonly achieved by subcutaneously implanted enzymatic electrochemical sensors such as, the MiniMed Paradigm, Freestyle Navigator CGMS, and DexCom STS CGMS. These FDA approved commercial products detect glucose by enzyme-catalyzed reactions. While electrochemical methods allow sensitive glucose detection, they also incur significant drawbacks, such as irreversible glucose consumption, drift from hydrogen peroxide production, and interference from electrode-eroding chemicals. As a result, electrochemical CGM sensors generally exhibit large drifts over time, and require frequent calibration, making long term operation difficult [1].

Miniaturized sensors, based on MEMS technology, have provided low-cost non-invasive or minimally-invasive glucose monitoring based on methods including electrochemistry, impedance, hydrogel swelling, optics, glucose binding protein, and synthetic glucose-responsive polymers [2]. We previously reported a MEMS glucose detecting device [3] adopting concanavalin A, a glucose-binding protein which suffered from immunogenicity and cytotoxicity [4]. In addition, due to material limitations and osmotic pressure imbalances, it showed limited mechanical reliability, poor reversibility, and significant drift. Here, we present a new MEMS affinity glucose sensor which exploits a biocompatible synthetic polymer for glucose detection and parylene-based construction to address problems such as immunogenicity, cytotoxicity, mechanical reliability, and reversibility. Additionally, due to its MEMS-based fabrication, the sensor is amenable to subcutaneous implantation for long-term, stable CGM applications.

PRINCIPLE AND DESIGN

Device design and operational principle. The MEMS viscometric glucose sensor is based on a cantilever situated inside a microchamber (Fig.1). The parylene cantilever is anchored onto the substrate at one end, and suspended over a cavity. A permalloy thin film is electroplated onto the cantilever at its free end, and subsequently passivated by an additional parylene layer. The microchamber is formed between the substrate and a cellulose acetate (CA) semi-permeable membrane, and is filled with a polymer solution for glucose sensing. The membrane is semi-permeable so that environmentally present glucose can permeate through the membrane and bind with the polymer inside the microchamber. This interaction between the glucose and the polymer increases the viscosity of the fluid in the microchamber, thereby damping cantilever vibration. As a result, decreased cantilever vibration amplitude along with a vibration phase shift occurs.

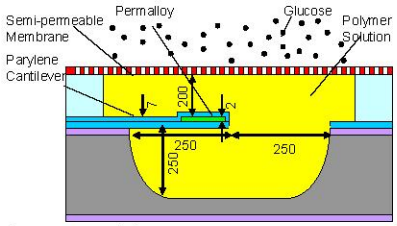

Fig. 1. Schematic of the MEMS viscometric glucose sensor.

This microcantilever is actuated by an electromagnetic field-producing solenoid. The electromagnetic field generates a torque on the magnetized permalloy film with a magnitude proportional to the product of permalloy volume, magnetic field, and magnetization along the length of the permalloy. This torque, distributed along the width of the cantilever, causes cantilever bending. Thus, a time-dependent electromagnetic field generated by an AC voltage actuated solenoid produces a time-dependent torque, leading to the vibration of the cantilever. This vibration is directly related to the solution viscosity. Therefore, by measuring the damped vibration, the viscosity of the sensing solution can be determined.

Glucose sensitive copolymer. The polymer sensing solution consists of PAA-*ran*-PAAPBA copolymer which is a stable and biocompatible glucose sensitive system compared to those conventionally-based on reactive proteins and enzymes. The boronic acid moiety in the polymer forms reversible, strong bonds with glucose, resulting in crosslinking of the polymer and an increase in viscosity (**Fig.2**). The biocompatible poly(acrylamide) (PAA) segment in this synthesized copolymer was chosen to improve the solubility of the sensing segment PAAPBA. Furthermore, PAA provides additional neighbor stabilizing effects besides the hydrogen bonding effect (e.g. the boronic acid moiety and amide coordination via B-N

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interaction), which could enhance the binding of boronic acid to carbohydrates.

