A Label-Free Biosensing Platform Using a PLL Circuit and Biotin-Streptavidin Binding System

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***Abstract*—This paper proposes a novel RF biosensor that utilizes a frequency synthesizer associated with a microstrip open-loop resonator for label-free biomolecular detection. The RF biosensor consists mainly of a resonance-assisted transducer and a phase locked loop (PLL) circuit. In this work, the performance of the RF biosensor is validated using the well-known biotin-streptavidin binding system. When biotin is bound to streptavidin, the input impedance of the resonator is varied, resulting in a change in the oscillation frequency. The concentration of the streptavidin is ultimately detected by a voltage signal of the PLL's loop filter with simple measurement equipment. According to the experimental results, the RF biosensor has revealed excellent sensitivity ($\sim 61\ \mathrm{kHz/ngml^{-1}}$) and a low detection limit ($\sim 1\ \mathrm{ng/ml}$), as well as a rapid response. These results demonstrate that the RF biosensor can be an effective sensing platform for label-free detection in a biomolecular binding system.**

***Index Terms*—Biomolecular RF sensor, biotin, dip-and-dry technique, microstrip open-loop resonator, phase locked loop (PLL) synthesizer, streptavidin.**

I. Introduction

In recent years, biosensors for biomolecular recognition have been studied in relation to resonance-optical systems. These types of studies have focused on whispering-gallery microcavities [1], photonic crystals [2], metamaterials [3], and other areas [4]. The resulting resonance-based sensing systems ensured very high levels of sensitivity in an *in vitro* environment [4]. However, the related equipment and fabrication procedures are often costly, time-consuming, and labor-intensive. In addition, to enhance the sensitivity and limit of detection, labeling techniques, such as the use of fluorescent dyes, gold and magnetic nanoparticle, are frequently used [5]–[7]. These biosensing techniques, however, can degrade the pure biomolecular binding system. From these reasons, the development of new biosensing platform is very challenging and of high interest, especially for the early diagnosis of and personalized treatments for various diseases.

Recently, mobile-linked wireless sensing platforms are now receiving considerable attention as part of the effort to realize a ubiquitous healthcare network system [8], [9]. This work demands a robust and miniaturized sensing platform for highly sensitive, label-free, rapid response, non-invasive and non-destructive biomolecules or cell detection mechanisms. The research on sensing platforms under these conditions has resulted in the design and development of various RF sensing schemes [10], such as the RF microelectromechanical system (MEMS) [11], resonator-based devices [12]–[14], meta-materials [15], and transmission line [16]–[18]. However, these schemes still must be validated by expensive equipment systems, e.g., vector network analyzers, high-speed digital sampling oscilloscopes, spectrum analyzers, or a fixture zig system. Therefore, the realization of a sensing platform that is cost-efficient, labor-saving, and associated with simple measurement systems is now relying on the progression of RF biosensors into active-system approaches from passive circuit approaches. Examples would be radio frequency identification (RFID) system and so on [19]–[25].

Fortunately, recently developed nuclear magnetic resonance (NMR)-based RF sensors show the possibility of serving as a highly sensitive and robust platform in the radio-frequency integrated circuit (RFIC) system [21]. The sensing platform has been fabricated with magnetic nanoparticles (MNPs) to enhance the sensitivity of biomolecular detection, e.g., streptavidin- biotinylated MNPs, and to interact with the RF magnetic field in a static field. The later-emerging active system-based RF sensors show the sensing schemes that are intended to reduce the assay time when detecting biomolecules [22], [23]. The sensor is based on a change in the resonant frequency following biomolecular binding, such that the binding effect results in a deviation of the oscillation frequency and the variation in the output level of surface acoustic wave (SAW) filter. Furthermore, the performance of the sensing system could be certified by voltage variation of the power detector via a digital multi-meter (DMM). Although these are remarkable improvements as a biosensing platform at the system level, the use of the SAW filter has a few drawbacks when integrated into a single integrated circuit (IC). In addition, with the narrow skirt frequency range used to enhance the sensitivity of the detector, the error is about 1.3 dB ($\sim 25\ \mathrm{mV/dB}$).

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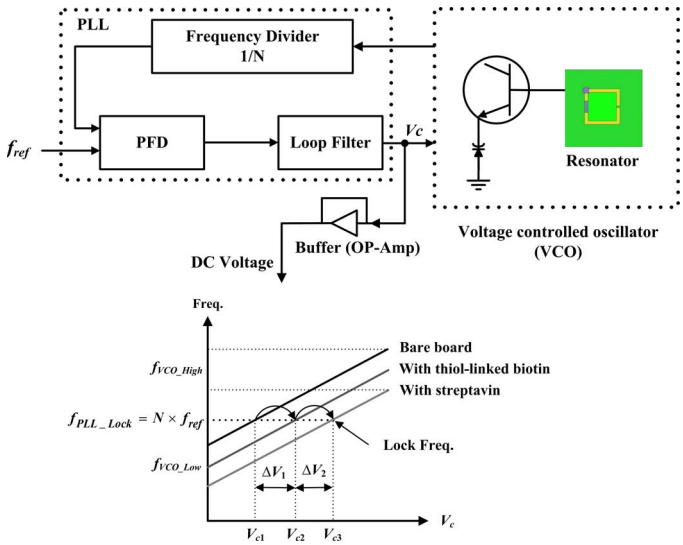

Fig. 1. System architecture of the proposed RF biosensor.

