A 3-µW CMOS Glucose Sensor for Wireless Contact-Lens Tear Glucose Monitoring

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Abstract—This paper presents a noninvasive wireless sensor platform for continuous health monitoring. The sensor system integrates a loop antenna, wireless sensor interface chip, and glucose sensor on a polymer substrate. The IC consists of power management, readout circuitry, wireless communication interface, LED driver, and energy storage capacitors in a 0.36-mm² CMOS chip with no external components. The sensitivity of our glucose sensor is 0.18 µA·mm⁻²·mM⁻¹. The system is wirelessly powered and achieves a measured glucose range of 0.05–1 mM with a sensitivity of 400 Hz/mM while consuming 3 µW from a regulated 1.2-V supply.

Index Terms—Contact lens, glucose sensor, heterogeneous integration, low power, noninvasive, potentiostat, wireless health monitoring.

I. INTRODUCTION

Diabetes is widely recognized as a leading cause of death and disability throughout the world, and the number of people diagnosed with diabetes mellitus is expected to increase dramatically in the next few decades [1]. Diabetes management mainly concentrates on maintaining normal blood sugar levels through frequent glucose monitoring and the correct dosage and timing of insulin injections. Continuous glucose monitoring can help early diagnosis and effective control of diabetes complications.

An enzyme-based finger-pricking method is the most commonly used diabetic assessment. However, the procedure is invasive and inconvenient, requires patient compliance, and may cause infection during the blood sampling processes. An alternative method uses near-infrared spectroscopy and provides a noninvasive way to monitor the glucose level in the body. This method analyzes the light reflection or transmission spectrum in the fingertip to infer metabolic concentration. Due to challenges of interference with other biochemicals, poor signal strength, and calibration issues, this method is not sufficiently accurate for clinical use [2]. Therefore, ongoing research focuses on the development of noninvasive and continuous glucose sensing.

Tear fluid is directly accessible on the eye and can be used as a chemical interface between a sensor and the human body. Tear fluid contains many biomarkers that are found in blood, such as glucose, cholesterol, sodium, and potassium [3], [4]. The glucose level in tear film is reported to be in the range of 0.1–0.6 millimoles per liter (mM), which is about ten times lower than the levels in blood.

Conventional contact lenses are transparent polymers placed on the eye to correct faulty vision and can simultaneously serve as a platform to directly access tear fluid. Integrating biosensors on a contact lens would provide a noninvasive way for continuously sensing metabolites in tear fluid. Contact-lens-mounted biosensors have been developed to measure eyelid pressure [5], tear glucose [6], and intraocular pressure [7], [8]. These sensors use inconvenient wired readout interfaces. Contact-lens functionality could be greatly expanded by creating heterogeneous systems with embedded electronics and wireless telemetry. Our previous works have demonstrated an active contact lens system with a µLED for information display [9], and a readout architecture connecting to an on-lens glucose sensor has been demonstrated to detect low glucose levels [10]. Through integrating biological sensors and telemetry, an active contact lens could provide health professionals with a new tool for research studies and for diagnosing diseases without the need for lab chemistry or needles.

In this paper, we will present a fully integrated active contact lens system for wirelessly and continuously monitoring glucose levels. The on-lens electrochemical sensor provides real-time continuous glucose monitoring and high sensitivity compared with conventional glucose monitoring. The sensor directly accesses the tear fluid and thus can improve the sensitivity and reduce the sampling processes and potential of infection during operation. Fig. 1 shows the conceptual diagram of wireless health monitoring using an active contact lens. The proposed active contact lens system includes glucose sensor, antenna, communication interface, and readout circuitry on a polymer lens substrate. The on-lens glucose sensor system detects the tear glucose level and then wirelessly transmits the information to an external reader. This system could potentially work as a point-of-care device in the future with the near-field communication feature of mobile phones.