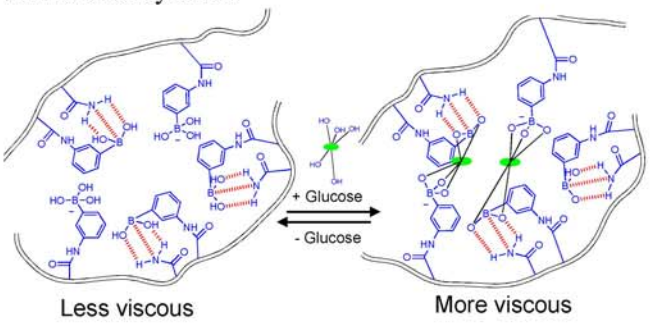

Fig. 2. The sensing principle of the biocompatible, glucose-sensitive copolymer PAA-ran-PAAPBA.

FABRICATION

The device fabrication process started with etching an anchor layer onto a silicon dioxide (SiO_2)-coated wafer to increase the adhesion between the wafer and the parylene layer (**Fig. 3**). After the deposition of a 5 μm parylene layer, a 100 nm copper layer was deposited as a seed layer for electroplating. S1818 photoresist was then spin-coated and patterned to form the electroplating area. Permalloy was then electroplated to a thickness of 1.5 μm at a deposition rate of approximately 150 nm/min for ten minutes with a 50 mA pulse current. This was followed by the removal of the photoresist and the copper seed layer. The second parylene layer, with a thickness of 2 μm, was then deposited to seal the permalloy. Next, the parylene layer was patterned to form a cantilever (250 μm × 250 μm). The exposed SiO_2 layer was removed by HF wet etching. Gas-phase XeF_2 etching was then used to release the cantilever by etching the silicon directly underneath it forming a cavity approximately 250 μm in height. The SiO_2 beneath the cantilever was then removed via another HF wet etch. The microcantilever was then fixed in a poly(dimethylsiloxane) (PDMS) microchamber and sealed by a CA semi-permeable membrane (MWCO 3500) forming the sensing chamber (30 μL). Another PDMS microchamber, for introduction of glucose samples, was attached on top of the CA membrane and functioned as a test cell. The inlet and outlet for the test cell and microchamber were provided via adhesive-affixed Teflon tubes (**Fig. 4**)

EXPERIMENTAL METHOD AND SETUP

Materials. 1 M glucose solution was obtained by dissolving glucose (1.8 g) in 10 mL of Phosphate Buffered Saline (PBS). A series of glucose concentrations (27 mg/dL, 54 mg/dL, 108 mg/dL, 216 mg/dL, and 324 mg/dL) were prepared by diluting the 1 M glucose with PBS. 1.9% PAAPBA was prepared using a method in [5].

Experimental method. Experiments were performed according to two methods. The first method was referred to as "premixed measurement", in which the microchamber and test cell were each filled with premixed samples of glucose and copolymer at the same concentration. The second method, referred to as "permeation measurement," was intended to simulate the environment of an implanted glucose sensor. The glucose concentration in the microchamber was changed according to physiologically relevant glucose levels, while the copolymer concentration inside the test cell remained unchanged. The glucose concentration in the test chamber and microchamber reached equilibrium due to diffusive transport of glucose across the permeable membrane.

