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Quantitative detection of glucose level based on radiofrequency patch biosensor combined with volume-fixed structures

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ABSTRACT

A concept for characterizing a radiofrequency (RF) patch biosensor combined with volume-fixed structures is presented for timely monitoring of an individual's glucose levels based on frequency variation. Two types of patch biosensors—separately integrated with a backside slot (0.53 µL) and a front-side tank (0.70 µL) structure—were developed to achieve precise and efficient detection while excluding the effects of interference due to the liquidity, shape, and thickness of the tested glucose sample. A glucose test analyte at different concentrations (50–600 mg/dL) was dropped into the volume-fixed structures. It fully interacted with the RF patch electromagnetic field, effectively and sensitively changing the resonance frequency and magnitude of the reflection coefficient. Measurement results based on the resonance frequency showed high sensitivity up to 1.13 MHz and 1.97 MHz per mg/dL, and low detection limits of 26.54 mg/dL and 15.22 mg/dL, for the two types of patch biosensors, respectively, as well as a short response time of less than 1 s. Excellent reusability of the proposed biosensors was verified through three sets of measurements for each individual glucose sample. Regression analysis revealed a good linear correlation between glucose concentrations and the resonance frequency shift. Moreover, to facilitate a multi-parameter-sensitive detection of glucose, the magnitude of the reflection coefficient was also tested, and it showed a good linear correlation with the glucose concentration. Thus, the proposed approach can be adopted for distinguishing glucose solution levels, and it is a potential candidate for early-stage detection of glucose levels in diabetes patients.

1. Introduction

Aqueous glucose solutions play a fundamental role in many biomedical processes in various chemical and biological systems. Therefore, sensitive detection of glucose concentration in water may be useful for studying biomedical properties (Wang, 2001; Kim, Dhakal et al., 2015; Yilmaz et al., 2014). Diabetes mellitus, commonly referred to as diabetes, is a disease caused by a metabolic disorder characterized by fluctuations in the blood glucose level outside the normal range. Such fluctuations result from either insufficient insulin production by the beta cells in the pancreas or the body's resistance to the action of insulin. For early detection and treatment of diabetes, it is important to monitor the glucose level of an individual suspected of having the disease (Aloraefy et al., 2014; Kim et al., 2013; Ricci et al., 2005; Hu et al., 2012; Abdalla et al., 2010).

Recently, biosensor design based on radiofrequency (RF) techniques has attracted considerable attention, and wide-ranging biomedical applications have been researched, such as bimolecular binding (Lee et al., 2012), DNA sensing (Lee et al., 2010), human cell dielectric spectroscopy (Dalmay et al., 2009), and stress biomarker characterization (Lee et al., 2013). Based on the interaction between microwave electromagnetic fields and the concentrations or physical characteristics of tested samples, the RF biosensor mechanism can be investigated through changes in the equivalent inductance and capacitance, center frequency, or magnitude of S-parameters. Moreover, the RF biosensor is considered as a promising and competitive candidate for implementing third-generation glucose biosensors for mediator-free glucose detection (Adhikari and Kim, 2016) owing to its advantages of easy fabrication, quick response time, high selectivity, and tolerable linearity. Furthermore, precise and efficient detection with a fixed testing area, stable shape, and quantified and minimized volume of testing samples should also be considered to prevent interference in the measurement tolerance by the liquidity, shape, and thickness of the tested sample (Ouyang et al., 2007; Siddiqui et al., 2012; Mirasoli et al., 2013; Rosa et al., 2015). Because the biosensor RF performance is closely related to the effective dielectric constant of the glucose sample, it is severely affected by the thickness and volume of the tested sample. Therefore, quantitative detection is crucial. During each test, the

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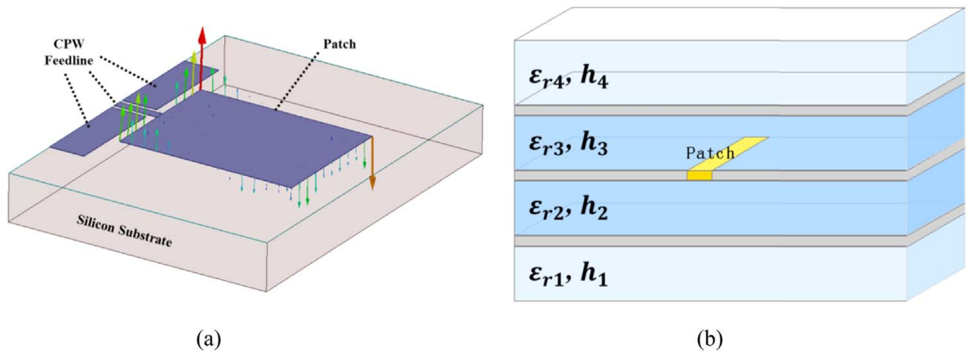

Fig. 1. (a) Electric field of the patch at resonance frequency and (b) cross-sectional view of the proposed patch biosensor with multiple layers.

sample should be stable, i.e., thickness-, volume-, and location-fixed, identical to the previous measurement condition.

