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Toward implantable Glucometer: Design, Modeling and Experimental Results

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***Abstract*— We put forward an implantable glucometers using a biologically inspired sensor (BioS) method. In this method, engineered glucokinase (GLK) molecules are used as nano-scale glucometers. Herein, we describe two computational and experimental models of GLKs exposed to glucose molecules. The simulation results significantly show the detection of GLK binding to glucose. We thereafter reveal the applicability of this technique for continuous glucose monitoring by demonstrating and discussing the experimental results. Based on these results the glucose measurement with various glucose concentrations (0.5 mM, 1 mM and 2.5 mM) were precisely performed and repeated for more than 4 weeks. These results prove the advantage of proposed BioS method for continuous measurement of glucose.**

I. INTRODUCTION

The World Health Organization (WHO) has estimated the number of persons with diabetes worldwide at approximately 171 million in 2000, and this is expected to increase to 366 million by 2030 [1]. Self-monitoring of blood glucose is one the most common methods for managing and controlling the diabetics. The conventional glucometers usually use Glucose Oxidase (GOX) electrodes with finger-pricking blood sampling. The development of non-invasive, continues, low cost, low complexity, reliable and high sensitive glucose sensor has been a challenging subject in recent years [2-3].

An implantable glucometer can offer all above mentioned advantages using a tiny chip under skin. As shown in Fig. 1, this chip can be implanted and transmit the glucose sensing data through the skin to external device. The implanted chip is coated with a recognition element which plays important role as glucose sensor and biocompatible element. Also, as seen in Fig. 1, a readout system is used to detect the minute changes of glucose and the sensing data is transmitted to external device through a wireless system. This system also supplies the required electrical power in conjunction with a watch-like external device. This device is designed to display and record data, and control the implanted chip. To date several papers reported wireless implanted devices for various applications including stimulation visual cortex and [4-5]. However, one of the major differences of this implantable chip with other devices is that the glucose sensor will be implanted very close to the skin surface. This issue leads to two major benefits, first, since no deep implementation is required, no complicated surgery procedures is needed. Second, due to the proximity to the skin surface, the power transfer efficiency of the inductive link will be very high; hence the power requirement will be much relaxed in this type of implants.

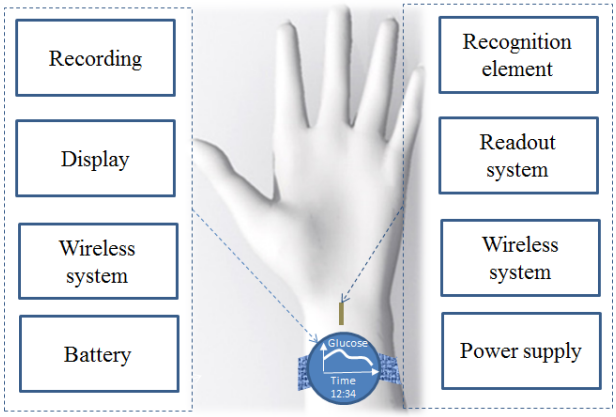


Fig. 1. Glucose sensor implanted under skin. This sensor consists of implanted chip and external readout system.

It should be mentioned that the location of implanting the sensor, the biocompatibility studies and other medical challenges are under investigation by our medical collaborators. In the direction of developing an implantable device, herein we are focusing on the recognition element. Commercially available glucometers mostly employ the GOX as the recognition element. As shown in equation (1), glucose molecules react GOX that results in a change in the resistance which can simply be detected with an ohmmeter.

$$C_6H_{12}O_6 + O_2 \Rightarrow C_6H_{12}O_7 + H_2O_2 \qquad (1)$$
$$H_2O_2 \Rightarrow H_2O + (1/2)\cdot O_2 + e$$

This reaction is not reversible and this method cannot be used for continuous glucose measurements. Therefore, we need to employ another material for coating the sensing electrodes. In this direction, GLKs as the in-vivo glucose

sensors associated with pancreatic beta cell are the best choice instead of GOX. GLKs can be derived using bioengineering method [6] and integrated on the surface of implantable chip using certain chemical protocol (Section II-A).

In the reminder of this paper, in section II, we put forward computational and experimental methods. The results are demonstrated in section III followed by a conclusion in Section IV.

II. Methods and Materials

The chemical protocol, COMSOL simulation method and the micro-fabrication process of developing microelectrodes (MEs) are described in this section.

