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A MEMS Dielectric Affinity Glucose Biosensor

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Abstract

Continuous glucose monitoring (CGM) sensors based on affinity detection are desirable for long-term and stable glucose management. However, most affinity sensors contain mechanical moving structures and complex design in sensor actuation and signal readout, limiting their reliability in subcutaneously implantable glucose detection. We have previously demonstrated a proof-of-concept dielectric glucose sensor that measured pre-mixed glucose-sensitive polymer solutions at various glucose concentrations. This sensor features simplicity in sensor design, and possesses high specificity and accuracy in glucose detection. However, lack of glucose diffusion passage, this device is unable to fulfill real-time in-vivo monitoring. As a major improvement to this device, we present in this paper a fully implantable MEMS dielectric affinity glucose biosensor that contains a perforated electrode embedded in a suspended diaphragm. This capacitive-based sensor contains no moving parts, and enables glucose diffusion and real-time monitoring. The experimental results indicate that this sensor can detect glucose solutions at physiological concentrations and possesses good reversibility and reliability. This sensor has a time constant to glucose concentration change at approximately 3 min, which is comparable to commercial systems. The sensor has potential applications in fully implantable CGM that require excellent long-term stability and reliability.

Keywords

Dielectric biosensor; continuous glucose monitoring; affinity detection; microelectromechanical systems technology

I. Introduction

SUBCUTANEOUSLY implanted continuous glucose monitoring (CGM) sensors can be achieved by affinity binding, in which glucose is detected via its reversible binding to a specific receptor molecule. Affinity glucose sensing offers an attractive alternative to electrochemical detection commonly used in existing CGM sensors [1]–[4] by providing improved stability and accuracy. Affinity glucose sensors have been realized by detection of glucose induced changes in fluorescence[5]–[7], viscosity [8]–[11], and hydrogel volume [12], [13]. However, these devices typically contain either mechanically moving parts or require complex detector or actuator designs, and are therefore susceptible to influences of human activities, flow disturbances, temperature fluctuations, and environmental factors.

In contrast, dielectric sensors that are typically based on parallel plate electrodes afford simplicity in structural design, leading to improved reliability in the face of ambient disturbances. Dielectric measurement principles have been used in applications such as assessment of the behavior of biological systems in solution under excitations in a broad frequency range from DC to microwave frequencies. Examples of such applications include determination of organic tissue compositions [14], [15], growth of bacteria [16], [17], culturing of cells[18], [19], DNA conformations [20], [21], and polymerization of monomers [22], [23]. The use of dielectric measurements in implantable affinity sensors, on the other hand, has not been widely explored. We have previously demonstrated the dependence of the permittivity of a glucose-binding polymer on glucose concentrations [24]. While experimental results indicate the potential in sensitive and specific detection of glucose through dielectric detection, the device used for measurements did not allow exchange of glucose with the surroundings and was hence not appropriate for CGM applications.

This paper presents a novel dielectric glucose affinity biosensor featuring a capacitive detector, which is formed between a pair of parallel electrodes fabricated using microelectromechanical systems (MEMS) technology. One of the electrodes is perforated, through which glucose molecules can freely permeate between the surroundings and a glucose-binding polymer solution contained in the capacitive detector. The permittivity of the polymer is thus measured capacitively to determine the glucose concentration. The device offers high sensitivity and reversibility while possessing excellent reliability due to elimination of mechanical moving parts commonly used in other MEMS affinity glucose sensors [25]–[27]. Results from *in vitro* characterization demonstrate the potential of this device for use in CGM.