In this work, we propose precise and quantitative detection of glucose levels on the basis of RF patch biosensor combined with volume-fixed structures. Two types of RF biosensors are developed: one has a backside slot structure with a volume of approximately 0.53 μL (2.5 mm × 2.0 mm × 0.106 mm), and the other has a front-side tank structure with a volume of approximately 0.70 μL (2 mm × 3.3 mm × 0.106 mm). Less than 1 μL of the testing sample is required, resulting in minimal consumption of the sample. Further, different concentrations of glucose can generate different effective dielectric constants; therefore, the electromagnetic field of the patch can be interfered by closely contacted samples. The variations in the resonance frequency and magnitude of the reflection coefficient acquired for various glucose concentrations ranging from 50 mg/dL to 600 mg/dL are efficiently characterized for glucose-level detection. Furthermore, to increase the patch biosensor sensitivity, the backside slot and front-side tank are constructed to be significantly larger than the entire patch in order to ensure that the patch will be fully covered by the tested glucose sample and the electromagnetic field will be fully engaged in the interaction accordingly. Moreover, a remarkably quick response time of less than 1 s can be realized because of the close contact as soon as the tested glucose is dropped into the volume-fixed structures. Excellent reusability of the proposed biosensor is verified through measurements conducted three times for each glucose sample. The final measurements of the patch biosensors with backside slot and front-side tank structures indicated sensitivities of 1.13 MHz and 1.97 MHz (with a variation of 1 mg/dL in the testing glucose), detection limits of 26.54 mg/dL and 15.22 mg/dL, and compact sizes with total volumes of 2.5 mm × 2.5 mm × 0.4 mm and 2.6 mm × 3.5 mm × 0.5 mm, respectively. Thus, the proposed RF methodology is applicable to advancing the field of glucose sensing.

2. Materials and methods

2.1. Patch biosensor operating mechanism

We selected a rectangular patch, which is the most widely employed configuration and is easy to analyze using transmission-line models, fed by a coplanar waveguide (CPW) for the biosensor application in the Ku band for ensuring minimal glucose sample consumption. The patch dimensions are finite along the length and width, and the electromagnetic fields at the patch edges undergo fringing. Therefore, considering the fringing effects, the resonance frequency of the proposed patch at dominant TM_{010} mode can be deduced as

$$f_{TM_{010}} = \frac{c}{2L_{eff}\sqrt{\varepsilon_{reff}}}, \quad (1)$$

$$L_{eff} = L + 2\Delta L, \quad (2)$$

where c is the speed of light in free space, L_{eff} and ε_{reff} are the effective length and dielectric constant of the patch, respectively, L is the patch length, and ΔL is the extended length along the patch owing to the fringing effect. A well-known and practical approximate relation for the normalized extension of the length, ΔL, is employed; it is given by (Balanis, 2005)

$$\Delta L = 0.412h\frac{(\varepsilon_{reff}+0.3)(\frac{W}{h}+0.264)}{(\varepsilon_{reff}-0.258)(\frac{W}{h}+0.8)}, \quad (3)$$

where W is the patch width and h is the substrate height. Based on Eqs. (1)–(3), the resonance frequency at dominant TM_{010} mode can be reproduced as

$$f_{TM_{010}} = \frac{2c\varepsilon_{reff}^{-\frac{1}{2}}}{L+0.824h(\varepsilon_{reff}+0.3)(\varepsilon_{reff}-0.258h)^{-1}(W+0.264h)(W+0.8h)^{-1}}. \quad (4)$$

When the length, width, and substrate height are fixed, the resonance frequency of the proposed patch is proportional to the effective dielectric constant, ε_{reff}. Further, the proposed patches are designed on the basis of Eqs. (1)–(4), and they operate at Ku band with a CPW feedline. The High Frequency Structure Simulator (HFSS) was employed to simulate the CPW-fed patch with volume-fixed structures. Finally, a miniaturized chip size as well as minimal volume of the volume-fixed structures can be achieved.

2.2. Patch biosensor permittivity analysis

As shown in Fig. 1(a), the electric field of the CPW-fed patch is demonstrated at the resonance frequency. It can be observed that the electric field appears perpendicular to the patch surface, and such an electric field could be affected by another dielectric material closely placed above or below the patch surface, resulting in a different ε_{reff} value. In this work, glucose samples are applied as the dielectric material. The proposed patch biosensor can be regarded as a multilayer structure considering of air, a microstrip pattern, a silicon substrate, and a glucose layer. For quasi-static analysis of multilayer microstrip transmission lines having two or more dielectric interfaces, the variation method is found to be the simplest (Bahl, 2003). Fig. 1(b) shows cross-sectional views of the proposed patch biosensor with multiple layers.

For the patch biosensor with a backside slot structure—corresponding to a two-layer open-microstrip mechanism—$h_3 = 0$ and $h_4 = \infty$, where ε_{r1}, h_1 and ε_{r2}, h_2 represent the dielectric constant and thickness of the glucose layer and silicon substrate, respectively. The effective dielectric constant can be derived as

$$\varepsilon_{patch\ biosensor\ with\ backside\ slot} = \frac{C}{C_a}, \quad (5)$$