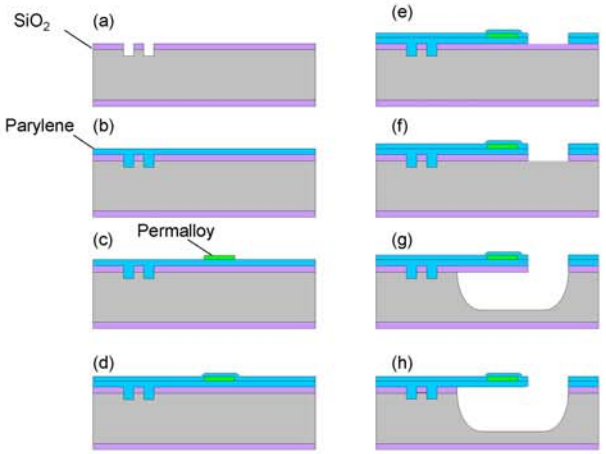

*Fig. 3. Fabrication process for the sensor chip: **(a)** Anchor layer etching; **(b)** First parylene layer deposition; **(c)** Permalloy electroplating; **(d)** Second parylene layer deposition; **(e)** Parylene and permalloy layer patterning; **(f)** SO2 layer around the cantilever removal to open a window for Si etching; **(g)** XeF_2 dry etching; **(h)** SO_2 layer beneath the cantilever removal.*

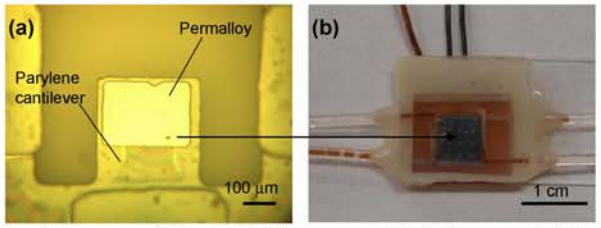

*Fig. 4. Images of the MEMS sensor: **(a)** before, and **(b)** after packaging.*

The experimental setup is shown in **Fig. 5** [3]. The cantilever vibration was driven by a home-made solenoid (2000 turns of a 200 um diameter copper wire on a 2.5 um diameter plastic core), which under a driving voltage of 5 V_{rms}, produced a magnetic field strength of about 500 kA/m perpendicular to the cantilever surface. A permanent magnet with field strength of 500 A/m was placed parallel to the cantilever surface to magnetize the permalloy film. The vibration of the cantilever was detected by an optical-lever.

Ultra-thin kapton heat-film was used to affix a K-type thermal couple to the bottom of the device. The thermocouple was connected to a multimeter (Agilent 34420A Nano Volt/Micro Ohm meter) to obtain temperature measurements. These values were then transmitted to a computer to control the voltage output of the DC power supply (Agilent E3631A DC power supply) connected to the heater. All experiments were conducted at 37°C with closed-loop temperature control. This temperature simulated a suitable in-vivo glucose monitoring environment.

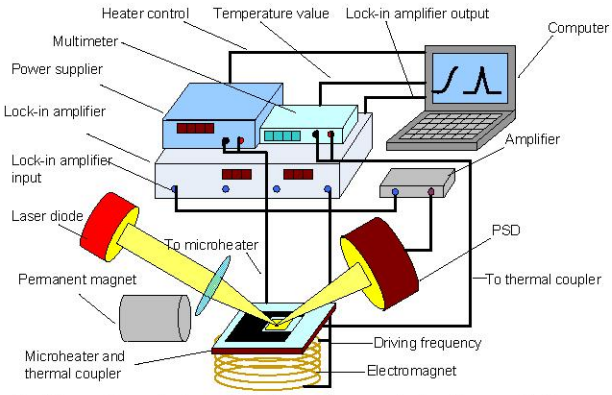

Fig. 5. Experimental setup for characterization of the MEMS glucose sensor. The cantilever vibration was measured with an optical lever system.

EXPERIMENTAL RESULTS

Time response. To characterize the basic measuring function of our device and obtain the time constant of its response, the chamber of the device was initially filled with PBS buffer, and was then exposed to 108 mg/dL glucose solution. The cantilever vibration amplitude, at a fixed frequency (28 Hz), was obtained over time (**Fig. 6**). We observed a gradual decrease in solution viscosity inside the test cell, corresponding to glucose permeation through the membrane followed by copolymer binding. 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. It was adequate for CGM applications [6], considering a 5-15 minutes detection period for current commercial CGM products.