A. Immobilization of GLK on Gold Electrode

A chemical linker is required to immobilize GLKs on a Gold interdigitated electrode (IE). As shown in Fig. 2a, the following three-step protocol can be performed to create such a linker: (1) self-assembly monolayer (SAM) of long chain organic molecules such as –SH, (2) the reaction of maleimide-NTA with the functional group of SAMs, (3) the bonding of Ni++ due to specificity of nitrilotriacetic acid (NTA) and nickel cations (Ni++), (3) the bonding of GLK due to specificity of Ni++ and His-tagged proteins.

B. Modeling of GLK confirmation

The confirmation of GLK results in a change in the positive and negative charge distribution in the simulation result using molecular dynamic software(Fig. 2b). The confirmation of GLK immobilized on electrode may result in a double layer capacitance As shown in Figs. 3a-3b, the immobilization of GLK can be modeled with a parallel capacitor (Ca), resistor (R_{1b}) in series with a resistor R_{2b}. We can verify these capacitance changes with COMSOL. The positive and negative charges associated with GLK can be located in COMSOL model using the simulation results of Fig. 2a. In such a coarse simulation model, the charges with critical position have precisely been placed to estimate the effect of GLK confirmation on capacitive properties of electrodes.

C. Microfabrication of MEs

MEs are implemented through a sputtering of metal layers on silicon substrate. At the first step, a thin layer of titanium (20 nm) is deposited on silicon as an interface layer, then, a 200 nm gold layer is deposited as sensing electrode. Thereafter, the MEs with 10 micrometer length are realized using photolithography and chemical gold etching techniques.

D. Measurement set-up

The impedance between the fingers of MEs can be measured using AD5934 (Analog Device Inc.). In this work, the complete system of impedance measurement based on this discreet device is employed to detect the impedance dropped on sensing MEs and transfer the digital data through USB to computer. The software for data acquisition is also modified to measure impedance as a function of time and demonstrates the results accordingly.

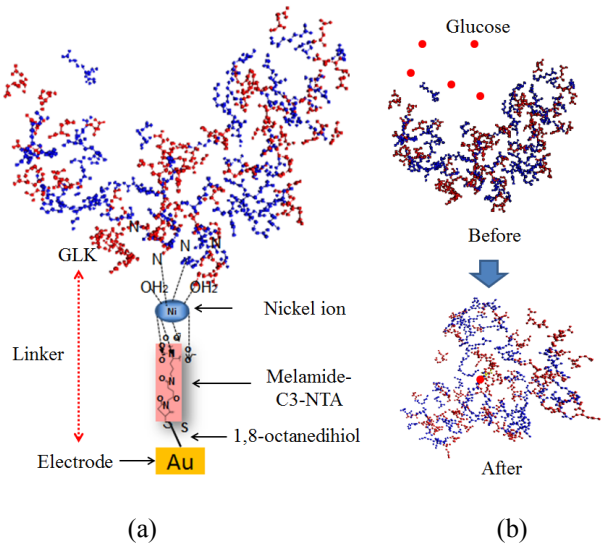


Fig. 2. GLK on Chip: (a) GLK confirmation prior and post glucose binding and (b) Immobilization of GLK on gold electrodes.

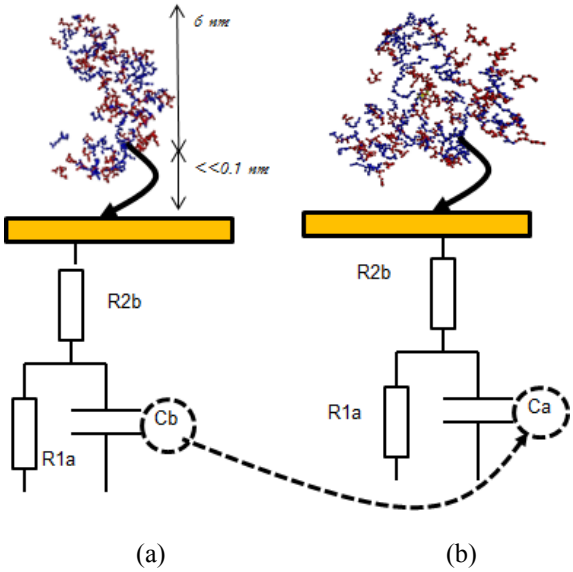


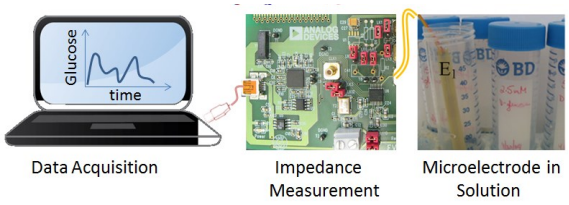
Fig. 3. GLK confirmation modelling : (a) prior to glucose binding and (b) after glucose binding. A double layer capacitance in parallel and series with other resistances.

