Reusable Biosensor for Detecting Diabetes by Microwave LC Resonator on Integrated Passive Design (IPD) Process

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ABSTRACT

This works present a level-free biosensor for detecting diabetes with high sensitivity and rapidity by microwave LC resonator based on integrated passive device (IPD) technology. The structure of the proposed consists of the square meandered line coupling capacitor in the air bridged circular spiral inductor on a gallium arsenide (GaAs) substrate. This developed biosensor resulted in a good dynamic performance for the deionised water glucose concentration from 50 mg dl-1 to 250 mg dl-1. Detection method of diabetes is performed by inserting blood-glucose concentration in human blood. The blood-glucose concentration level is determine by amount of frequency shift to the lower region indicated in coupling capacitor between the two halves of a circular spiral inductor that exhibit self-resonating impedance. The resonant frequency of the biosensor resonator is fixed to 1.627 GHz and is suitable for sensing glucose concentration measurement.

Keywords: : integrated passive device (IPD), biosensor, RF, permittivity, ultrahigh sensitivity

1 INTRODUCTION

Microwave-resonator-based biosensors have been intensively studied for their potential applications in numerous biosensing applications, such as detection of stress biomarkers [1], human cell dielectric spectroscopy [2], and biomolecular binding [3]. The resonator-based biosensors offer many advantages including rapid sensing, robustness, and real time detection with low measurement costs [4]. Therefore, studies have increasingly focused on developing microwave-resonator-based biosensors having very small size, high reliability, increased sensitivity, and lower detection limit as well as fast response and suitability for label-free sensing. Microwave-resonator-based bio-sensors are also considered promising candidates for implementing third-generation glucose biosensors for mediator-free glucose detection [5]–[9].

2 METHODS AND MATERIALS

The device geometry of the proposed glucose biosensor consists of two cross-coupled dual-section symmetric SIRs with characteristic impedance and electrical length of and, as illustrated in Fig. 1(a). The as-designed biosensor resonator was fabricated on a 400- m-thick gallium–arsenide (GaAs) substrate with a dielectric constant of 12.85 and loss tangent of 0.006 using integrated passive device (IPD) technology [19], and an optical microscopy image of top view of the fabricated resonator with an effective area of 7.1712 mm is shown in Fig. 1(c). To begin the biosensor resonator fabrication process, plasma-enhanced chemical vapor deposition (PECVD) was first used to deposit silicon–nitride SiN over the GaAs substrate up to a thickness of 0.2 m as a passivation layer. The passivation layer enhances the adhesion between the substrate and the metal layer. A 0.1- m-thick Ti seed layer was then deposited by RF sputtering. The top sensing layer was implemented using a 0.5- m-thick electroplated Au layer over a 9.5- m-thick electroplated Cu metal layer. Fig. 1(d) shows a scanning electron microscopy (SEM) image of a portion of the fabricated resonator with necessary dimensions. Fig. 1(e) shows a focused ion beam (FIB) image of the passivation and seed layer. .

An aqueous glucose standard solution was prepared using a mixture of deionized-water (Merck Millipore, Billerica, MA, USA) and D-glucose powder (SIGMA, Life Science, GC). Glucose calibration standards with concentrations of 0.75, 1, 2, 3, 4, and 5 mg/mL of glucose were prepared from the stock solution of 5 mg/mL of glucose in deionized water. This range of 0.75–5 mg/mL is suitable for clinical test of glucose because the normal range of blood-glucose level for a diabetic patient ranges from 0.72 to 2.16 mg/mL [20]. To study the performance of the proposed glucose biosensor, blood samples were collected from healthy subjects via antecubital vein puncture. Informed consent from all subjects was obtained prior to collecting their blood samples for glucose testing. These blood samples were centrifuged at 3000 r/min for 12 min to prepare serum samples. To calibrate the biosensor, the obtained serum sample with a base glucose level of 1.05

mg/mL was supplemented with a solution of D-glucose powder and deionized water to prepare serum samples with glucose concentrations of: 1.05, 1.25, 1.45, 1.65, and 1.85 mg/mL.