II. Principle and Design

The MEMS dielectric glucose sensor detects glucose-induced permittivity changes of a solution of a synthesized, glucose-sensitive polymer contained in a capacitive detector formed between two parallel electrodes situated inside a microchamber (Fig. 1). The upper electrode is perforated and is passivated in a perforated diaphragm, while the lower electrode lies on the substrate. The perforated diaphragm is supported by several anti-stiction posts, which prevent the diaphragm from collapsing, while providing stability against mechanical disturbances (e.g., shock, vibration). The polymer solution is contained in the microchamber, whose ceiling is formed by a cellulose acetate semi-permeable membrane that prevents the polymer from escaping while allowing the glucose to permeate into and out of the chamber. The portion of the polymer solution that fills the gap between the two electrodes serves as the dielectric material for the capacitive detector, so that measurement of the capacitance yields the permittivity of the polymer solution, which depends on the binding of the polymer with glucose.

The dielectric properties of the polymer solution in an electric field (E-field) are in general influenced by a number of mechanisms of polarization (i.e., shift of electric charges from their equilibrium positions under the influence of an electric field [28]), such as electronic polarization, ionic polarization, dipolar polarization, counterion polarization, and interfacial polarization [29]–[31]. Electronic polarization and ionic polarization involve the distortion of electron clouds with nucleus and the stretching of atomic bonds, while counterion polarization and dipolar polarization reflect redistribution of ions and reorientation of electrical dipoles. The combined effect of these polarization mechanisms can be represented by the complex permittivity of the polymer solution: $\varepsilon^* = \varepsilon' - j\varepsilon''$, where the capacitive component ε' represents the ability of the polymer solution to store electric energy and is reflected by the capacitance of the capacitive detector, while the resistive component ε'' is related to dissipation of energy. The frequency-dependent ε' can be expressed as [32]

$$\varepsilon'(\omega) = \varepsilon_\infty + (\varepsilon_s - \varepsilon_\infty) / (1 + \omega^2 \tau^2) \quad (1)$$

where ε_s and ε_∞ permittivity at low (static) and high-frequency (optical) limits, respectively; ω radian frequency; τ dipolar relaxation time given by [33].

$$\tau = 4\pi\eta a^3 / (kT) \quad (2)$$

Here, a is the effective radius of the polymer's molecules, η and T respectively the viscosity and temperature of the polymer solution, and k Boltzmann's constant. The sensor, with the gap between its electrodes filled with the polymer solution, can be represented by a capacitor (capacitance: C_x) and resistor (resistance: R_x) connected in series. Correspondingly, the real and imaginary parts of the complex permittivity can be further expressed as

$$\varepsilon' = C_x / C_0 \quad (3)$$

and

$$\varepsilon'' = 1 / (\omega R_x C_0) \quad (4)$$

where C_0 is the capacitance when the electrode gap is in vacuum. The interaction of the polymer with glucose may cause changes in its composition and conformation, and hence changes in the dielectric properties (ε' and ε'') of the polymer solution. Here, we can measure C_x that is directly related to ε' to indicate dielectric property changes within the solution due to the glucose-polymer binding.

The glucose-sensitive polymer utilized in the sensor is poly(acrylamide-*ran*-3-acrylamidophenylboronic acid) (PAA-*ran*-PAAPBA), a boronic-acid based polymer who recognizes glucose by specific affinity binding. The characteristics of this polymer have been described in detail elsewhere [34],[35]. In brief, when added to an aqueous solution of PAA-*ran*-PAAPBA, glucose binds reversibly and specifically to the phenylboronic acid moieties in the acrylamidophenylboronic acid (AAPBA) segments to form strong cyclic boronate ester bonds, resulting in an effective change in the permittivity of the dielectric solution as well as a change in the sensor capacitance [24]. Excellent selectivity of PAA-*ran*-PAAPBA in dielectric glucose detection has been demonstrated previously[24], enabling highly specific glucose detection in the face of potential interferents such as other sugars.