There are many challenges in the implementation of the on-lens sensor system. First, the system is extremely constrained by power and area. A standard contact lens has an area of about 1 cm² and a total thickness of about 200 µm. Component size in the design is severely restricted, roughly 0.6 × 0.6 mm², which is determined by the curvature of the
eye and our assembly process. Clearly, standard surface-mount components are too large for integration onto a contact lens. In addition, volume limitations eliminate the possibility of large energy storage devices. Therefore, a biosensor on a contact lens must be powered wirelessly through external sources (e.g., RF power, inductive power, or optical power). Third, the active contact lens system requires the heterogeneous biocompatible integration of different devices/materials on a plastic substrate. Finally, possible issues of using the sensors on the eye may include RF-power-caused eye temperature increase, vision-blocking, and damage from on-lens device. The regulation of RF-power-caused temperature rises is still under study for human eyes. We have adhered to the IEEE C95 standard to minimize risk in this area. Further studies are underway. To reduce the intrusion and damage of devices, on-lens devices can be embedded into the lens. The devices on the contact lens are out of the focus of human eyes and are placed in the outer of a lens to further avoid vision blurring.

This paper presents a fully integrated and wirelessly powered glucose sensor prototype embedded in a functional contact lens system. This paper is organized as follows. Section II presents the design and fabrication of a glucose sensor on a plastic substrate. System architecture and circuit design of the readout chip are described in Sections III and IV, respectively. The assembly and integration techniques are shown in Section V. Section VI presents the measurement setup and experimental results. Finally, conclusions are discussed in Section VII.

II. DESIGN AND FABRICATION OF THE GLUCOSE SENSOR

Compared with traditional analytical techniques, electrochemical methods, based on oxidizing or reducing the target analytes, can achieve a real-time, quick-response, high-efficiency, and cost-effective analysis. The electrochemical reaction of an enzyme-based glucose sensor can be expressed as [11]

\[ D \rightarrow \text{Glucose} + O_2 \underset{\text{GOD}}{\rightarrow} H_2O_2 + D \rightarrow \text{Glucolactone} \]  

\[ H_2O_2 \rightarrow 2H^+ + O_2 + 2e^- \]  

The basic electrochemical reaction for sensing glucose starts from catalyzing glucose to hydrogen peroxide (H$_2$O$_2$) using the enzyme glucose oxidase (GOD). H$_2$O$_2$ is further oxidized at the electrode to release electrons, generating a current signal proportional to the glucose concentration.

A. Glucose Sensor Design and Fabrication

To make a stable electrochemical sensor, three electrodes are typically used: a working electrode (WE) where the target analytes are involved in an oxidation or reduction process, a counter electrode (CE) (also known as an auxiliary electrode) operating as a current drain to make an electron loop, and a reference electrode (RE) that provides a stable voltage potential for the whole system. In the proposed sensor [Fig. 2(a)], the working and counter electrodes are designed as concentric rings with widths of 50 and 75 \( \mu \text{m} \), respectively, which have a 50-\( \mu \text{m} \) pitch to decrease the resistance and thus enhance the sensor sensitivity. The reference electrode is designed as a rectangular bar (1.6 mm x 0.25 mm) close to the sensing area. Fig. 2(b) shows the fabrication process of glucose sensor. The fabrication starts from a transparent polyethylene terephthalate (PET) polymer film (100-\( \mu \text{m} \) thickness). Three metal layers, Ti, Pd, and Pt, are evaporated in sequence to achieve thicknesses of 10, 20, and 100 nm, respectively, to create electrodes. Then, the exposed Ti/Pd/Pt sensor surface is pretreated with a GOD/titania sol-gel membrane. The detailed fabrication and pretreatment process is reported in [12].

B. Sensor Calibration

We designed and fabricated a polydimethylsiloxane (PDMS) eye model mimicking a human eye [13] to test the sensor in a continuous microfluidic system, as shown in Fig. 3. A FI-Alab-3000 fluidic analyzer (6 multi-position valves) is applied to continuously deliver different solutions into the tear duct, and another syringe pump aspirates at the same flow rate from the tear drain. The sensor was tested using the PDMS eye model, which more closely resembles an on-eye scenario than beaker testing. Fig. 4 shows measured results of continuous glucose flow tests. The average response time to reach the maximum value in the continuous flow setup is about 35 s, including 15 s for the pump to deliver the test solution to the eye model and sensor response time of 20 s.

