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Short communication

Radio frequency based label-free detection of glucose

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ABSTRACT

We investigated the frequency based mediator-free glucose sensor in the radio-frequency (RF) range. Frequency dependent power signal showed clear dependence on the glucose concentration with free enzymatic condition. Also, the passive electrical components such as the resistance, inductance, shunt conductance, and capacitance were extracted based on the transmission line model for further analysis. These various parameters proposed by the signal processing provided more effective verification for instant multi-components in-situ readings without any added supporters. Additionally the residual signal (RS), impedance (Z), and propagation constant (γ) were also calculated from measured S-parameters for glucose analysis. These parameters basically showed amplitude variation and interestingly, some parameters such as inductance and impedance showed frequency shift of resonance dip. The results support that the frequency based sensing technique including the parameter based analysis can enable effective multi-dimensional detection of glucose. Moreover, this technique showed that glucose sensing is also possible over a diabetic patient's serum.

1. Introduction

Diabetes mellitus has been considered one of the highly injurious diseases to the human's body due to its complications. This disease is caused when human's body fails to regulate their glucose level, and thus it is out of normal range, the excess or the deficiency. This abnormal condition can be controlled using glucose sensor. Glucose sensor helps keep glucose level in the proper range by monitoring its level. Thus, for a couple of decades, many researchers' effort has been made on improving the glucose sensing performance based on the selective, direct detection of monosaccharides in the serum as well as devising various sensing techniques, such as electrochemical (Jian et al., 2009; Hao et al., 2004), optical (Paul et al., 2005; Chul et al., 2006; Xu et al., 2009), Raman spectroscopy (Karen et al., 2003; Jonathan et al., 2010), and I–V characteristic method (Lakshmi et al., 2010). Among those, the electrochemistry and the fluorescence resonance energy transfer have been thought of as the most fascinating and innovative detection methods. Especially, in the case of the electrochemistry, known as an enzyme-supported mechanism, it has shown the tremendous commercial prospects over a long period of time of the easy-to-use sensing technique.

This electrochemical technique has passed through second generations so far. In first generation, the oxygen was used as the cosubstrate, and for hydrogen peroxide, it serves as the product that is derived from the redox of cosubstrate in the process of a change of glucose to gluconic acid (Kathryn and Richard, 2010). In second generation, the enzyme is useful for selective detection of glucose molecule more than the mediator. However, there is one major problem coming from the structure of the enzyme. The chemical reaction actually occurs in the center of the bulky enzyme, so called Flavin–adenine–dinucleotide (FAD). This is a crucial factor to prevent the direct, smooth electron transfer to the working electrode (Joseph, 2008). Hence, this intrinsic, resistive nature of the enzyme results in the lack of the stability and electrical sensitivity.

Glucose sensing mechanism is currently approaching to the third generation that is based on direct sensing mechanism without any mediator or enzyme. This mechanism is highly beneficial for avoiding electrically being distorted (Jin et al., 2008; Xiao et al., 2012). As one of the highly influential candidates, Radio-frequency (RF) was adopted for enzyme free glucose detection. Until now RF has evidently been demonstrated in various bio sensing areas, such as antigen–antibody reaction (Hyun et al., 2008), metamaterial Hee et al. (2011), and microwave based glucose sensing mechanism (Buford et al., 2008). These techniques showed the mechanism directly interacting with glucose molecule, which is based on the capacitive and inductive change from the dipolar effect of the solvent. This leads to the scattering (S)-parameter change. In addition, S-parameter also has the advantage of separating it into various multi-dimensional

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parameters (Whan et al., 2010). Such an analytical component can effectively approach into bio-complexity analysis and then make steps further to advanced sensing of biological process. This multi-variable detecting method can contribute to broadening up selectivity of the target material.

In this study, by focusing on the precise and fast reading in the real time, *S*-parameter was introduced for easy and convenient measurement of target solution. This can minimize the scattering signal loss in lab-on-a chip scale. For the decomposing process, it can provide various parameters, and thus it can be more powerful technique on glucose sensing mechanism with the accurate verification. Thus, this is possible to read out complex composition. In the future, this method will develop for data-collected based verification collected from various measurements and speed up opening the in-situ multi-variables sensing.

2. Material and methods

2.1. Structural design of sensing device

In order to minimize the signal loss, Silicon (Si)/silicon oxide (SiO_2, 500 nm) substrate was prepared first for glucose sensing device, and then Ground-Signal-Ground (GSG) pattern was deposited by the standard photolithography using titanium (Ti, 10 nm)/gold (Au, 500 nm), as shown in Fig. 1(a). This GSG pattern is consists of two kinds of electrodes. One is a pair of transmission electrodes (*S*), which shapes V-notch to minimize signal loss on transmission line (Fig. 1(b)), and the other is a pair of ground electrodes (*G*), the symmetrical shape to each other (Fig. 1(c)).