III. Fabrication Process

The fabrication of the device started with deposition and patterning of a thin film gold layer to form a bottom electrode ($1\text{ mm} \times 1\text{ mm} \times 100\text{ nm}$) as well as a resistive temperature sensor on a SiO_2 coated silicon substrate [Fig. 2(a)]. A Parylene passivation layer ($1\text{ }\mu\text{m}$ in thickness) was then deposited via chemical vapor deposition, followed by a patterned sacrificial photoresist layer ($3\text{ }\mu\text{m}$ in thickness) [Fig. 2(b)] and an additional Parylene layer ($1.5\text{ }\mu\text{m}$ in thickness). A gold layer was then deposited and patterned to form a perforated electrode ($1\text{ mm} \times 1\text{ mm} \times 100\text{ nm}$) with 6×6 arrays of holes ($50\text{ }\mu\text{m}$ in diameter and $150\text{ }\mu\text{m}$ in center-to-center spacing) [Fig. 2(c)]. The perforated electrode was then passivated by another Parylene layer ($3\text{ }\mu\text{m}$ in thickness) [Fig. 2(d)] and a patterned SU-8 reinforcement layer ($20\text{ }\mu\text{m}$ in thickness) [Fig. 2(e)], resulting in nine anti-stiction posts with diameters of $50\text{ }\mu\text{m}$. A SU-8 layer ($80\text{ }\mu\text{m}$ in thickness) was finally spin-coated and patterned to form a microchamber as well as an inlet and an outlet for polymer solution handling. The two successively coated SU-8 layers also acted as masks for patterning of the underneath Parylene layers by reactive ion etching to expose the sacrificial photoresist layer, resulting in a diaphragm with holes for glucose diffusion. The diaphragm was at last released by removal of the sacrificial layer in a photoresist stripper (AZ 400T Stripper, AZ Electronic Materials). A regenerated cellulose semi-permeable membrane (Membrane Filtration Products Inc) was in turn glued onto the microchamber [Fig. 2(f)] by epoxy (Devcon Inc). The sensor was encapsulated into an acrylic test cell with a total volume of approximately 1 mL . Fig. 3 shows images of the sensor before packaging.

IV. Experimental Method

PAA-*ran*-PAAPBA polymer was synthesized in house through free radical polymerization of acrylamide (AA) and acrylamidophenylboronic acid (AAPBA) monomers [34], [35]. To prepare the polymer solutions, 284 mg of PAA-*ran*-PAAPBA, were dissolved in 6 mL of phosphate-buffered saline (PBS). The PAA-*ran*-PAAPBA polymer has an AA to AAPBA molar ratio of 20 (or approximately 5% PAAPBA content in the polymer) and a molecule weight of $170\text{ }700$. The PBS buffer, pH 7.4, was prepared by diluting a Ringer's stock solution (Nasco, Inc.) at a ratio of 1:9. D-(+)-glucose was purchased from Sigma-Aldrich. Glucose stock solution (1 M) was prepared by dissolving glucose (1.8 g) in with sterile water (Fisher Scientific) at a rPBS to 10 mL . A series of glucose solutions ($30, 60, 90, 120, 240,$ and 480 mg/dL) were prepared by further diluting the stock solution with PBS.

The microsensor was characterized using a previously reported experimental setup [24] (Fig. 4). Briefly, the temperature of the polymer solution was maintained at 37 degC via a closed-loop controlled Peltier heater (Melcor, CP14), whose voltage is determined according to the feedback from the on-chip temperature sensor. The device was integrated into 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). The amplitude and the phase shift of the output voltage from the circuit were recorded with the lock-in amplifier using a time constant of 1 s , which was considered sufficiently long for noise minimization in the sensor output to allow an adequate signal-to-noise ratio. The equivalent capacitance (C_x) that was directly related to the polymer permittivity was determined from the circuit outputs when the microsensor and a reference capacitance (C_R) were in turn coupled into the circuit by switching T between position S and R .

V. Result and Discussion

We first investigated the microsensor response to varying glucose concentrations in an AC E-field at various frequencies. The temporal course of the sensor capacitance due to glucose concentration changes was then obtained to determine the time responses and the reversibility of the device. Finally, the drift in the sensor output over an extended measuring period was investigated to evaluate the potential suitability of the device for long-term stable CGM applications.