The linearity curve (Fig. 5) is generated by collecting the current peak response from five independent sensors. Normal glucose levels in human tear film are roughly 0.1–0.6 mM. The usable glucose concentration range of the proposed sensor is 0.05–2 mM, which safely covers the relevant human range. The electrochemical current generated is around 1–20 nA in the glucose levels relevant for human tear sensing. The sensitivity of our glucose sensor is 0.18 \( \mu \text{A} \cdot \text{mm}^{-2} \cdot \text{mM}^{-1} \). In this sensor design, a layer of Nafion used previously in [10] and [12] to improve the sensitivity and the interference rejection was removed since Nafion promotes random protein absorption due to eventual foreign body encapsulation [14]. The measurement discrepancies among these five sensors mainly result from the different surface circumstance and enzyme immobilization of
the sensors, which are caused by the manual microfabrication processes.

III. WIRELESS READOUT CHIP ARCHITECTURE

The goal of the on-lens sensor readout system was to implement a low-power (< 5 μW), low-current-noise (<1 nA rms) design in a severely constrained area (0.36 mm²). Fig. 6 shows the proposed sensor readout architecture. The IC consists of a power management block, readout circuitry, wireless communication interface, LED driver, and energy storage capacitors in a 0.36 mm² CMOS chip with no external components (e.g., quartz crystals, inductors, capacitors, or batteries). The system is wirelessly powered using RF power sent from an interrogator. The challenges in making an integrated RF power-harvesting system include designing an efficient rectifier, low-power voltage reference/regulator, and a sufficiently large on-chip storage/filtering capacitor. These challenges are greatly exacerbated by the fact that large value high-Q surface-mount passives and an efficient antenna cannot be used.

In addition, accurate detection of the low sensor current requires stable supply voltage, reference voltages, and low-noise electronics. To reduce the supply fluctuation caused by varying strength of incident RF power and digital switching noise, we designed an ultralow-power linear regulator, bandgap reference, and bias current generation, which provide stable bias and supply for the chip. The low-noise readout electronics include a potentiostat to enforce a stable potential between WE and CE to start the oxidation reaction. The CE2 node can be connected to a reference sensor for biochemical interference rejection [13]. The sensor current is amplified and then injected into an oscillator-based current-to-frequency (f–F) converter that directly encodes the sensor current as a modulated tone. Finally, the
system wirelessly communicates with the interrogator through RF backscatter (by either absorbing or reflecting the carrier signal sent by the interrogator).

IV. CIRCUIT IMPLEMENTATION

A. Antenna Design

The design of the antenna is severely constrained by the required contact lens size, flexibility, and transparency. A 5-mm-radius loop antenna is used to receive RF energy without obstructing wearer vision. For an on-lens system, surface mount parts are prohibitively large, so the chip and antenna must be directly connected without an external matching network. The impedance matching between chip and antenna is absorbed into the antenna design. The loop antenna was designed and fabricated using gold traces on a PET substrate [9]. To determine power received by the on-lens antenna, we simulated the gain for a loop antenna with a 5-mm radius, 0.5-mm trace width, and 5-μm thickness. The received power is calculated using the Friis transmission equation, assuming perfect antenna-chip matching and minimum transmit antenna gain (1.76 dBi for a dipole antenna). Fig. 7 shows the results of received power in the air and on an eye model (tear film, cornea, aqueous humor, and vitreous humor) at a distance of 15 cm from an isotropic transmitter (1-W output power). At low frequency, the received power is limited by the efficiency of the antenna; at high frequency, the path loss dominates the received power. An optimal frequency exists between 1.5–2.5 GHz for our size-constrained antenna design in free-space communication. The simulated antenna gain on the eye model in the direction of the transmitter (perpendicular to the plane of the loop antenna) is 17 dB lower than the antenna gain in air in the 1.8 GHz ISM band, giving about 20 μW received power. Therefore, the maximum power...
consumption of readout electronics should be less than 5 μW (assuming 25% power transfer) to provide a reasonable communication distance.