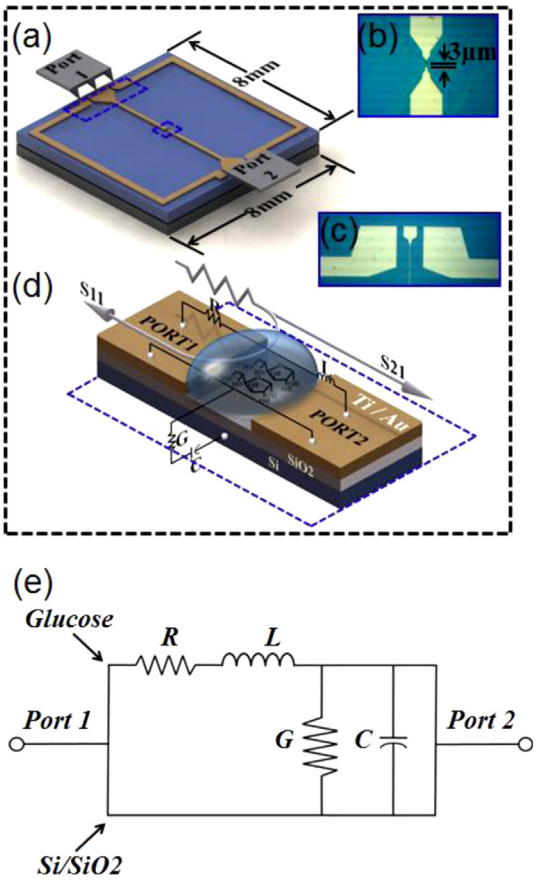

Fig. 1. Schematic diagrams of (a) GSG electrode for frequency based measurement. (b) The optical microscope image of detection area and (c) probing area. (d) The cross-sectional view of glucose detection region and (e) the equivalent circuit involving *R*, *L*, *G* and *C* in between two ports after glucose solution was dropped.

Fig. 1(d) is a magnified view at the center of the signal electrodes, and the mechanism about detecting glucose molecules between two ports is schematically presented with *S*-parameter and its decomposed parameters, the resistance (*R*), the inductance (*L*), the conductance (*G*), and the capacitance (*C*).

2.2. Electrical sensing mechanism

S-parameter was measured by GSG probing with a network analyzer (E5071C). *S*-parameter, "S_{ij}" can be defined as the ratio between the incident voltage to port '*j*' and the voltage measured at port '*i*', providing four components, S_{11}, S_{21}, S_{12}, and S_{22}. Because this mechanism is based on a symmetric two port network ($S_{11}=S_{22}$ and $S_{21}=S_{12}$), all the data of *S*-parameter can completely be analyzed by plotting the reflected signal (S_{11}) and transmitted signal (S_{21}). Because of the linear electrical network of *S*-parameter, it can be also separated into various components, *RLGC*. As shown in Fig. 1(e), these components can be expressed using the equivalent circuit. More specifically, *R* and *L* are closely related to the transmission line on the sensing chip, and *G* and *C* are indirectly affected by sensing property through the effects of dielectric on target material.

3. Results and discussions

3.1. Characteristic of glucose molecule

Glucose solution was analyzed by three kinds of measurements. First, in order to get the structural information of glucose molecule, glucose solution (1 mM) was dropped and dried on Si wafer, and then measured by X-ray diffraction (XRD). Fig. S1 (a) results from XRD spectrum, which presents 10–90° in angle. In the spectrum, three kinds of peaks are depicted at around 37.3°, 65.7° and at 68.9°. The sharply rising peak at around 68.9° is derived from the silicon oxide substrate, and the other two with high intensity at around 37.3° and 65.7° means the crystallized solution, which is directly related to aqueous molecule bonded to ionized glucose molecule (Benjamin and Walter, 1956).

Second, UV/visible absorption spectrum of the glucose solution was also measured in the range of 5 mM to 1 M in order to analyze the optical property of glucose molecule, as seen in Fig. S1(b). For the absorption measurement, the wavelength was set up from 250 nm to 900 nm. Glucose solution presents the maximum absorbance peak at around 280 nm (the inset of Fig. S1(b)), and for each values, it is in series 0.207, 0.195, 0.188, 0.179, 0.124 and 0.083. The results have the linear decreasing trend with increase of glucose concentrations. This is because of its intrinsic property to transmit more and absorb less than water-based PBS solution (Harold and Martha, 1959; Matthias et al., 1995).

The last characteristic is the viscosity of the target material when adding the glucose molecule in the solvent. As shown in Fig. S1(c), the sample is gradually viscid with an increasing amount of glucose molecule in the ranging from 5 mM to 1000 mM. This is one of a crucial factor to affect a decreasing, electrical performance of glucose solution.

3.2. I–V measurement of glucose solution

To measure current–voltage (*I*–*V*) curve, which will be used to support RF characteristic, we prepared the devices on three kinds of conditions, the open, deionized (DI) water, phosphate buffer solution (PBS) and 1 mM of glucose in PBS, as shown in Fig. 2 (a) and (b). Fig. 2(a) presents the results for all four conditions. In open, no any electrical signal occurs, but when DI was dropped on between the signal electrodes, electrons start flowing through