A. Sensor Frequency Response to Various Glucose Concentrations

The device glucose response was measured under an E-field at a range of driving frequencies. The device's equivalent capacitance as a function of frequency for the glucose-free PAA-*ran*-PAAPBA polymer solution was first obtained. As shown in Fig. 5(a), the sensor capacitance decreased consistently with the frequencies due to the frequency-dependent dielectric relaxation of the polymer. In addition, we also observed a rapid decrease of sensor capacitance from 72.7 to 20 pF with the frequency changed from 5 to 20 kHz. By exposing the device to various glucose concentrations ranging from 30 to 480 mg/dL, the sensor capacitance decreased with increasing glucose concentrations at all measured frequencies [Fig. 5(b)]. For example, at 100 kHz frequency, the sensor capacitance decreased by 0.3 pF at 480 mg/dL with respect to the sensor capacitance in the glucose-free polymer solution. These experimental results suggest that we can determine the glucose concentration through permittivity measurement at a fixed frequency where the sensor has the largest response to glucose concentration changes (e.g., 100 kHz).

The permittivity of the PAA-*ran*-PAAPBA polymer solution may be determined by considering several polarization effects mentioned above. The dipolar polarization [29] induces the permanent dipoles such as AAPBA and AA segments that are rigidly attached to the polymer backbone to align with the E-field. In addition, the counterion polarization [30] causes the attraction of cations (e.g., Na⁺, K⁺, and H₃O⁺) to the negatively charged appending groups of PAA-*ran*-PAAPBA, forming a counterion cloud that surrounds the polymer. Under the E-field, the counterions migrate unevenly within the cloud, resulting in a net dipole moment. Furthermore, the interfacial polarization involves dipole moments due to electrical double layers formed at the interfaces of the ionic buffer with polymer molecules (i.e., Maxwell-Wagner-Sillars polarization [29]) as well as the passivated electrode surfaces (electrode polarization) [31]. These interfacial polarization effects dominate the low-frequency regions, and are generally exhibited as a sharp decline of permittivity with increasing frequencies as shown in the abnormal decrease of the electrode capacitances at frequencies lower than 20 kHz [Fig. 5(a)]. Crude estimate for the polymer suggests that the relaxation frequency of electronic and ionic polarization is on the order of 1 THz, and interfacial polarization is on the order of 1 GHz, while those of dipole reorientation and counterion polarization are on the order of tens and hundreds of MHz according to (3). Thus, all of these polarization mechanisms may be significant for the polymer.

At measurement frequencies used in our experiments, PAA-*ran*-PAAPBA may undergo several changes in polarization behavior due to its binding to glucose. For example, the binding of glucose and polymer may result in partial crosslinking of the polymer. This increases the viscosity (η) of the polymer solution as well as the effective radius of polymer molecules (a), making it more difficult for dipoles in the polymer to align with electrical field and causing the dipolar relaxation time (τ) to increase according to (2). In addition, binding between the polymer's AAPBA segments and glucose at a two to one ratio leads to the formation of cyclic esters of boronic acid and elimination of two hydroxyl groups. This may cause a decrease in net permanent dipole moments and reduce the overall electrical energy that can be stored in the dipoles, resulting in a decreased low-frequency (static)

permittivity (ϵ_s) (1). However, the high-frequency (optical) permittivity ϵ'_∞ , which is significantly smaller than ϵ_s [36], experiences limited changes attributed to the variations in the number of electrons [37] in the polymer solution due to the addition of glucose. As a result, the capacitive component ϵ_s in the complex permittivity decreases with glucose concentration (1). Furthermore, glucose binding may lead to variations in the net charge of polymer segments as well as changes in the polymer conformations, which would alter the electric double layer structure and result in changes in Maxwell-Wagner-Sillars and counterion polarization. The combination of these effects likely explains that at a given frequency, the measured sensor capacitance decreased with glucose concentrations (3) [Fig. 5(b)]. While the glucose-induced changes in the device's capacitance were greater in absolute value at the lower frequencies, the differences of these changes for two given glucose concentrations increased with frequency [Fig. 5(b)]. This can be attributed to a complex interplay of the various dielectric relaxation mechanisms discussed above. A specific explanation of this behavior can be provided by a detailed study of these mechanisms, which is a subject of future work.