B. Power Delivery and Rectifier Design

The on-chip power management circuits comprise a full-wave rectifier to convert RF power to a dc voltage and a low power regulator to provide a stable 1.2-V voltage supply, which is subsequently filtered by a 500-pF on-chip capacitance. The rectifier is built using a five-stage Dickson full-wave architecture. Low-Vth pMOS transistors with the body terminal tied to the source are employed to eliminate the body effect and enhance sensitivity by reducing the turn-on voltage of transistors. The simulated peak power efficiency of the rectifier is about 20%.

C. Regulator and Bias Generation

Two major problems of an RF-powered wireless sensor system are the supply fluctuation due to the varying incident RF power and supply noise due to the fast switching of digital circuits. First, to reduce supply variations, a low-power regulator with bandgap reference was employed, providing a clean and temperature-stable 1.2-V supply to the entire system. A large filtering capacitor is desired to reduce high-frequency supply noise and large voltage drops. To reduce area, the on-chip capacitor is stacked vertically with dual metal–insulator–metal (MIM) capacitors and metal finger capacitors using the middle four metal layers and MOS capacitors. An on-chip capacitance of 500 pF is implemented in an area of ~ 0.2 mm². Second, a separate digital and analog supply regulation technique is employed to reduce noise coupling into the sensing element (sensor and readout circuitry) from the oscillator as well as logic switching noise. The schematic of the regulator is shown in Fig. 8. To provide isolation between digital and analog supplies without adding an extra regulator, the regulator pass transistors are separated [15]. This topology achieves 30-dB isolation between digital and analog supply while consuming 500 nW. The low-power bias circuit and amplifier design is described in more detail in [16]. Fig. 9 shows the measured output unregulated/regulated voltage versus swept input RF power.

D. Potentiostat

For electrical current measurement, a transimpedance amplifier is a popular approach that measures low current levels by using high measurement resistance. However, the transimpedance amplifier configuration usually has an inductive input impedance, which may cause instability in the potential control loop due to the large and varying capacitive components of an in-eye electrochemical cell. To accommodate high uncertainty in the sensor capacitance, a current mirror-based topology was used to copy and measure the sensor current [17].

Fig. 10 shows the schematic of proposed readout circuitry. The voltage control loop, consisting of a bandgap reference, amplifier (A1) and a pass transistor (M1), provides a stable potential of 400 mV between the working and counter electrodes. The choice of a 400-mV potential achieves the optimal signal-to-noise ratio (output current/background noise) as given by previous measured results of our glucose sensor. A frequency-compensation capacitor is added at the output of feedback amplifier to stabilize the potential control loop. The sensor current is mirrored with a cascode topology that improves the precision of current replication.

E. Current-to-Frequency Converter

A ring oscillator-based current-to-frequency (I–F) converter (Fig. 11) directly converts the sensor current signal into a rail-to-rail digital output without an explicit ADC. This saves area, power, and complexity. The oscillator normally operates at 350 kHz and consumes 300 nA. The output frequencies of the reference and sensor oscillator are divided down to reduce high frequency noise/instability. The sensor current is injected into an oscillator-based I–F converter. The oscillation frequency of a current-starved ring oscillator can be expressed as

\[ f_{osc} = \frac{I_d}{N \cdot C_{tot} \cdot V_{ddl}} \]  

(3)

where \( I_d \) is the current of each stage, \( N \) is the number of stages, \( V_{ddl} \) is the supply voltage, and \( C_{tot} \) is capacitance at the output of each stage. The oscillator frequency shifts proportionally to the injected sensor current. Fig. 12(a) shows the measured output frequency (after dividing by 512) versus sweep injected current. The I–F converter achieves a gain of 9.9 Hz/nA.
The process, voltage, and temperature variations of the ring oscillator are reduced by using large devices and careful layout, a regulated voltage supply, and differential measurement using a reference oscillator and the sensing oscillator. Fig. 12(b) and (c) shows the measured output frequency (divided by 512) of the \( I-F \) converter versus supply voltage and temperature, respectively. The temperature coefficient of the \( I-F \) converter is 20 Hz/°C from 30 °C to 60 °C and can be effectively reduced to 2.6 Hz/°C by subtracting the result of the reference oscillator from the result of the sensor oscillator.

