A Label-Free Low-Cost Radio Frequency Driven Noninvasive Lab-on-Chip System for Creatinine Detection

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***Abstract*—This paper illustrates a label-free, low-cost, fast detection of creatinine using a noninvasive lab-on-a-chip (LoC) Interdigitated capacitor (IDC) based sensor. Creatinine is a metabolic product of creatine phosphate in muscles, which provides energy to muscle tissues. The detection is done on an IDC made of copper (Cu) metal over an FR4 substrate. The sensor has been designed using a high-frequency structure simulator (HFSS) tool. Then the design is fabricated over the FR4 printed circuit board (PCB) and tested using a Vector Network Analyzer (VNA). The creatinine sample under the test is confined using a Polylactic Acid (PLA) wall attached to the sensor. A 52 MHz difference is observed between the simulated and experimental operating frequencies. The principal idea implemented in the biosensor design is to track the shift in the operating frequency in the presence of different concentrations of creatinine diluted in water and compare it with the operating frequency of the sensor with water as a reference. The testing is done in the medical range of 0.5 mg/dL to 2 mg/dL of creatinine solution.**

***Keywords*— Interdigitated capacitor (IDC), Lab on Chip (LoC), Creatinine, Radiofrequency (RF), High-frequency structure simulator (HFSS), Vector Network Analyzer (VNA)**

I. Introduction

The increasing demand for biomedical diagnosis methods in research requires low-cost, fast, highly sensitive, and easy-to-use detection methods [1,2,3,4]. Among the different chemical compounds in the human blood and urine, creatinine (2- amino-1-methyl-5H-imidazol-4-one) $C_4H_7N_3O$ plays an important role in kidney function [3,4]. Therefore, Creatinine has become the preferred marker for renal dysfunction. It has been considered as an indicator of renal function specifically after dialysis, thyroid malfunction, and muscle damage [5]. The typical range of serum creatinine for adult men is 0.74 to 1.35 mg/dL, and for adult women: 0.59 to 1.04 mg/dL. The level of creatinine reaches >1000 µM in serum during renal, thyroid, and kidney dysfunction or muscle disorder [4-8].

Several conventional methods such as colorimetric, spectrophotometric, and chromatographic are available for the determination of creatinine [7-10]. However, these methods have some drawbacks such as being time-consuming, the requirement of sample pre-treatment, high-cost instrumental set-up, and the skilled person requirement to operate. Additionally, they are often not reusable and require expensive fabrication and synthesis methods. Therefore, there is a need to explore possible alternatives that can tackle the challenges faced by these traditional techniques.

The development of an ideal creatinine biosensor is a challenging task for the medical industry. Different techniques have been used in the construction of creatinine biosensors. Moreover, creatinine biosensors can be classified as electrochemical sensors, immunosensors, conductimetric biosensors, chemical sensors, nanomaterials-based electrochemical biosensors, and enzyme nanoparticles (ENPs) based biosensors [11]. However, such methods require expensive setup, chemical preparation, labelling and are less sensitive.

Radiofrequency (RF) based sensing has emerged as a suitable alternative. The basic principle lies in the dielectric features of many samples which are unique across the microwave spectrum and offer a wealth of possibilities for analysis techniques. [12-18].

These sensors study the interaction of Electromagnetic (EM) waves with matter. The response of the sensor changes in the presence of different samples due to the unique interactions between the EM waves and the sample. They study the variation in different electrical and magnetic quantities such as permittivity, permeability, and conductivity. Subsequently, the variation in these parameters is mapped to perform qualitative and quantitative analysis. RF sensing offers fast and facile solutions. It involves highly simplified procedures for both sample preparation and testing, most of these techniques are also label-free. The need for sophisticated instrumentation and lab facilities is also reduced. Moreover, a minute volume of liquid is required for analysis [19-21].

This paper shows the potential application of interdigitated-based capacitance sensors in the detection of creatinine concentrations. We have made solutions of different concentrations of creatinine which is in the medical interest range of the human body i.e., 0.5 mg/dL to 2 mg/dL with an interval of 0.5. For each concentration, a sufficient amount of 400 μL volume of creatinine sample to cover the IDC fingers has been tested over the sensor via VNA.