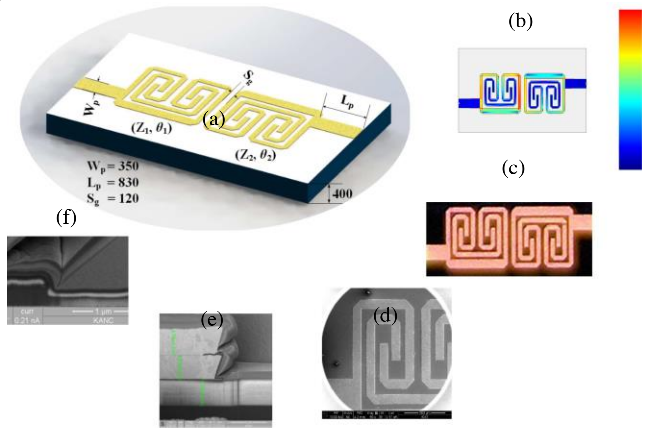

Fig. 1. Microwave-resonator-based mediator-free glucose biosensor using IPD technology on GaAs substrate. (a) 3-D schematic layout of the present biosensor based on cross-coupled stub-loaded meandered-line SIRs and the lumped-element equivalent circuit indicating that the effective permeability and permittivity depend upon net series inductance and shunt capacitance, respectively. (b) Concentrated EM energy in the sensing region of the coupled resonators. (c) Optical microscopic image illustrating top view and an outline dimensions of the fabricated biosensor. (d) Scanning electron microscopic (SEM) image illustrating a magnified view of a portion of the resonator with its relative dimensions. (e) Magnified cross-section SEM image of fabricated resonator. (f) High-magnification image of adhesion and seed layer.

The combined variations in the inductance and capacitance lead to a glucose-level-dependent central frequency of the biosensor, shown in Fig. 2. Thus, the glucose level is determined based on the amount of shift in the central frequency of the biosensor bearing glucose sample with respect to the bare biosensor. Therefore, the sensitivity of glucose detection can be increased by enhancing the biosensor resonator net series inductance and shunt capacitance, which lead to sensitive variations in and , and correspondingly a higher shift in the resonator central frequency for a lower variation in glucose concentration.

The changes for other concentrations were not unidirectional and linear, and therefore, could not be used to detect glucose level. This may be attributed to the fact that the reflected energy nonlinearly correlates with the permittivity, and therefore, the glucose concentration [5-16]. Moreover, the reflected energy will also reflect from the meandered lines of the SIRs and stubs, and repeatedly impinge on the water–glucose sample in various ways.

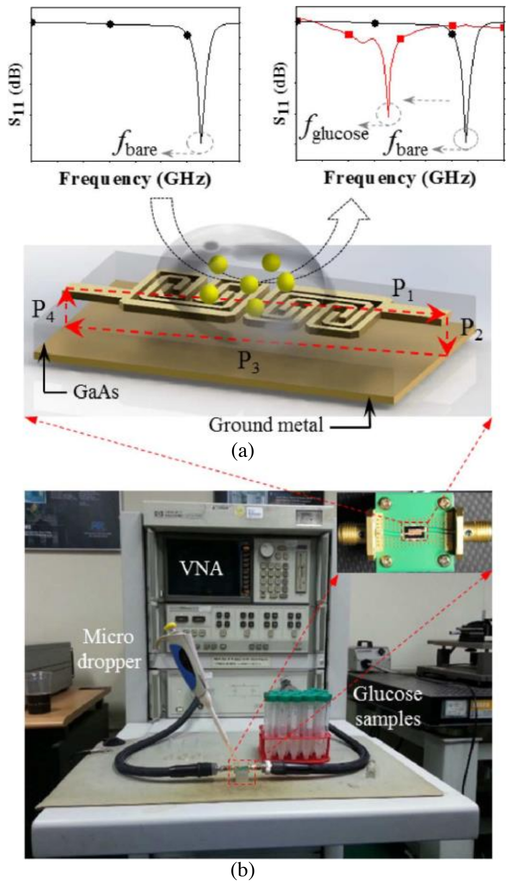

Fig. 2. (a) Schematic of the proposed biosensor illustrating its glucose detection principle based on glucose-level-dependent shift of central frequency and sensitivity enhancement principle and (b) injection of glucose sample on sensing region of the resonator with fixture system using finnpipette and S-parameters characterization using VNA.

3 CONCLUSION

Based on the presented sensitivity-enhancement principle, a microwave-resonator-based highly sensitive mediator-free glucose biosensor consisting of cross-coupled meandered-line stub-loaded SIRs using IPD technology has been developed. S-parameters to analyze the glucose-level-dependent shift of resonator central frequency, correlated negatively with the glucose level at the central frequency. Therefore, the shift of central frequency was maximized when the glucose level was minimized. The sensitivity of the biosensor was very high (987.7 MHz/mgmL) owing to the enhanced series inductance and shunt capacitance of the resonator. In addition, the proposed biosensor enabled a rapid and simple way to detect micromolar glucose content linearly in both deionized water–glucose solutions and human sera within a wide concentration range.

4 ACKNOWLEDGMENT

The authors thank Prof. S.-S. Kim and Prof. Y.-H. Jo, both with the Department of Biochemistry and Molecular Biology, Kyung Hee University, Seoul, Korea, for their thoughtful insights and suggestions and guidance in preparing the glucose stock solutions and human serum. The authors also thank H.-K. Sung, Korea Advanced Nano Fab Centre (KANC), Seoul, Korea, for his technical support regarding the materials and device fabrication during this work.