III. Results and Discussions

This section includes the simulation and experimental results for the modelling of GLK confirmation and glucose measurement.

A. COMSOL Simulation

The displacement of charges influences the electrical properties between the electrodes as seen in Figs. 5a-5b. The capacitance variation in between MEs can be around 25% as the result of GLK confirmation. This effect can also be observed in the variation of energy density as shown in Fig. 6.



(a) (b) (c)

Fig. 4. Measurement set-up: (a) Computer for data analysis (b) Impedance readout system (Analog Device Inc.) and (c) microelectrodes exposed to buffer solutions mixed with various glucose concentrations.

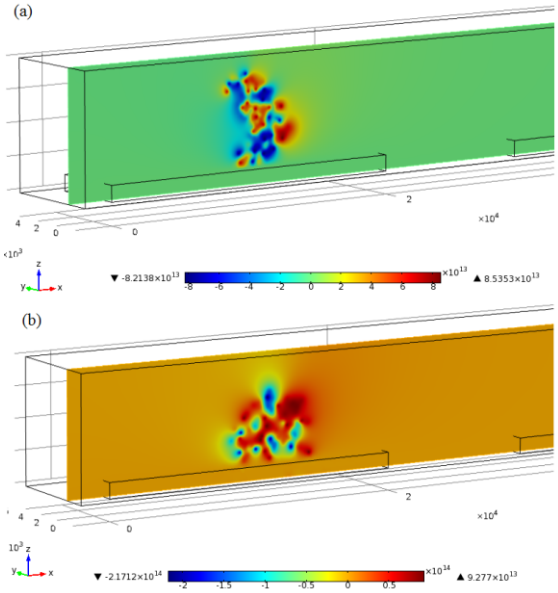


Fig. 5. Simulation results of GLK Confirmation: (a) before and (b) after glucose binding.

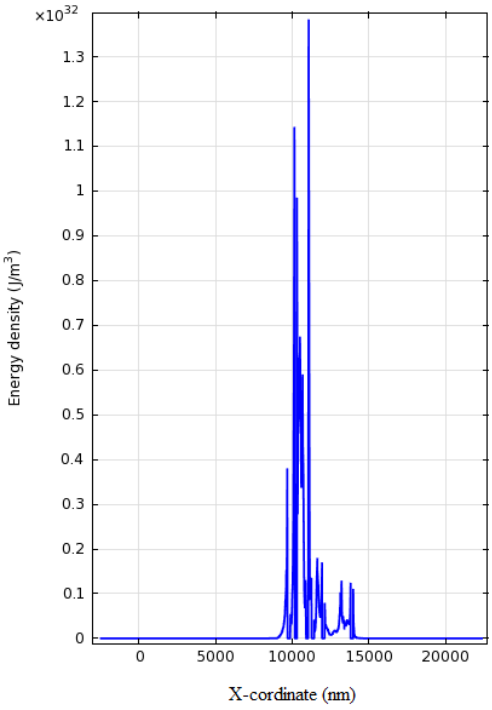
B. Fabrication Results

The microfabricated MEs can obviously seen in Fig. 7b while Fig. 7 shows the connected an MEs into PCB.

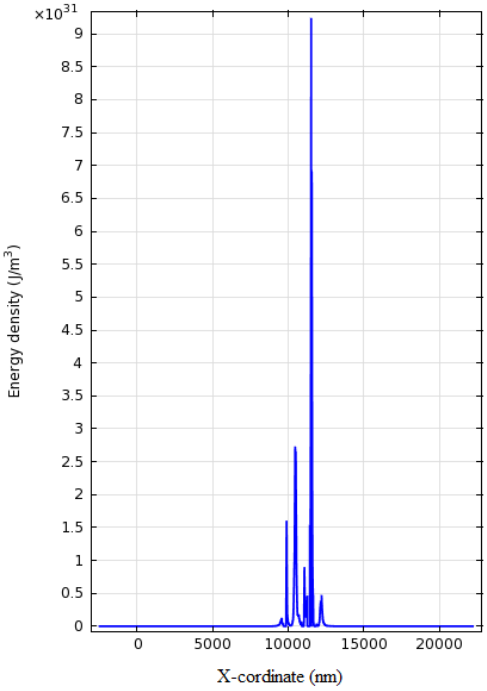
The electrodes are coated with GLKs and their linkers. Fig. 7c shows the SEM image of a piece of gold ME coated after coating process.

C. Measurements

The impedance variation of MEs are measured for various concentrations of glucose in buffer.