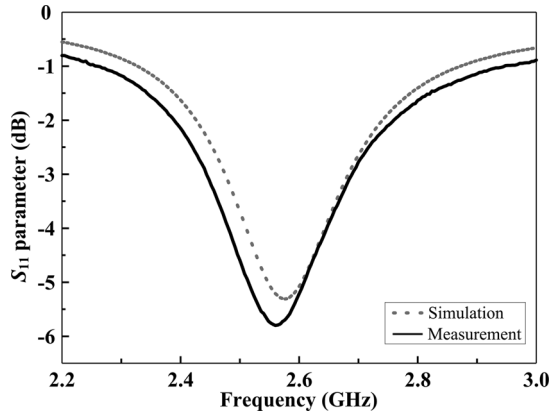

Fig. 2. S_{11} characteristics of the designed resonator.

This work proposes an RF biosensing platform for biomolecular detection based on a PLL synthesizer. Similar studies have shown the possibility of this configuration as a biosensor, with a focus on well-known organic liquids such as alcohol, xylene, and so on [26]. This work extends these ideas to label-free detection by adding a target analyte, streptavidin, which induces a resonant frequency shift following biomolecular binding.

This article is organized as follows: the proposed system configuration, the transducer, the VCO, and the PLL are introduced in detail in the Materials and Methods session. In the Results and Discussion section, the performance of the RF biosensor is experimentally verified with a biomolecular binding system and the sensing mechanism is analyzed. The limitations of the sensor are also described. Finally, the advantages and characteristics of the RF biosensor are discussed in the Conclusion section.

II. Materials and Methods

A. System Configuration

The system architecture of the proposed RF biosensor is illustrated in Fig. 1. The biosensor consists of three main blocks: a VCO with a built-in microstrip open-loop resonator, a PLL, and an operational amplifier (OP-Amp). In this study, the PLL circuit serves as a frequency detector, i.e., frequency to voltage converter, whereas a conventional PLL synthesizer is usually used to assign a desired channel in the transmit/receive path.

In this study, the resonator acts partly as a transducing element, i.e., transducer, as well as the series feedback element of an oscillator. In particular, as a sensing device, the input impedance of the resonator should change sensitively due to changes in various electrical effects, such as the surface conductivity, the dielectric constant, etc. [11], with the immobilization of the biomolecules. The frequency shift of the oscillator stems from the impedance variation of the resonator itself. For this reason, the output frequency of the VCO is shifted toward a lower frequency region ($\sim$ a few MHz) compared to a bare resonator. The VCO control voltage (Vc) will vary depending on the biomolecular concentration. For the investigation of the biosensing capabilities, three different states are considered: a bare-board, thiol-linked biotin, and streptavidin. In principle, the PLL lock frequency (f_{PLL_Lock}) depends on the N-counter (N) and reference frequency (f_{ref}), while the output of the loop filter is a constant voltage (V_{c1}) in the case of constant N and f_{ref}. When the thiol-linked biotin is bound on the resonator, the oscillation frequency of the free-run oscillator as a function of the varactor control voltage is changed toward a low frequency region from a bare board state. At that time, the loop of the PLL is locked under the identical condition of N and f_{ref}, by varying the varactor control voltage to a higher voltage (V_{c2}). In this study, we would like to find the voltage differences ($\Delta V_1 = V_{c2} - V_{c1}$ or $\Delta V_2 = V_{c3} - V_{c2}$) according to the three different biomolecules. The difference in the voltage (ΔV_1) mainly results from the thiol-linked biotin concentration, which is 25 μg/ml (2.5%), while ΔV_2 is changed with the streptavidin concentrations of 100, 10, and 1 ng/ml. These voltage differences can easily be measured by a DMM. The voltage difference is measured in a stable state by using a PLL synthesizer.