B. Sensor Time Response to Glucose Concentration Changes and Reversibility

Sensor time response to glucose concentration changes and its reversibility were also characterized by repeatedly introducing two glucose solutions with different concentrations into the test cell. The glucose concentration was initially allowed to be equilibrated at 60 mg/dL in the test cell and the microchamber. Next, the solution in the test cell was replaced with another glucose solution at 120 mg/dL. After the equilibration of the glucose concentration inside the microchamber and test cell, a reverse process was initiated to refill the test cell with 60 mg/dL glucose solution again. Throughout this concentration equilibrium process, an AC voltage of a fixed frequency of 100 kHz was applied to the sensor, and the sensor capacitance changes at this frequency were obtained.

From the experimental data (Fig. 6), it can be seen that as the glucose concentration varied from 60 to 120 mg/dL, the sensor capacitance decreased consistently from 11.951 to 11.935 pF, corresponding to a decrease in the permittivity of the polymer solution due to glucose binding. While in the reverse process in which glucose concentration changed from 120 mg/dL back to 60 mg/dL, the sensor capacitance returned to 11.952 pF. The sensor capacitance finally saturated to constant levels for both forward and reverse glucose concentration changes, reflecting that the processes of glucose permeation and binding have reached a dynamic equilibrium. Assuming the glucose concentration change in the test cell as an input of a step response, the time constants, which are defined by the time for the system's step response to reach 63.2% of its final value, were 2.49 and 3.08 min respectively for the forward and reverse processes. The longer reverse time constant could be due to the smaller diffusivity of glucose molecules in the initially more viscous polymer solution. These time constants were shorter than the physiological time lag (5–30 min) due to the diffusion of the glucose between the blood and the interstitial fluid. This device has the potential to be applied as implantable CGM sensor, and can be further improved by shortening the height of the microchamber.

We can also assess the reversibility of the device response by comparing differences in sensor output between two separated measurements at the same glucose concentration. For example, as shown in Fig. 6, the sensor capacitance at 60 mg/dL glucose concentration varied from 11.951 (averaged over the period between 0 and 5 min) to 11.952 pF (averaged over the period between 26 and 31 min). The difference between the average sensor outputs over the two periods with the glucose concentration at 60 mg/dL was only about 1 fF, indicating that our sensor possessed excellent reversibility with respect to glucose

concentration variations. This result also indicated that our sensor has the ability to carry out long-term and stable *in vivo* glucose testing, where good repeatability is highly demanded.

C. Drift in Sensor Output at Fixed Glucose Concentration

Finally, we investigated the drift of the device by exposing it to a constant glucose concentration (60 mg/dL) over an extended measurement period. The sensor capacitance at 100 kHz is shown in Fig. 7. It can be seen that the sensor capacitance was steady at 11.955 pF over a period of about 4 h with slight drift. The low drift demonstrated that our device holds potential to offer highly stable measurements for long-term CGM. However, we also observed some fluctuations during the measurement, which can be explained as the environmental disturbances, such as shocks, vibrations, and human activities, which randomly appeared in the testing environment. The sensor signal returned to the original level upon the disappearance of these interferences, indicating a high reliability of our sensor. These interferences can be further compensated in the future by differential measurements that minimize the common mode disturbances in the measurement setup.

