

Label-free DNA sensing using millimeter-wave silicon WGM resonator

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Abstract: A planar dielectric waveguide based structure for bio-sensing purpose is introduced. The proposed device is a silicon-based WGM disc resonator operating within the range of 75-110 GHz (W-band). The sensor is an integrated, miniaturized, low-cost, and easy-to-fabricate bio-sensor structure. The proposed sensor can be used for a number of DNA characterization tasks including Mutation in DNA oligonucleotide. Two types of DNAs, single strand and double strand DNAs, are successfully tested by our integrated sensor. The measurement repeatability and selectivity of the proposed sensor are examined through the different experimental lab-tests.

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1. Introduction

The description of an individual genetic background (DNA and RNA) has become a powerful tool in the diagnosis of diseases, genetic disorders and pathogen infection. The recent discovery that most cancers have widely varying genetic backgrounds indicates that successful intervention may require individualized therapeutic strategies [1]. The present technology, used to evaluate one's individual genetic makeup, is based on the ability of an immobilized single-stranded DNA to hybridize to a complementary sequence forming a double-stranded structure, which is then detected through an optical method [2]. Until now this has required time-consuming modification, fluorescent labeling and enzymatic amplification of the sample being analyzed. While these techniques have proven to be sensitive, they run the risk of experimental bias as well as the cost and complicated methodology being beyond the scope of local healthcare providers. The development of an integrated, cost-effective, and ultra-high sensitivity bio-sensor holds the promise of quick and effective healthcare practices that are tailored to individuals.

Resonator based structures are basis of many optical bio-sensors [3–5]. Micro-ring, micro-sphere, surface plasmon, and planar resonators are few examples, picked from this category. The operation principle of these devices can be explained by the concept of evanescent field interaction. Among the resonator-based sensors, the ones that use Whispering Gallery Mode (WGM) are of huge interest [6]. Very few WGM-based devices are introduced at Millimeter-wave (mm-wave) range of frequencies for sensing application such as nanolitre liquid sensing [7]. On the other hand, the WGM technique has been well recognized for sensing applications in optical range of frequencies [8].

Although, resonator-based bio-sensing is vastly studied at optical wavelengths, the introduced techniques and devices in optics have some drawbacks. Most of the existing optical sensing systems are generally non-planar structures, e.g. in the form of a micro-sphere. Therefore, the mass production, reproducibility, and integration of such systems are extremely difficult [8]. The total cost of these sensing systems, including the device cost, and required lab facilities such as tunable-laser, are high. The optical bio-sensing systems are mostly used for liquid and gas samples. Such optical sensing systems have essentially been proposed for sensing at molecular level [8,9]. The aforementioned issues encourage us to investigate alternative structures with better performance and characteristics. As a promising alternative approach, a planar and potentially low-cost sensor for differentiation of different DNA segments, after evaporation of the buffer solution, is proposed here. This sensor works in sub-mm-wave range of frequencies, where DNA molecule shows stronger inter-molecule vibration. This approach can be used for defective gene and mutated DNA detection. The system is particularly realized with a one mask process in a high resistivity Silicon-On-Insulator (SOI) technology, which was originally introduced in [10], as a liquid ring resonator sensor. The SOI technology allows us to have accurate control on the gap size between the disc and waveguide, which is a critical parameter determining the performance of the sensor. Design and implementation of the WGM disc sensor based on SOI technology at W-band range of frequencies using a simple and cost-effective one-mask process is the main novelty of this work. In another work [11], we introduced a mm-wave image waveguide WGM disc resonator, made from Alumina, for Sugar sensing. The disc resonator-based sensors are not appropriate for liquid sensing, since liquids have huge absorption in millimeter-wave and THz range of frequencies. Therefore, the liquid sample, placed on the disc resonator, suppresses

the resonance effect and therefore the frequency resonance shift measurement will not be possible in the millimeter-wave and sub-millimeter-wave ranges of interest in the proposed method. Difficulty in integration with other available Integrated Circuit (IC) technologies was the main drawback of the previous work. On the other hand, SOI technology is very convenient for introducing a potentially integrated mm-wave system. Furthermore, high resistivity Si enables us to design a low-loss, and consequently a high Q-factor resonator. The fabrication cost of the proposed sensor, which is one mask process, is low. Accordingly, a fast, low-cost, reliable, and highly sensitive sensor is feasible. The proposed device in this paper is tested within 75-110GHz range of frequency (W-band) using a network analyzer. In the next stage of this project, the network analyzer will be replaced with a simple diode detector and a low-cost tunable source. So, the whole integrated system will eventually become a highly cost-effective solution for a wide range of sensing applications.