II. Materials And Methods

A. Design and Fabrication of an Interdigitated Capacitor

IDC has interdigitated fingers-like electrodes as two ports of the capacitor, as shown in Fig.1. Unlike uniformly distributed electric fields in parallel plate capacitors, the electric field of an IDC starts from one group of signal electrodes having higher potential, coming up and penetrating the material under test (MUT), then down to another group of ground electrodes.

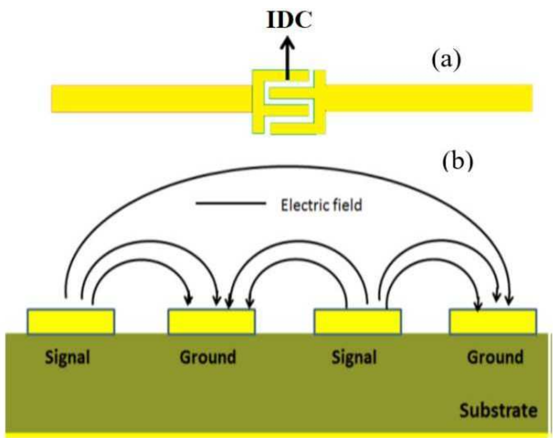

Fig. 1. (a) Top view of IDC (b) E-Field distribution across IDC.

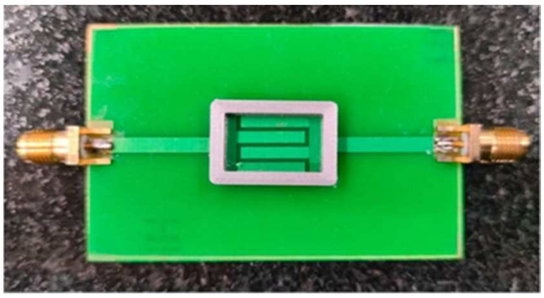

Fig. 2. Fabricated Interdigitated Capacitor (IDC) sensor with PLA wall around the fingers.

The sensor is designed using HFSS and operates at 5.19 GHz. It is built using FR4 PCB as a substrate material of 1.6 mm thickness, with a Cu coating of 0.035 mm at the bottom acting as a ground. The IDC sensor on top which is the radiating patch is made in 0.035 mm of Cu thickness. The resonator is 2.5 mm wide and 19 mm long. The IDC has four fingers, and they are each 12.7 mm long, and 1.9 mm wide with a gap of 0.76 mm between them. The simulated structure has been fabricated over the FR4 substrate and has been covered with a green mask of epoxy resin to protect the Cu from oxidation leaving the contact 4 mm from each side for connections as shown in Fig. 2. A PLA wall-printed using a 3-D printer is attached around the sensor to restrict the sample under test (SUT).

When designing IDC, the dielectric material selection and choosing its specified range is crucial. Like many capacitors, IDC can have sensitive performance to temperature changes. In applications with extensive temperature ranges, the capacitance value alters, which might be a drawback. To avoid this issue, we strictly maintained the room temperature where the experiment was performed.

B. Sample Preparation

A 400 mg creatinine brought from SRL [for molecular biology, 99%, MW 113.12] is dissolved in 100 mL of de-ionized (DI) water to make 400 mg/dL creatinine stock solution {CS400}, which is diluted (V/V) in DI water 20 folds to prepare 20 mg/dL creatinine stock {CS20}.

Then CS20 is further diluted (V/V) in DI water to target concentrations range. The creatinine powder and the stocks were store at 8 °C. We have made a solution of different concentrations of creatinine which lies in the blood range in the human body. In our experiment, it is 0.5 mg/dL to 2 mg/dL with an interval of 0.5 mg/dL.

C. Experimental Setup

A complete experimental setup using two-port VNA is shown in Fig. 3. For handling the SUT, the PLA wall was fixed around the IDC fingers which keeps the liquid sample that will be dropped inside the chamber. To fix and hold the sensor, a PCB holder of PLA material was also fabricated using a 3D printer to achieve stable readings.