B. A Resonance-Assisted Transducer

First, the resonant characteristics are investigated by simulating the designed resonator by a full-wave electromagnetic (EM) solver based on the finite element method (FEM). The simulated result is in good agreement with the measured result, as shown in Fig. 2. The loaded-Q factor of the resonator is about 10 at 2.56 GHz. The simulated results clearly show that the electric field is highly confined in the gap region between the tips, whereas the surface current is maximal at the opposite side of the gap, as shown in Fig. 3. Commonly, immobilization processes are sensitive to surface properties such as roughness, skin depth, and surface resistance of the electrode. For this reason, the local sensing part on the resonator is set to the area of the maximum surface current. In addition, this configuration has the advantage of being able to detect very small bio-specimens. Thus, for the local sensing area, a masking layer (thickness $\sim 10 - 20$ μm) is coated onto the overall surface of the resonator, excluding the gold coated local sensing area ($\sim 4 \times 0.76$ mm^2) [27], [28]. Furthermore, a SMCX connector is used to provide an easy connection with the PLL active circuit

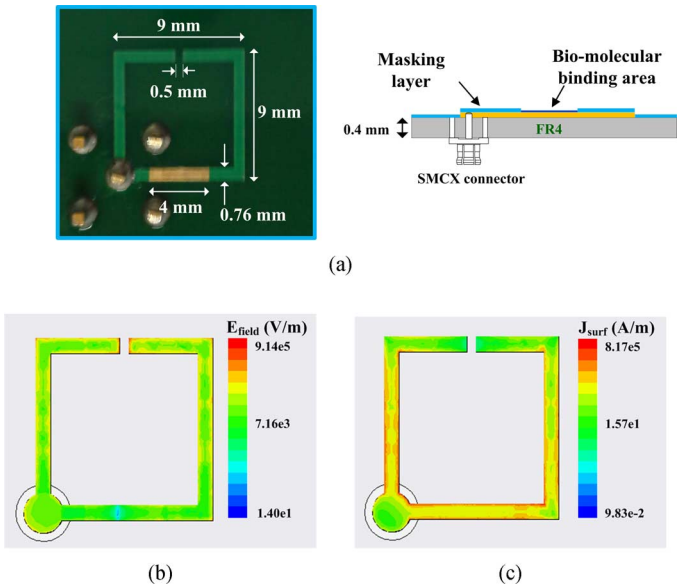

Fig. 3. Layout of the fabricated microstrip open-loop resonator. (a) Top/Side view. (b) Electric field. (c) Surface current density.

and for the rapid replacement of numerous samples, i.e., resonators. Fig. 3 indicates the layout of the fabricated resonator, which is a half-wavelength ($\lambda_g/2$) resonator on a FR-4 substrate (t $=$ 0.4 mm, $\varepsilon_r = 4.4$, and $\tan\delta = 0.02$) [29]. The input impedance of a half-wavelength resonator can be written in lossless condition [30]

$$Z_{io} = \left.\frac{v_1}{i_1}\right|_{i_2=0} = \frac{Y_0\cos(\beta\cdot l_g) + jY_g\sin(\beta\cdot l_g)}{jY_0{}^2\sin(\beta\cdot l_g) + 2Y_0Y_g[\cos(\beta\cdot l_g) - 1]} \quad (1)$$

where l_g is effective length of the resonator. The imaginary parts of the impedance are exactly canceled out at $l_g = \lambda_g/2$.

C. Voltage Controlled Oscillator and PLL

The design of the VCO with tunable negative resistance is based on previous work, with some modifications [31]: First, a circularly planar resonator is replaced with a microstrip open loop resonator to ensure a smaller area. Second, a varactor diode for a high-frequency system is used such that the total capacitance ranges from 2.67 pF to 0.63 pF [32]. Finally, a snap-on type of connector is employed for the repeatable and reliable measurement of a large number of samples. The modified VCO design is necessary because most biomolecules are nano-sized and have a small weight-mass. Additionally, the binding effect on the resonator is minute. Thus, to maximize the effect, the sensing area should be as large as possible compared to the overall dimensions of the resonator. Second, a small gain of the VCO is necessary to enhance the sensitivity and resolution, i.e., the limit of detection (LOD). Here, the capacitance of the varactor diode ranges from 18 pF (0 V) to 1.7 pF (5 V) at 2.4 GHz. Finally, a snap-on type of connector (length $\sim$ 6 mm), a disposable part, is adopted.

Regarding the oscillator, oscillation occurs at the frequency of the zero-degree phase shift rather than at the minimum peak

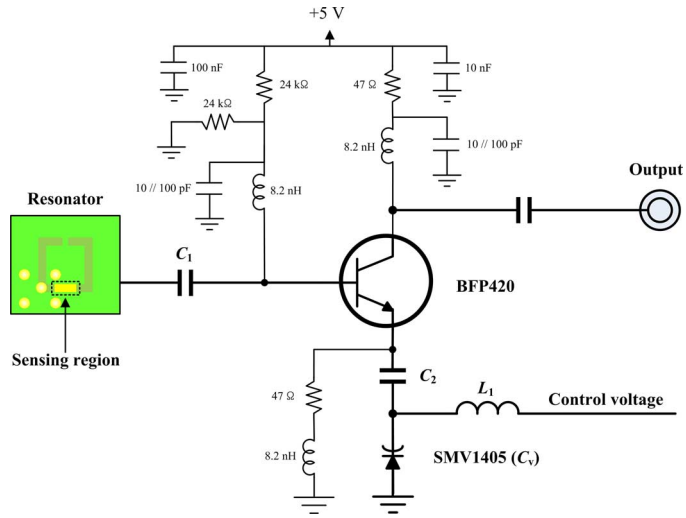

Fig. 4. Schematic diagram of the VCO with negative resistance.