Section 2 describes the design of prototype disc-shape sensor, which is fabricated, and successfully tested, for single and double strand DNA samples, after evaporation of the annealed buffer. In Section 3, the simulations results are presented. Section 4 focuses on the experimental results of loading the sensor with the DNA oligonucleotides. Finally, Section 5 concludes this paper.

2. Sensor configuration and mathematical formulation of WG mode of disc resonator

Figure 1(a) shows the schematic of the proposed sensor. The proposed sensor consists of a Dielectric Wave-Guide (DWG) and a Dielectric Resonator (DR) coupled to the waveguide. The structure is designed for unidirectional and critical coupling. The device supports $WGH_{n,0,0}^y$ mode in which E^y is the dominant mode. The permittivity and conductivity of the high resistive Silicon, used in the DR and DWG, are estimated as 11.8 and 0.01 S/m, respectively. The top layer of the SOI-based wafer has a thickness about 500 μ m while the handle wafer has a thickness of 130 μ m. The buried oxide layers has a thickness of 1~2 μ m. The fabrication process is a simple single-mask process as similar to one which is explained in [10]. The dielectric waveguide is excited by the standard rectangular metallic waveguide (WR-10). The dielectric waveguide is linearly tapered at both ends for smooth transition to the rectangular metallic waveguide. The total length of dielectric structure is 20 mm. The dielectric waveguide is designed to support a single mode operation (E_{11}^y). The dielectric waveguide channel has a cross section of 0.5 $\times$ 0.6 mm². The DR has a radius of 1.91 mm, which supports four distinct $WGH_{n,0,0}^y$ modes within the range of 75-110 GHz.

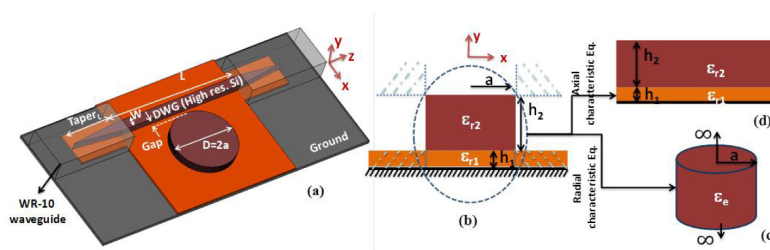


Fig. 1. a) General configuration of the proposed sensor. b) Cross section of a general insulated DR. c) The equivalent model for calculating the radial characteristic equation. d) The equivalent two-layer slab waveguide for calculating the axial characteristic equation.

The disc surface area is suitable for placing the exact 10 μ l DNA sample. In addition, the designed DR provides the non-radiative WG modes ($n>6$) within the desired frequency range. It should be notified that a disc with larger diameter supports relatively higher order $WGH_{n,0,0}^y$ modes, which are essentially more confined. In this case, the field outside the

resonator has a shorter evanescent tail as compared to that in a smaller resonator. Thus, the excitation of the resonator would be more challenging. Also, larger radius of DR decreases the sensitivity of the device. Figure 1(b) shows a general configuration of an insulated DR placed on a ground plane. In this paper, the approximate Effective Dielectric Constant (EDC) method is adopted to calculate the resonance frequency of an insulated image resonator [11,12]. Following the method, the electromagnetic parameters are obtained by solving two dependent characteristic dependent radial and axial characteristic equations respectively.

The radial characteristic equation of the structure, shown in Fig. 1(b), is obtained by matching the tangential electromagnetic fields at the side wall of an infinite dielectric cylinder with permittivity of ϵ_e [Fig. 1(c)]:

$$\left[\frac{J'_n(k_\rho a)}{(k_\rho a)J_n(k_\rho a)} + \frac{K'_n(\alpha_\rho a)}{(\alpha_\rho a)K_n(\alpha_\rho a)} \right] \left[\frac{J'_n(k_\rho a)}{(k_\rho a)J_n(k_\rho a)} + \frac{K'_n(\alpha_\rho a)}{\epsilon_e(\alpha_\rho a)K_n(\alpha_\rho a)} \right] = \left[n(\epsilon_e - 1) \frac{k'_y k_0}{k_\rho^2} \right], \quad (1)$$

where J_n , K_n are the first Bessel and Hankel functions, respectively. Also, k_ρ , α_ρ and k'_y are the radial wavenumber, radial attenuation constant, and axial wavenumber, respectively. The effective permittivity, ϵ_e , is approximated in [13]. The axial characteristic equation for TM^y , which corresponds to WGH mode, is obtained by matching the tangential fields at the boundaries of a grounded two-layer slab waveguide [Fig. 1(d)]