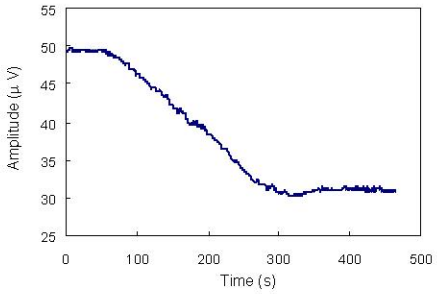

Fig. 6. Time history of the cantilever vibration amplitude at 28 Hz.

Evaluation of equilibrium binding through the membrane. To study the efficiency of molecular permeation through the membrane, an experiment comparing the cantilever response in premixed measurements and permeation measurements was carried out. The premixed measurement involved placing samples consisting of the same glucose and copolymer concentration (108 mg/dL glucose solution and 1.9% copolymer) in both the microchamber and the test cell. In the permeation measurement, the glucose concentration was initially zero in the microchamber and 108mg/dL in the test cell. The glucose in the test cell would then penetrate though the membrane and bind with the copolymer in the microchamber until the concentrations reached equilibrium. The resulting cantilever vibration responses during premixed and permeation conditions were compared (**Fig. 7**). The resonance frequency was 27 Hz in premixed measurements and 27.2 Hz in permeation measurements, while the vibration amplitude (from 10 Hz to 40 Hz) was almost identical. The likely cause of the negligible resonance frequency shift (0.2Hz) was inconsistencies during sample preparation. The good agreement between the premixed measurement and the permeation measurement indicated efficient glucose molecular transmembrane diffusion and interaction with the copolymer.

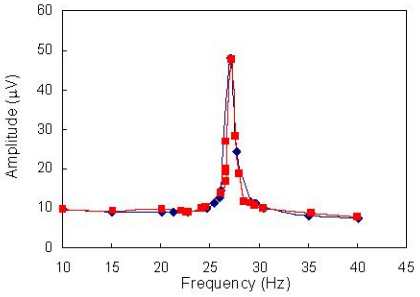

Fig. 7. Comparison of the device's amplitude frequency response after glucose concentration was equilibrated between the two sides of the membrane (diamonds) with that from an experiment where glucose concentration was set to 108 mg/dL from the start (squares).

Sensor response at varying glucose concentrations. 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) using the permeation experimental protocol (**Fig. 8**). These experiments compared the signal changes in vibration and phase spectrum of each glucose solution. 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 and a drop of Q-factor from approximately 29 to 7, which indicated a significant increase in vibrational damping and hence, viscosity of the polymer solution. Moreover, there was a significant change in the phase shift for the cantilever vibration (**Fig. 9**). For example, at 10 Hz, the phase shift increased from 2.2° at 27 mg/dL to 28.3° 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 are most distinguished.

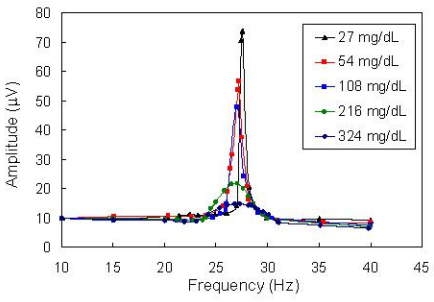

Fig. 8. Frequency dependent amplitude of the cantilever vibration at physiologically relevant glucose concentrations.

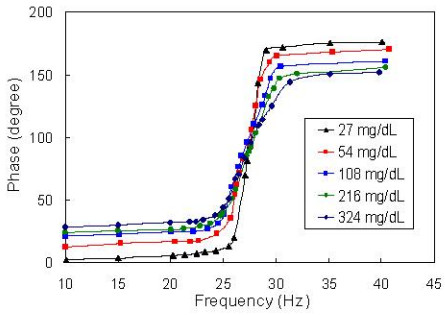

Fig. 9. Frequency dependent phase shift of the cantilever vibration at physiologically relevant glucose concentrations.