(a)



(b)

Fig. 6. Simulation results of energy density (a) before and (b) after GLK confirmation. These results show the variation in the charge distribution around the electrodes due to the GLK conformation.

Each testing tube (see Fig. 4) includes a buffer solution with a certain glucose concentration. Over a range of frequencies (KHz), the impedance variation can be observed in Fig. 8a. Figure 8b shows the impedance variations of IEs over time for different concentrations (0.5mM, 1mM and 2.5mM) where the measurement electrode is rapidly removed from a testing tube and immersed in another one.

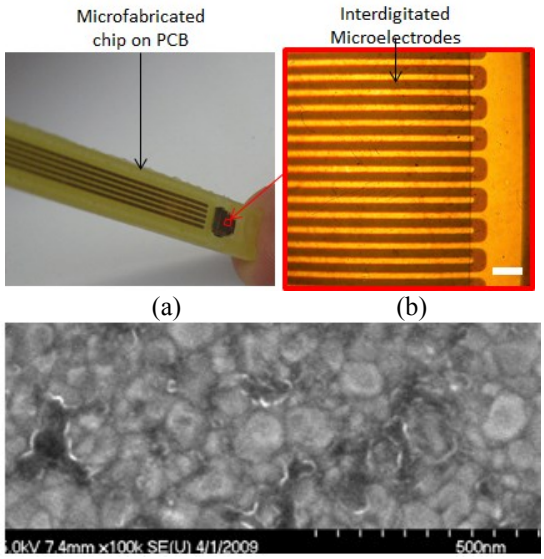


Fig. 7. Microfabrication of sensing electrodes: (a) IE on PCB, (b) IE and (c) SEM of IE coated with GLK.

D. Discussion

The confirmation of GLK was detected using COMSOL and experimental models. In this paper, we used a coarse model to verify the electrical effects of charge displacements. The measurement results demonstrate the advantages of continuous glucose monitoring provided by GLK. Our experiment rsults show around 4 weeks stability and functionality of GLK coating on gold electrode. The main advantage of the proposed reagent-less technique is for implantable glucose sensors. A wireless CMOS glucometer can be implanted under skin in order to measure glucose over a long period of time (for instance several weeks) and control the insulin pump continuously.

IV. Coclusions

In this paper we present the design, modeling and characterization of glucometer for implantable glucometer purposes. The proposed biologically inspired glucose sensor is the best alternative technique for implantable glucose sensor as it plays the role of glucose sensor in the beta cells. CMOS technology can efficiently be employed to develop an implantable glucose sensor to transmit the sensing data to an external device using a wireless technique. As the critical part of implantable design is the development of a recognition element with advantages of highly sensitivity, anti-fouling and biocompatible properties, this paper put further in this direction by proposing a biologically inspired method.

Acknowledgement

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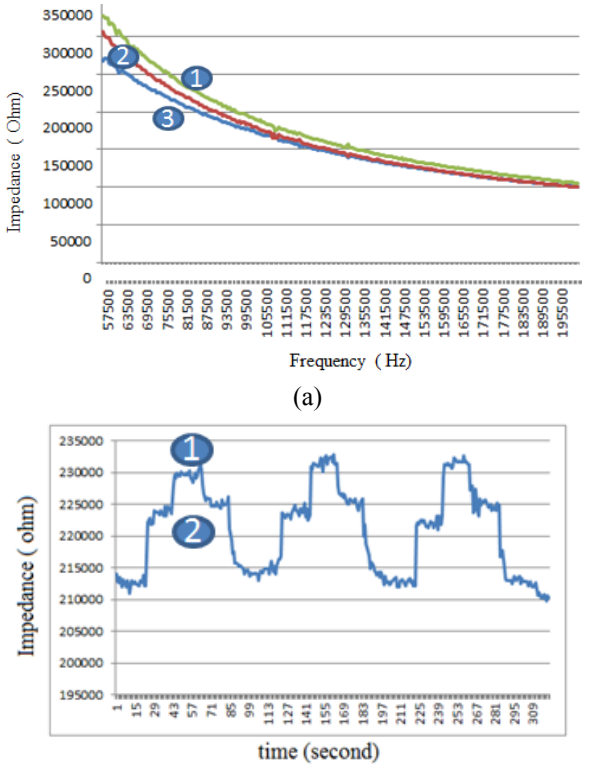

Fig. 8. Glucose measurement for (1) 2.5, (2) 1 mM and (3) 0.5 mM, mM glucose concentrations.: (a) Impedance vs. frequency (b) Impedance vs. time (at frequency around 87kHz).

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