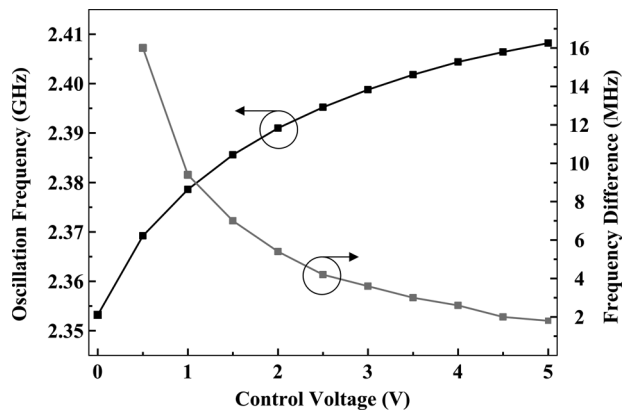

Fig. 5. Tuning range of the measured oscillation frequency and frequency difference with the varactor control voltage.

of the S_{11} parameter. Moreover, the additional length, including the connector and microstrip line, affects the shift of the reference plane of the zero-phase from 2.56 GHz to approximately 2.4 GHz. With above mentioned modifications, the VCO adopts a series feedback topology and the resonator is connected to the base terminal of a bipolar junction transistor (BJT), as shown in Fig. 4. The capacitors (C_1 and C_2) serve to block the DC component. In particular, C_2 can be used to adjust the gain of the VCO. The bias circuit is employed with a general voltage divider scheme to achieve the operating point stabilized against junction temperature variation. The current consumption of the BJT, the BFP420 model, is approximately 10 mA at a collector-emitter voltage of 4 V.

In particular, the VCO performance, which is affected by the varactor diode, is dependent on the average gain, the tunable frequency range, and the phase noise. The tunable range of the employed varactor is about 50 MHz at a control voltage range of 5 V, and the average gain is approximately 10 MHz/V at room temperature (17 to 25°C), as shown in Fig. 5. Relevant parameters are listed in Table I. The working range of this VCO is determined using the biomolecular concentration. The LOD is also affected by short-term frequency drift, which is

TABLE I
PERFORMANCE RELATED VCO AND COMPARISON

Items		Ref [31]	This work	Remark
Resonator	Type	Circular planar	Open-loop	
	Surface area	1,590 mm^2	24.7 mm^2	
BJT	Current	20 mA	10 mA	
Varactor	Model[32]	SMV1245	SMV1405	
	Tuning range	7.37 – 2.09	2.67 -1.17	Unit: pF
VCO	Avg. gain	6 MHz/V	5.2 MHz/V	@ 2.5 – 5V

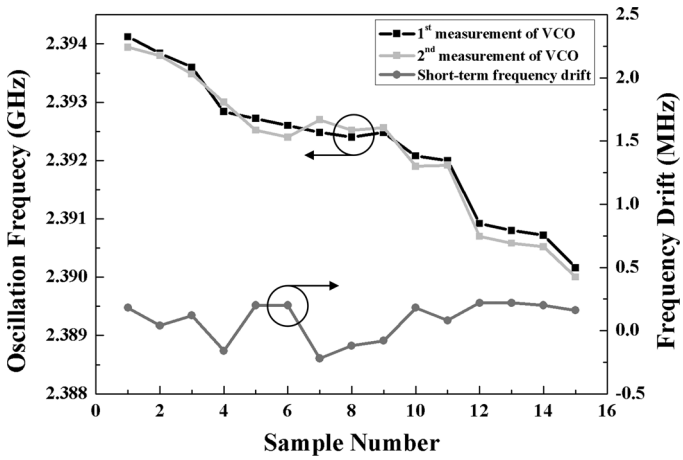

Fig. 6. Short-term frequency drift of 15 samples.

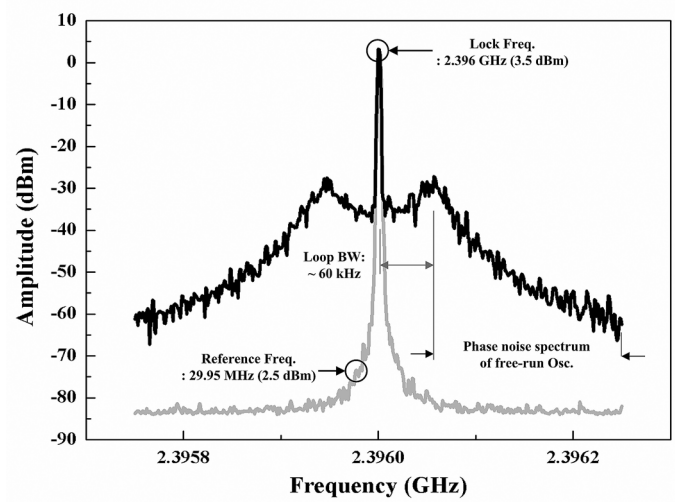

Fig. 7. Measured phase noise spectrum of the phase locked signal.