Reversibility. The reversibility of the sensor determines the potential of our device for long-term glucose monitoring without repeated calibration. We tested and observed reversibility of the device with respect to glucose concentration changes by alternatively measuring 0 and 108 mg/dL glucose solutions (**Fig. 10**). The measured vibration amplitude at 28 Hz repeatedly alternated between 37 and 43 μV. This result reflected an excellent reversibility of the device, indicating its ability for long-term continuous monitoring of glucose in subcutaneous tissue free of laborious recalibration.

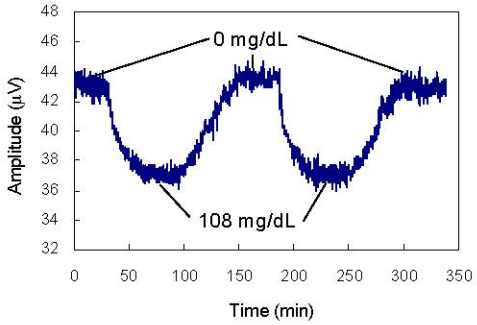

Fig. 10. Reversibility of the MEMS sensor to glucose concentration changes. (The noise shown reflects environmental disturbances to the optical setup.)

Drift. Drift is also a common obstacle with continuous glucose monitoring devices. Here, we assessed the drift in the device as it was exposed to glucose (108 mg/dL) over a long duration of time (**Fig. 11**). We observed a consistent vibration amplitude measurement of 37 V and found that there was virtually no drift of this measured signal over a preliminary measurement period of 5 hours. Compared with our previous system [3], this result indicated a significant improvement and highlighted the excellent stability of the current device.

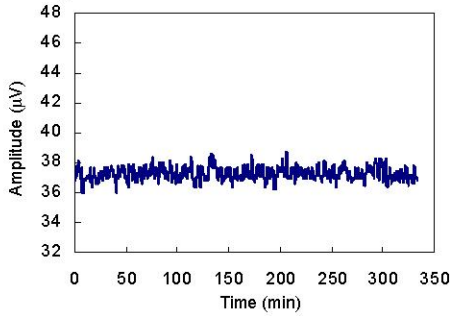

Fig. 11.evaluation of drift for the MEMS glucose sensor.

CONCLUSIONS

In this paper, a MEMS viscometer utilizing a novel biocompatible glucose-responsive copolymer is presented. The device, consisting of a magnetically driven parylene microcantilever coated with a permalloy thin film, is located in a PDMS microfluidic chamber. The sensing fluid, consisting of PAAPBA copolymer, exchanges 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 affects 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 device time response was also found to be 3 minutes, comparing well to 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 long experimental time (~5 hours). These measurements have shown that the MEMS viscometer using PAAPBA to specifically detect glucose has the potential for long-term, stable, continuous monitoring of ISF glucose.

ACKNOWLEAGEMENTS

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REFERENCES

[1] J. C. Pickup et al., "In vivo glucose monitoring: the clinical reality and the promise", *Biosens. Bioelectron.*, 20:1897-1902, 2005.

[2] K. Kataoka et al., "Totally synthetic polymer gels responding to external glucose concentration: Their preparation and application to on-off regulation of insulin-release", *J.Am.Chem.Soc.*, 120: 12694-12695, 1998.

[3] Y. Zhao et al., "A MEMS viscometric sensor for continuous glucose monitoring", *J. Micromech. & Microeng.*, 17: 2528-2537, 2007.

[4] T. Kataoka et al., "Immunogenicity and amplifier cell production by tumor vaccines enhanced by concanavalin A", *Gann*, 73:193-205, 1982.

[5] S. Li et al., "Development of novel glucose sensing fluids with application to MEMS-based continuous glucose monitoring", *J. Diabetes Science & Tech.*, (in press)

[6] J. Reifman et al., "Predictive monitoring for Improved management of glucose levels", *J. Diabetes Science & Tech.*, 1: 478-486, 2007.