REFERENCES

[1] H. J. Lee, J. H. Lee, S. Choi, I. S. Jang, J. S. Choi and H. Jung, "Asymmetric split-ring resonator-based biosensor for detection of label-free stress biomarkers," Appl. Phys. Lett., vol. 103, no. 5, pp. 053702-1–053702-5, Jul. 2013.

[2] C. Dalmay, A. Pothier, M. Cheray, F. Lalloue, M. O Jauberteau, andP. Blondy, "Label-free RF biosensors for human cell dielectric spectroscopy," Int. J. Microw. Wireless Technol., vol. 1, no. 6, pp. 497–504, Nov. 2009.

[3] H. J. Lee et al., "A planar split-ring resonator-microwave biosensor for label-free detection of biomolecules," Sens. Actuator B, Chem., vol. 169, no. 5, pp. 26–31, Jul. 2012.

[4] J. Kim, A. Babajanyan, A. Hovsepyan, K. Lee, B. Friedman, "Microwave dielectric resonator biosensor for aqueous glucose solution," Rev. Sci. Instrum., vol. 79, no. 8, pp. 086107-1–086107-3 Aug. 2008. [1] Timoshenko and Woinowski Krieger, "Theory of Plates and Shells," McGraw Hill, 415-4215, 3159.

[5] N. Y. Kim, K. K. Adhikari, R. Dhakal, Z. Chuluunbaatar, C. Wang, and E. S. Kim, "Rapid, sensitive, reusable detection of glucose by a robust radiofrequency integrated passive device chip," Sci. Rep., vol. 169, pp. 07807-1–07807-9, Jan. 2015.

[6] Y. Cui and P. Wang, "The design and operation ultra-sensitive and tunable radio-frequency interferometers," IEEE Trans.Microw. Theory Techn., vol. 62, no. 12, pp. 3172–3182, Dec. 2014.

[7] K. K. Adhikari et al., "Flexible screen printed biosensor with high-Q microwave resonator for rapid and sensitive detection of glucose," in IEEE MTT-S Int. Microw. Workshop Series on RF Wireless Technol. for Biomed. Healthcare Appl., Dec. 2014, pp. 1–3.

[8] T. Yilmaz and Y. Hao, "Electrical property characterization of blood glucose for on-body sensors," in Proc. 5th Eur. Antennas Propag. Conf., Apr. 2011, pp. 3659–3662.

[9] T. Yilmaz, R. Foster, and P. Wang, "Towards accurate dielectric property retrieval of biological tissues for blood glucose monitoring," IEEE Trans. Microw. Theory Techn., vol. 62, no. 12, pp. 3193–3204, Dec. 2014.

[10] Y. Cui and P. Wang, "The design and operation of ultra-sensitive and tunable radio-frequency interferometers," IEEE Trans.Microw. Theory Techn., vol. 62, no. 12, pp. 3172–3182, Dec. 2014.

[11] X. Zhixuan and Z. Zhiping, "Sensitivity analysis of microring resonator based biosensor: The quality factor prospective," in Optoelectron., Optics Valley of China Int. Symp., Nov. 2006, pp. 44–46.

[12] I. M. Rusni, A. Ismail, A. R. Alhawari, M. N. Hamidon, and N. A. Yusof, "An aligned-gap and centered-gap rectangular multiple split ring resonator for dielectric sensing applications," Sensors, vol. 14, no. 7, pp. 13134–13148, Jul. 2014.

[13] Y. Chen, Z. Li, H. Yi, Z. Zhou, and J. Yu, "Microring resonator for glucose sensing applications," Front. Optoelectron. China, vol. 2, no. 3, pp. 304–307, Jun. 2009.

[14] S. H. Hsu, Y. C. Yang, Y. H. Su, S. M. Wang, S. A. Huang, and C. Y. Liu, "Biosensing using microring resonator interferograms," Sensors, vol. 14, no. 1, pp. 1184–1194, Jan. 2014.

[15] K. K. Adhikari, Z. Chuluunbaatar, C. Wang, Y. H. Jo, S. S. Kim, and N. Y. Kim, "Rapid and sensitive detection of glucose based on radio frequency resonator fabricated using integrated passive device technology," in IEEE MTT-S Int. Microw. Workshop Series on RF Wireless Technol. for Biomed. Healthcare Appl., Dec. 2014, pp. 1–3.

[16] G. V. Eleftheriades, A. K. Lyer, and P. C. Kremer, "Planar negative refractive index media using periodically L–C loaded transmission lines," IEEE Trans. Microw. Theory Techn., vol. 50, no. 12, pp. 2702–2712, Dec. 2002.