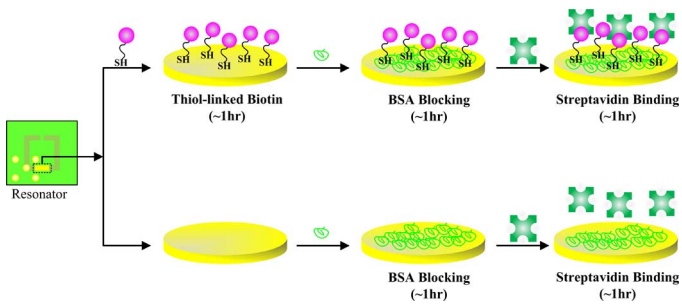

Fig. 8. Immobilization process on the gold layer of the resonator.

mainly caused by the Q factor of the resonator. In addition, the frequency drift is a critical factor of the proposed sensor because a few samples are measured after each biological process. The measured frequency drift is less than ± 250 kHz, which reflects the test data including the related error term, as illustrated in Fig. 6.

The PLL circuit used as a frequency detector consists of an integrated PLL IC (the HMC698LP5 model) including a PFD, a programmable frequency counter (1/80), and a second-order active loop filter. The lock state is directly confirmed in the phase noise spectrum, as shown in Fig. 7. The performance is measured at 2.396 GHz ($N = 80$, $f_{ref} = 29.95$ MHz) with a targeted loop bandwidth of 60 kHz and power output of 3.5 dBm. The measured phase noise performance revealed eighty times higher compared to that of the TCXO.

D. Biological Process for Functionalization

In our work, we validate the performance of the RF biosensor using biotin and streptavidin, which form a well-known coupling system with a strong affinity ($K_a = 10^{15}$ M^{-1}) [33]. In general, a specific binding is commonly used to immobilize enzymes, antibodies, or DNA. Moreover, its formation is useful in a wide variety of applications. Here, biotin ($\sim$ 647 Da) is a small molecule compared to streptavidin ($\sim$ 55 kDa), a tetrameric protein with four identical binding sites for biotin, as illustrated in Fig. 8. These materials are also commercially available and easy to handle.

The biological procedure for the RF biosensor is represented in Fig. 8 [10], [23]. First, all samples are washed and then simultaneously immobilized with thiol-linked biotin ($\sim$ 25 μg/ml) for about 1 hour, followed by rinsing and drying. The dried samples are then immediately measured by a RF measurement system. Next, to deactivate and block the excess reactive groups remaining on the surface, the devices are treated with bovine serum albumin (BSA) at a concentration of 25 μg/ml for about 1 hour. Finally, the biotin is bound to different concentrations of streptavidin (100, 10, and 1 ng/ml in this case) for about 1 hour at room temperature (17 to 25°C) in a general laboratory environment. In this process, a deionized solution is used to rinse and immobilize the samples. A control experiment without thiol-linked biotin is also conducted to compare the samples with the biotin-streptavidin binding system.

III. RESULTS AND DISCUSSION

A. Sensing Elements

First, the samples are measured to set the reference point for the frequency shift characteristics depending on three different states, with streptavidin concentrations of 100, 10, and 1 ng/ml. The reference point (bare sample) with regard to phase term is not identical in all samples. This discrepancy results from man-made error with soldering and fabrication tolerances including etching and different mask layer thicknesses (10 – 20 μm). Nevertheless, the measured data are useful because the proposed sensor is dedicated to measure the