$$\left[1 + \left(\frac{\alpha_1 \epsilon_{r2}}{k_y \epsilon_{r1}} \right) \tanh(\alpha_1 h_1) \tanh(k_y h_2) \right] = \frac{-k_z}{\alpha_0 \epsilon_{r2}} \left[-\tanh(k_y h_2) + \left(\frac{\alpha_1 \epsilon_{r2}}{k_y \epsilon_{r1}} \right) \tanh(\alpha_1 h_1) \right], \quad (2)$$

where α_0 and α_ρ are the axial attenuation constants in air and in the substrate, respectively. Solving (1)-(2) numerically, using the algorithm explained in [11], one can find the common axial wavenumber, $k_y = k'_y$. Afterward, the resonance frequency of the resonator is calculated. The achieved results are approximate ones due to the assumption of zero-field at the corner regions of the DR. The accuracy of the calculated values can be improved by using a variational expression for the resonant frequency [11,14].

3. Simulation results

The resonance characteristics of the DR for different WGMs are obtained from the full-wave Eigen-mode simulation, performed by HFSS (Ansys), and compared to those calculated by the EDC and variational method (Table 1). Obviously, a good agreement is achieved between the results. However, the proposed numeric method is much faster than the HFSS one.

Table 1. Comparison between the Resonance FREQUENCIES Obtained from EDC-variational Method and Full-wave Simulation for an Insulated SOI Disc

Mode	f_c (GHz) EDC method	f_c (GHz) Variational method	f_c (GHz) full-wave
$WGH_{8,0,0}$	86.61	87.12	87.52
$WGH_{9,0,0}$	94.31	95.35	95.75

4. Experimental results and discussion

To examine the capabilities, sensitivity, and selectivity of our proposed sensor we prepared a number of DNA samples. Complementary 38 base pair synthetic oligonucleotides (short and single-stranded DNA molecules), were obtained from Sigma Genosys Canada.

Oligo #1: 5'-GGT GCT ACA GTT GCT CAT GAG CTG GGG CAC AAC TTG GG-3'
Oligo #2: 5'-CCC AAG TTG TGC CCC AGC TCA TGA GCA ACT GTA GCA CC-3'

The individual oligonucleotides used for single strand DNA tests were denatured at 95°C for 3 minutes in annealing buffer (10 mM Tris, pH 7.5, 50 mM NaCl, 1 mM EDTA) and then rapidly cooled on ice. A double stranded DNA was generated by combining oligonucleotide 1 and 2 at equimolar concentration. The samples were denatured at 95°C for 3 minutes in a heat block. The block was then allowed to cool to room temperature over 1 hour. Annealed oligos were stored on ice. Single and double stranded oligos were tested at equal molar concentrations, 20 nmol, with total weight of 2.33×10^{-9} g and 4.67×10^{-9} g, respectively.

The prototype sensor was tested with a Vector Network Analyzer (VNA), Agilent PNAX, equipped with two external mixer modules. The input and output ports of the measurement system are metallic waveguide-based. The fabricated DWG has a length (L) of 13 mm and two 3 mm tapered sections. To provide a high Q-factor resonant for $WGH_{9,0,0}$ mode, the gap between the disc and DWG is 160 μm . The measurement setup including the sensor device is illustrated in Figs. 2(a)-2(c). The measured transmission and reflection responses of the device within the range of 75-110GHz are plotted in Fig. 2(d), and compared with the simulated ones. A good agreement is achieved between the measurement and the simulation results. The higher loss, observed in the measured results, is due to the misalignment and metallic fixture issues. The related Free Spectral Range (FSR) for this structure is around 8.15 GHz.

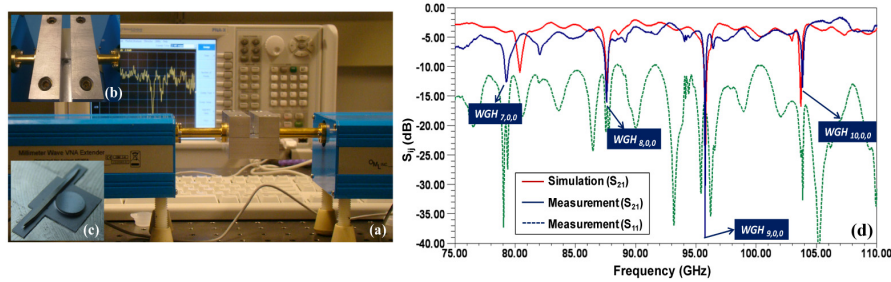


Fig. 2. a) The measurement setup, b) The sensor inside the fixture, c) SOI sensor, d) The comparison between the S_{21} obtained from measurement with that of simulation.