Fig. 3. Experimental setup (VNA model N9918A, Keysight Technologies)

Additionally, the holder features two via holes for SMA cables one end of the cable is connected to the sensor, and the other end is connected to VNA via holes. To prevent contamination during the experiment, the upper portion of the holder has been covered with an acrylic sheet that prevents human errors, when the sample is dropped, ensuring that high accuracy is maintained throughout the experiment. The entire setup provides exceptional stability during the experiment.

III. RESULTS AND DISCUSSION

The experimental and simulated operating (resonant) frequencies in the air are shown in Fig. 4. The experimental operating frequency is 5.138 GHz; however, the simulated value was 5.19 GHz the small variation of 52 MHz is because of some variation during the fabrication steps.

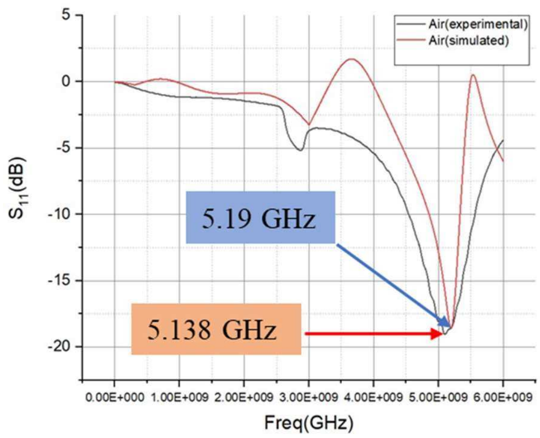

Fig. 4. Reflection coefficient (S_{11}) versus operating frequency of simulated and experimental values of the IDC structure.

The 400 μL solution of each concentration of creatinine has been taken through a micropipette and dropped directly inside the PLA chamber, which is over the sensing region of the IDC. According to the experiment, Fig.5 shows the operating frequency shift for each concentration with the operating frequency in water as a reference.

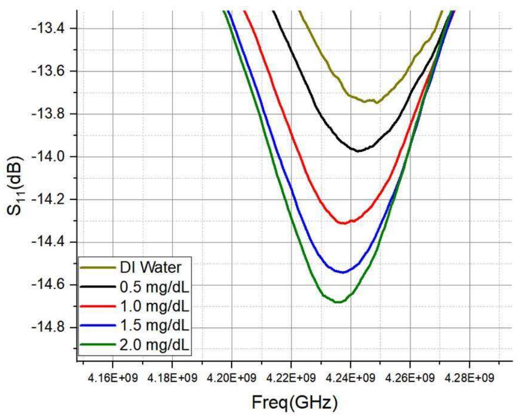

Fig. 5. S_{11} versus operating frequency for water and various concentrations of creatinine.

As the concentration is raised, the resonance frequency peak for creatine with respect to water shifts to the left. The results are shown in Table I which clearly shows the utility of RF biosensors for creatinine detection.

TABLE I. RESONANCE FREQUENCY PEAK VALUE OF WATER AND DIFFERENT CONCENTRATION OF CREATININE

The sample under test (SUT) volume of 400 μL	Operating frequency (Peakvalue)
DI Water	4.246 GHz
0.5 mg/dL creatinine	4.242 GHz
1.0 mg/dL creatinine	4.238 GHz
1.5 mg/dL creatinine	4.236 GHz
2.0 mg/dL creatinine	4.235 GHz

CONCLUSION

This study investigate the use of an RF biosensor-based IDC sensor to detect creatinine concentration in the medical interest range. Therefore, over the IDC, different concentrations of creatinine in the range of 0.5 mg/dL to 2 mg/dL have been examined. Each concentration exhibits a shift in the resonant frequency value concerning the water resonant frequency as a reference. The simulated and experimental operating frequencies differ by 52 MHz, which may be the result of fabrication-related variations. Additional safety measures might be implemented to maintain a clean environment for the best reading conditions. In the future, the sensitivity of biosensors can be improved by altering the dimensions and design. The 400 μL of sample volume used by the sensor will eventually be aimed at reducing. The immense potential of RF-based sensors in the biomedical field demonstrated by this work.

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