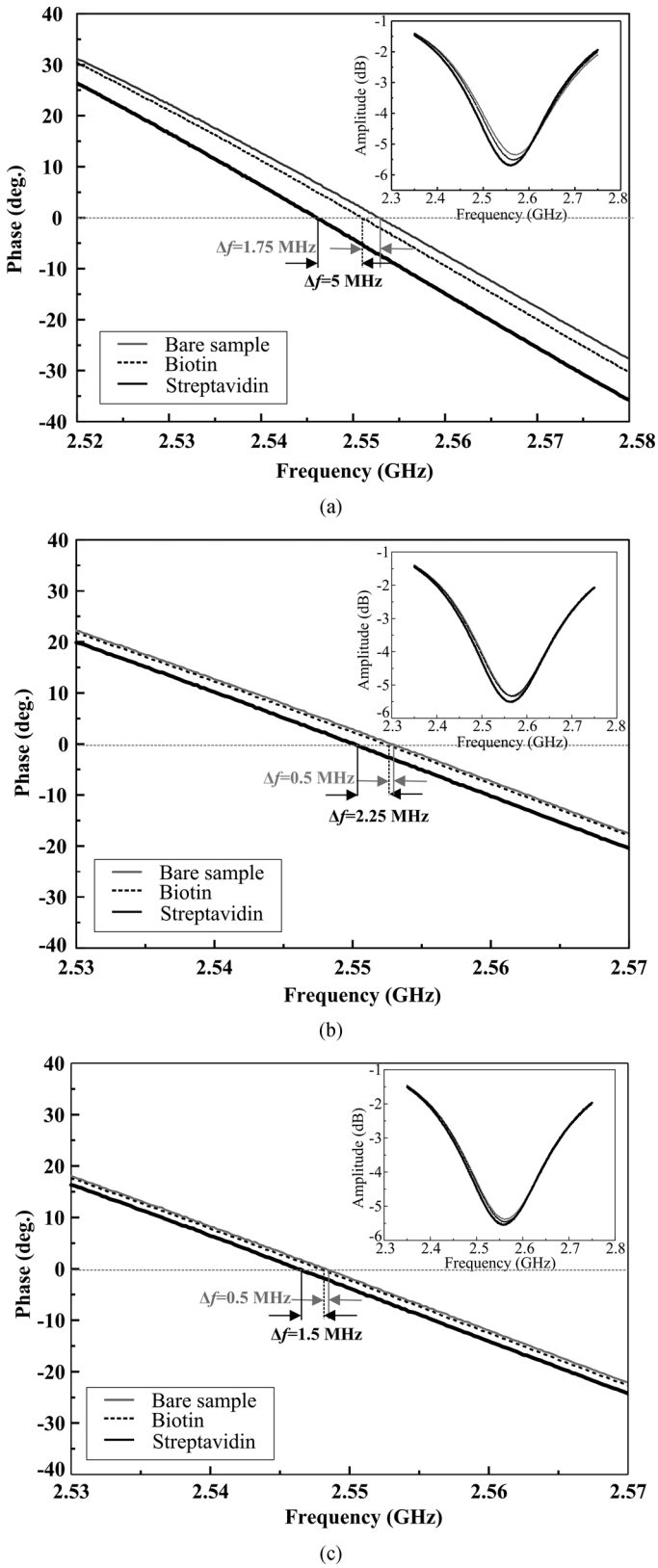

Fig. 9. Measured phase and amplitude of the S_{11} characteristics for sensing elements depending on three different concentrations. (a) 100 ng/ml. (b) 10 ng/ml. (c) 1 ng/ml.

amount of relative phase shift, not an absolute phase variation. As shown in Fig. 9, the amplitude responses reveal a slight

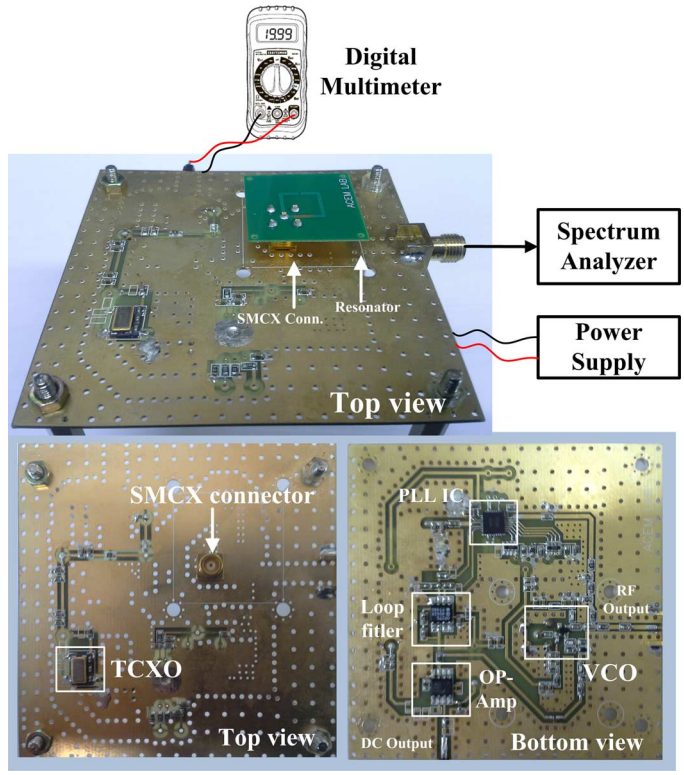

Fig. 10. Fabricated PCB sample and measurement setup.

increase in the loss, most likely due to the decrease in the surface conductivity [34]

$$\alpha_C = \frac{R_S}{Z_0 W} \quad \frac{\text{Np}}{\text{m}}, \tag{2}$$

where $R_s = \sqrt{\omega\mu_0/2\sigma}$ is the effective surface resistivity of the gold immobilized with the biomolecule. In addition, the resonant frequency moves slightly toward a lower frequency because the sensing surface can be considered as biomolecular bilayers having greater effective permittivity than the air coupled microstrip geometry [15].