The loaded quality factor of the resonator can be calculated based on the coupling coefficient, κ , and total attenuation of the resonator, α . α and κ are obtained by the expressions given in [15]. The calculated κ for the mode $WGH_{9,0,0}$ is around 0.94, which is close to critical coupling value. The calculated loaded quality factor for this mode is about 1100. Therefore, the unloaded Q-factor is $Q_0 = Q_L(1 + \kappa) = 2134$.

In the aforementioned experiments the temperature was controlled around $23 \pm 1^\circ\text{C}$, which guarantee the accuracy of our resonance frequency within ± 2 MHz. In order to coat the DR with DNA, approximately 10 μl of the oligonucleotide in annealed buffer is pipetted on the top surface of DR. The liquid is evaporated and resulting in a uniform thin layer ($\sim 250\text{nm}$) of DNA. The DNA samples can be modeled as a thin dielectric layer, with specific permittivity, placed on top of the DR [16]. In the first set of experiments, two DNA oligonucleotides of the same length but with different base pair order are used. Figure 3 shows changes in the resonance frequency of the transmission response after loading the DR with oligo #1. A 380 MHz resonance frequency shift is achieved. The same measurement procedure is followed for oligo #2 resulting in a 390 MHz shift. These results describe a distinct 10 MHz difference in resonance frequency shift for the two DNA oligos. To ensure repeatability, multiple trials of each test are conducted. After each measurement, the resonator is completely washed using distilled. The resonance frequency and its depth are re-checked with the reference point before evaluating the subsequent DNA sample.

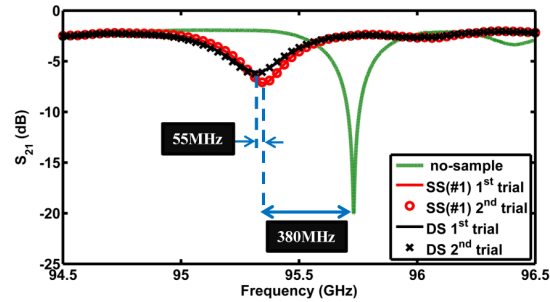


Fig. 3. The measured resonance frequency shift for single strand (SS) and double strand (DS) DNA samples. The repeatability is validated for each sample.

Next, we evaluated the ability to distinguish between single and double-stranded DNA. Equimolar amounts of the double-stranded DNA resulting from the annealing of oligo#1 and oligo#2 are placed on top of DR and the changes in the transmission response are recorded. For comparison, the results obtained from double strand DNA is overlaid on the results of single strand DNA [Fig. 3]. A significantly higher 55 MHz shift in the resonance frequency is achieved. This was expected as double-stranded DNA has higher equivalent permittivity compare to the single-stranded DNA. Also, a stronger damping, which is related to lower Q-factor, is noticed in the resonance frequency for the double-strand DNA. This is due to the fact that double-stranded DNA has higher absorption loss.

5. Conclusion

An integrated, compact, and low-cost W-band (75-110GHz) sensor has been designed, fabricated, and successfully tested. The structure is realized using SOI technology. The proposed sensor is a dielectric disc resonator, operating in resonant WGM resonance. The resonator is designed and analyzed using a fast numerical method based on EDC and variational technique. The calculated $WGH_{n,0,0}$ resonance frequencies are verified by full-wave simulation and experiment. The sensing mechanism is based on the changes in the frequency of the WGM resonance of a disc resonator in the absence and the presence of the sample.

The sensor was tested for its ability to repeatedly distinguish two complementary DNA oligos of the same length. We were able to measure distinct 10 MHz shift (2.5%) between the resonance frequencies of each individual oligo. We then demonstrated the proposed sensor ability to discriminate between single and double-stranded DNA samples. The new sensor, proposed in this research, easily and accurately identifies individual single-stranded oligonucleotide sequences as well as double-stranded molecules. The experimental results demonstrate the efficiency of device in distinguishing different types of DNAs. As such the planar Silicon-based WGM sensor can be considered as a low-cost, fast and reliable alternative for the commonly used optical-based detectors of DNA hybridization. The Introduced VNA-based measurement system is essentially for proof-of-concept. Our ultimate goal is to implement the sensor with a simple diode detector and a low-cost tunable source for particular class of sensing over a narrow range of frequencies.

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