### F. Pulse Generator and Backscatter Modulator

To wirelessly read out sensor data, backscatter communication is adopted in our system. Backscatter modulation is attractive for active contact lens applications because it allows for a nearly zero power lens-to-reader communication. Since the body glucose level changes slowly, it is not necessary to store/transmit data frequently. However, there is a tradeoff between power delivery and backscatter signal strength. A strong backscatter signal may cause large supply voltage drops, which can be problematic in our system due to small energy storage capacitance on the chip and the low tolerable supply ripple. Therefore, a pulse generator is integrated to allow a low duty cycle (10%) modulation signal to achieve a reasonable compromise between supply voltage droop and backscatter strength.

Fig. 13(a) shows the schematic of pulse modulators. The divided signals from the fifth and ninth bits of a 16-bit divider chain are used to create the pulses. The pulsewidth equals the period of the reference oscillator and the pulse period is twice the period of the sensor oscillator. Using this technique, frequency information from both the sensor and reference oscillator are simultaneously transmitted to the interrogator and can be decoded in the reader. A single transistor switch is used to modulate the reflection coefficient. A 3.3-V-thick oxide device and a diode-connected voltage limiter are used to prevent breakdown when the system is placed near the reader.

An alternative method of wireless communication is to slowly modulate an on-lens \( \mu \)LED for immediate visual feedback to the contact lens wearer. The \( \mu \)LED design and fabrication is shown in our previous work [9]. Since lighting a customized \( \mu \)LED consumes much more power (\( \sim 70 \mu \)W at 2.5 V for visible light) than the sensor, we duty-cycled the LED to save power. Fig. 13(b) shows the pulse generators used for optical detection. The frequency of the reference signal is divided down to 4 Hz with the 16-b counter. The LED is lit in the first half period to transmit data and turned off in the second half period to conserve energy. A pulse generator that drives the LED creates a narrow pulsewidth (\( \sim 3 \mu \)s) to reduce LED on-time and effectively lower the LED power consumption. The number of pulses in an on-cycle represents the frequency difference between reference oscillators and sensor oscillator, which corresponds to the glucose concentration.
V. SYSTEM ASSEMBLY

Here, we describe the on-lens integration of the sensor, IC, and antenna. First, we cut 100-mm wafers from PET films and cleaned them with acetone, isopropyl alcohol, and deionized (DI) water. Then, a 6-μm layer of positive photoresist (AZ4620) was spin-coated, soft baked, and patterned. Cr, Ni, and Au (20, 80, 350 nm) were evaporated and lifted off in acetone to create contacts for solder coating, an adhesion layer for the electroplated antenna, and low resistance connections from the chip to the sensor. After lift-off, SU-8 was deposited to restrict solder wetting. Next, a 40-nm seed layer of Au was deposited over the wafer, AZ4620 was used to pattern the antenna, and 5 μm of Au was plated to reduce the antenna ohmic loss (improve the antenna efficiency). The seed layer was etched using Gold Etch TFA (Transene) mixed with DI water in a ratio of 5:1 (vol/vol). Then, a 25-μm layer of SU-8 was used to mask the metal features and create an opening for the sensor. The wafer was dried with nitrogen gas, and then individual contact lenses with 1 cm in diameter were cut out using a CO₂ laser cutter.

The aluminum IC pads were nickel/gold plated using an electroless technique (CVinc.). Then, the chip and exposed solder pads on the contact lens were coated with a low melting temperature solder. To accomplish this, indium-based solder (Indium Corporation, Indalloy 19, 60 °C) was heated in a beaker while covered by 10-mL ethylene glycol (EG) and 60-μL HCl. After the solder had melted completely, a pipette was used to solder coat all exposed pads on the IC and contact lens. The chip was then roughly aligned over the contact lens using tweezers in a petri dish of 25 mL of EG and 10-μL HCl. The petri dish was heated on a hotplate until the solder reflowed, and the chip was aligned by solder capillary forces. The lens can be molded with heat and pressure to the curvature of the eye and then Parylene can be deposited (except the sensing area) for biocompatible encapsulation.