Since the RF biosensor is based on a PLL synthesizer, the phase variation of the resonator is more important than the amplitude response. The measurements clearly demonstrate that the zero-crossing frequency of the phase response changes from 0.5 MHz to 1.75 MHz depending on the concentration level of the biotin linking, while streptavidin binding causes a shift in the zero-crossing frequency ranging from 1.5 MHz to 5 MHz with the concentration level. As mentioned earlier, the additional transmission lines, including the connector and microstrip lines of the PLL board, enable the zero-phase point to shift toward the lower frequency region. Moreover, the extent of the frequency shift at the zero-phase point of the new reference plane (with a lag of 120°) is less than that with only a resonator.

B. RF Biosensor

The RF biosensor is fabricated with bilayered PCBs; one is for the analog sensor circuit and the other part is for the snap-on type of open-loop resonator, as shown in Fig. 10. The RF sensor

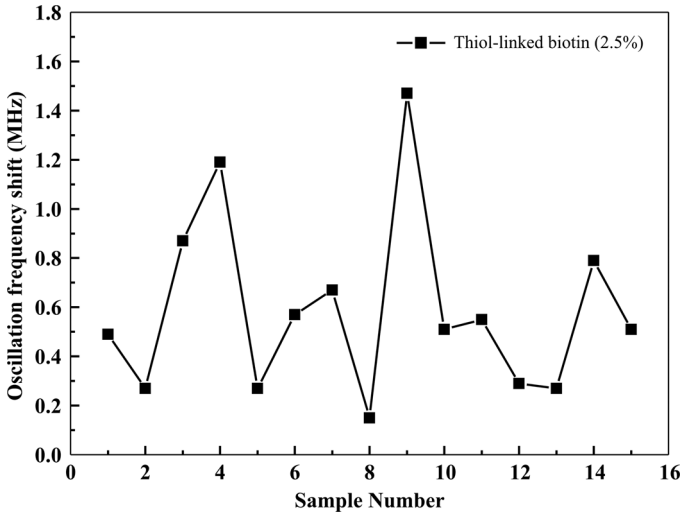

Fig. 11. Frequency shift with the thiol-linked biotin (2.5%).

TABLE II
SUMMARY OF THE EXPERIMENTAL RESULTS

Items		Streptavidin Concentration (ng/ml)		
		100	10	1
Oscillation freq. shift (MHz)	Max	3.20	1	0.52
	Avg	2.54	0.94	0.39
	Min	1.44	0.8	0.28
DC output (mV)	Max	688	209	130
	Avg	505	197	95
	Min	279	169	59

circuit is designed to measure the shift in the resonant frequency and the corresponding change in the DC voltage, and the output can be displayed with a spectrum analyzer and a DMM. The applied DC voltage to the RF biosensor is $+5$ V, and current consumption is about 330 mA. Note that a temperature compensated crystal oscillator (TCXO) is employed to minimize the phase noise of the VCO. In addition, a warm-up time of five minutes is necessary to reduce the frequency drift of the VCO due to the low-Q resonator.

Fifteen samples with different streptavidin concentrations were prepared for testing. Each concentration was allocated to five samples, and each sample was measured twice. Fig. 11 shows the variations in the oscillation frequency shift for all samples after biotin immobilization. The difference in the extent of the frequency shift after the biotin treatment arises from several factors, including the imperfect manual manipulation and the slight difference in the shape of the open area of the resonator. Note that these variations do not play an important role in the overall measurement accuracy, as the relative frequency shift after streptavidin binding is measured. At this stage, with these samples that have a biotin layer, streptavidin-biotin binding experiments are conducted with various streptavidin concentrations. As summarized in Table II and as shown in Fig. 12, a frequency shift and resulting voltage change are clearly shown for different streptavidin concentrations. The detectable limit of our biosensor is about 1 ng/ml; this RF biosensor has sufficient sensitivity to detect the frequency and