VI. Conclusion

This paper presents a MEMS dielectric affinity glucose biosensor that continuously measures glucose concentration through dielectric detection. The device consists of a Parylene diaphragm embedded with a perforated electrode, which is sealed inside a microchamber by a regenerated cellulose semi-permeable membrane and is filled with a solution of a glucose-specific synthetic polymer PAA-*ran*-PAAPBA. The semi-permeable membrane prevents the polymer from escaping while allowing the permeation of glucose into and out of the chamber. The perforated electrode forms a capacitor with a bottom electrode on the substrate with the polymer solution sandwiched between the electrodes as the dielectric. Affinity binding between the polymer and glucose results in the crosslinking of the polymer and a decrease in the permittivity of the solution. Thus, by measuring the capacitance of the electrodes, the glucose concentration can be determined.

The capacitance of the MEMS sensor obtained at several selected glucose concentrations indicates that the device is capable of detecting glucose by permittivity measurements. Experimental results have also shown that the device responded quite rapidly to glucose concentration variations with time constants of approximately 2.5–3 min. This was shorter than the time responses of commercially available electrochemical CGM sensors, and can be further reduced by improved MEMS sensor design. Additionally, we also observed that the device response to glucose concentration changes was highly reversible; as the glucose concentration changed from 60 to 120 mg/dL and then reversed to 60 mg/dL, the deviation in the sensor capacitance was only 83 ppm. Finally, we demonstrated that the device had low drift. For example, as the glucose concentration was held constantly at 60 mg/dL, the drift rate in the sensor capacitance was 14 ppm/h. Fluctuations in the sensor signal can be occasionally observed due to environmental disturbances. This device represents a significant improvement to our proof-of-concept device that only measured pre-mixed polymer solutions. The experimental results demonstrate the potential of the device for measurement of glucose concentration in subcutaneous tissue. Its accuracy and resolution can be further improved by optimized polymer and sensor designs that aim to improve the device sensitivity to glucose concentration changes, and minimize the effects of nonspecific disturbances and artifacts (e.g., environmental temperature fluctuations and parasitic capacitances) by methods such as differential measurements.

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Qiao Lin received the Ph.D. degree in mechanical engineering from the California Institute of Technology in 1998 with thesis research in robotics. Dr. Lin conducted Post-Doctoral research in micro-electromechanical systems (MEMS) at the Caltech Micromachining Laboratory from 1998 to 2000, and was an Assistant Professor of Mechanical Engineering at Carnegie Mellon University from 2000 to 2005. He has been an Associate Professor of Mechanical Engineering at Columbia University since 2005. His research interests are in

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

Fig. 2.

Fabrication processes. (a) Gold layer deposition and patterning to form a bottom gold electrode, and passivation of the electrode by Parylene. (b) Sacrificial photoresist layer deposition and patterning. (c) Parylene deposition and gold layer deposition and patterning to form a perforated electrode. (d) Parylene passivation layer deposition. (e) SU-8 deposition and patterning to form a diaphragm and a microchamber. (f) SU-8 patterning, sacrificial layer removal, and semi-permeable membrane bonding.

Fig. 3.
Images of a differential MEMS affinity glucose sensor before packaging.

Fig. 4. Experimental setup and a capacitance/voltage transformation circuit for capacitance measurement.

Fig. 5.

Sensor frequency response to various glucose concentrations with PAA-*ran*-PAAPBA as the dielectrics. (a) Frequency-dependent equivalent capacitance of the microsensor in the absence of glucose. (b) Capacitance differences of the microsensor at various glucose concentrations as compared with the sensor capacitance in the absence of glucose.

Fig. 6. Time course of the sensor capacitance at 100 kHz as the sensor responded to glucose concentration changes from 60 to 120 mg/dL, which was then reversed to 60 mg/dL.

Fig. 7. Sensor capacitance at 100 kHz over an extended time duration as the glucose concentration was held constant at 60 mg/dL.