VI. PERFORMANCE

The chip was implemented in a 0.13-μm CMOS process. Fig. 14 shows a micrograph of the readout IC. The chip area is 0.6 x 0.6 mm². A ground shield made of the 4-μm-thick top aluminum metal covers the sensitive regulator and readout circuitry to reduce the impact of EMI and light sensitivity.

The chip and sensor are first assembled on a PCB to characterize functionality and performance. The measured Allan deviation (over 6 h) of the readout circuitry is shown in Fig. 15. A minimum standard deviation of 0.31 Hz (center frequency = 850 Hz) is achieved while data are sampled at a period of 5 seconds. The measured results of a continuous glucose flow test (Fig. 3) are shown in Fig. 16. A buffer solution was
Fig. 16. Measured output response of readout IC (continuous glucose flow test).

Fig. 17. Measured output frequency versus glucose concentration.

Fig. 18. Measured LED driver outputs versus glucose levels.

added after each concentration to flush out the remaining ions of previous solutions. The output was sampled every 5 s to achieve a low noise floor, corresponding to the minimal Allan deviation. Fig. 17 shows the measured modulation frequency versus glucose concentration. The measured gain of the glucose sensor is 400 Hz/mM with a linear correlation (R-square) of 0.98 in 20 measurements from two different sensor assemblies. The resulting noise floor of readout circuitry is 0.775 μM (0.31 Hz/400 Hz/mM). Fig. 18 shows the measured outputs of LED driver with a buffer solution and glucose concentration of 2 mM. Each pulse above the baseline (3) for buffer solution represents a glucose level increase of ~0.15 mM.

We assembled a loop antenna, a readout IC, and glucose sensor on a PET substrate, shown in Fig. 19. The chip is first gold-plated and flip-chipped on the substrate to reduce the contact resistance and bondwire inductance. The glucose sensor system consumes 3 μW, which gives a power link budget in the design and can be powered over 15 cm from an effective isotropically radiated power (EIRP) of 40 dBm at 1.8 GHz. This power level complies with the IEEE C95 standard, which regulates a maximum power density of 6 mW/cm² at 1.8 GHz for human exposure to an RF electromagnetic field [18], requiring a safety distance of at least 11 cm from an EIRP of 40-dBm power source. The transmitted RF power can be reduced by improving impedance matching, reducing antenna loss, and exploiting different rectifier designs.

Fig. 20 shows the measured backscattered signal from the assembled lens. The glucose concentration of 1 mM results in a 400-Hz frequency deviation of the backscattering carrier. Table I is the performance summary of our CMOS glucose sensor.
VII. CONCLUSION

Advances in technology scaling, sensor devices, and ultralow-power circuit design techniques have now made it possible to integrate complex wireless electronics onto the surface of a wearable contact lens. In this paper, we demonstrate an on-lens sensing platform that allows wireless readout of glucose present in tear film. The proposed system contains an on-lens loop antenna for power and data transfer, low-power sensor interface readout IC, and glucose sensor to monitor tear glucose levels wirelessly. The system has a linear gain of 400 Hz/mM in the glucose range of 0.05–1 mM while consuming 3 $\mu$W from a regulated on-chip 1.2-V supply. The system can be wirelessly powered from a distance of 15 cm. The readout architecture can also be used to connect an on-lens LED for immediate visual feedback to the contact lens wearer when interrogated by a simple continuous wave transmitter. The small chip area, high level of integration, and low power of our system provides a platform for application in multiple bio-sensing tasks on contact lenses. Our future work in this area includes addressing protein-caused desensitivity, sensor lifespan improvement, improvement of antenna-IC co-design, and clinical tests.

REFERENCES


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