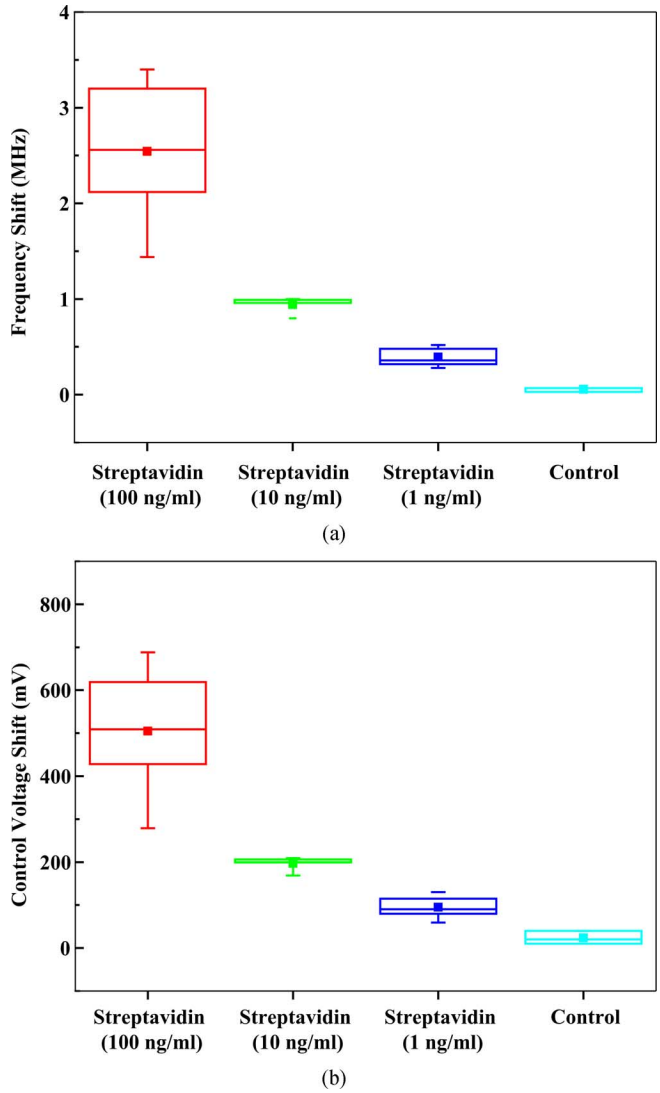

Fig. 12. Measured results with three different streptavidin concentrations. (a) Shift of the oscillation frequency. (b) Variation of the control voltage.

TABLE III
SENSITIVITY PERFORMANCE OF LABEL-FREE RF BIOSENSORS

	Sensor type	Target biomolecules	LOD
Lee [12]	Passive device	Biotin-streptavidin	55 μg/ml
Yoon [14]			100 ng/ml
Saravan [18]		C-reactive protein	5 ng/ml
Kim [23]	System	Biotin-streptavidin	1 ng/ml
This work			1 ng/ml

control voltage shift compared to thiol-linked biotin exposed state. The values are respectively 0.39 MHz and 95 mV on average, at streptavidin concentration of 1 ng/ml. Control samples without a thiol-linked biotin layer do not react with streptavidin solutions. In addition, the sensitivity of the proposed RF biosensor reveals excellent performance compared to other published works, as summarized in Table III. The proposed RF biosensor is clearly a very effective and powerful device for label-free biomolecule detection.

Although significant progress has been made, fundamental and practical challenges remain to be addressed. For instance, the sensitivity is limited by the magnitude of the short-term frequency drift, meaning that the sensor includes an error term of less than ± 250 kHz. To resolve this issue, the Q-factor of the resonator must be increased at the expense of a reduced shift in the oscillation frequency corresponding to the biomolecular concentration. In addition, it is important to note that the deposit area of the resonator occupies about one-eighth ($\sim 4 \times 0.76\ \mathrm{mm}^2$) of the overall area of the resonator. Thus, to improve the LOD with our sensor further to the $\sim \mathrm{pg/ml}$ range, the sensing area has to be as long as possible. On the other hand, if one increases the operating frequency of the sensor to the millimeter-wave region, it would become possible to increase the sensitivity of the sensor based on the dip-and-dry method. Therefore, it is desirable to have a small resonator with a high Q-factor greater than a few tens so that the biomaterial covers most of the resonator area and the short-term frequency drift is minimized. The small variation of the oscillation frequency due to the high Q-factor of the resonator can then be offset by the large deposit area of the resonator, resulting in improved sensitivity and an improved LOD.

IV. Conclusion

In this work, we have developed an RF biosensor based on PLL circuit-based architecture that is able to recognize differences in target biomolecular concentrations up to 1 ng/ml. The proposed sensing device successfully demonstrates label-free detection in the biotin-streptavidin binding system. It has been confirmed that the proposed RF biosensor reveals good sensitivity, good selectivity, and good reproducibility. In addition, the proposed biosensor is cost-efficient and enables a real-time assay of the target biomolecule. According to the obtained data, the sensitivity and LOD with regard to streptavidin detection are approximately 61 $\mathrm{kHz/ngml^{-1}}$ and 1 ng/ml, respectively. In the future, we expect that our device could be continuously developed for further enhancements to its performance.

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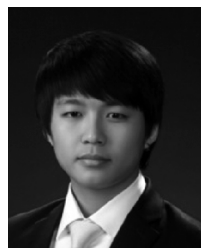

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