

Low-cost optical cavity based sensor with a large dynamic range

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Abstract: We have proposed an optical cavity based biosensor using a differential detection method for point-of-care diagnostics. For experimental demonstration of the proposed device using a two-laser system through refractive index measurements, an optical cavity structure is designed, fabricated, and measured. The differential value calculated with intensities of two different wavelengths has a larger responsivity with respect to the refractive index change as compared with the intensity of an individual wavelength. However, the repeatability test shows that the two-laser system has a tight fabrication tolerance due to its small dynamic range. In this paper, we introduce a three-laser system for an optical cavity sensor with a chained differential detection method and present the experimental measurement results showing a large dynamic range and large fabrication tolerance. The measured dynamic range of this system is more than three times greater than that of the two-laser system. The repeatability test using the three-laser system demonstrates a larger fabrication tolerance as a result of the increased dynamic range.

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1. Introduction

Early detection of diseases, such as cancers, allows patients to receive proper medical treatments timely, which in turn increases their chances of survival [1–3]. Enzyme-linked immunosorbent assay (ELISA) is well developed and currently used in blood tests to detect biomarkers, measurable indicators of diseases. This technology has been typically operated by a trained operator at a centralized laboratory due to its complex procedures. It also requires large sample and reagent volumes. Therefore, it is not adequate for early detection of diseases [4–6]. A point of care (POC) biosensor has received much attention these days as an enabling tool for early disease diagnosis because it is designed to be used at or near the patients, by the patients themselves [6–8]. In order for a biosensor to be a POC device, it must be label-free, low-cost, easy-to-use, stand-alone, highly sensitive, highly selective, multiplexable, and requiring a small sample volume [9,10].

We have proposed an optical cavity based biosensor using a differential detection method for POC diagnostics [13–15]. An optical cavity structure is created by two partially reflective mirrors (thin metal layers). The light wave from the light source impinges on the optical cavity, and small amounts of the light wave traveling back-and-forth in between the mirrors exit the cavity during each round trip. The interference among the multiple transmitted waves causes a resonant response in the output side. As a sample fluid is introduced into the optical cavity, the biomarkers in the sample fluid bind to specifically functionalized areas with biomarker-specific bioreceptors. This binding event increases the local refractive index, which leads to a shift of the resonant response curve [11,12]. Rather than detecting the entire resonant response curve shift with an expensive spectrometer or tunable laser, our system measures changes in intensities of low-cost laser diodes at designated wavelengths with a CMOS camera. In addition to being a low-cost, our system is a label-free system that doesn't require any additional steps with reagents. By measuring intensities with a CMOS camera, our system is also multiplexable (i.e., simultaneously detecting multiple target biomarkers). Various biomarker-specific bioreceptors will be immobilized within the beam diameter of the laser diodes. By properly addressing the locations of different bioreceptors in the CMOS images, the changes due to the adsorption of target biomarkers on them can be detected simultaneously. Since the optical cavity naturally forms a fluidic channel, our system can be very easily integrated with a microfluidic system which requires only a small sample volume. While the high specificity is accomplished by the use of biomarker-specific bioreceptors, we have proposed to accomplish the high sensitivity by employing a differential calculation method.

To demonstrate our system with standardized materials without ambiguity, we have performed refractive index measurements using standard refractive index liquids (Cargille) in the range 1.3–1.395 with an interval of 0.005. The optical cavity structure is designed to provide a linear change in differential values near the refractive index of 1.33 that is close to the refractive index of typical biological sample fluids [16–18].

In this paper, we present the simulation and measurement results of the two-laser system followed by the discussion about the fabrication tolerance analysis based on a repeatability test. We then present the design and measurement results of a three-laser system with a chained differential detection method showing a large dynamic range. A repeatability test of the three-laser system validates the improved fabrication tolerance due to the increased dynamic range.

2. Two-laser system

Figure 1 shows a schematic diagram of the two-laser system. Two laser diodes are used as light sources at wavelengths of 780 nm and 850 nm. These are chosen from available low-cost off-the-shelf laser diode wavelengths such as 780 nm, 808 nm, 832 nm, 850 nm, 880 nm, 904 nm, and 980 nm. After the light waves from the laser diodes are collimated using collimators, they are combined by a 50:50 ratio beam splitter. The light waves propagate through the optical cavity structure along the same path and reach the CMOS camera. The images captured by the camera are then processed to determine the intensities for both wavelengths.

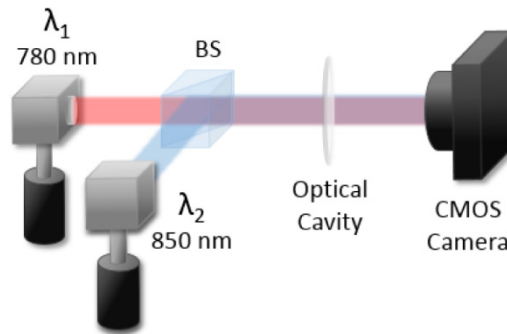


Fig. 1. Schematic diagram of the two-laser system.

The equation to calculate differential value using the measured intensities is given by:

$$\eta = \frac{I_1 - I_2}{I_1 + I_2} \quad (1)$$

where I_1 and I_2 are the optical intensities of 780 nm and 850 nm laser diode, respectively. A differential detection method has been used to enhance the signal change and improve the dynamic range [19–22]. In the range where I_1 and I_2 are changing in opposite directions, the change in the differential value using the Eq. (1) is enhanced. We employ it for the optical cavity sensor to improve the responsivity (i.e., the slope of the quantity used for either biosensing or refractive index measurement) of the proposed low-cost system.

2.1 Simulation results

The optical cavity structure for the two-laser system is optimized for refractive index measurements using FIMMWAVE /FIMMPROP (Photon design) so that intensities (or efficiencies for the simulation) of 780 nm and 850 nm change in the opposite directions near the refractive index of 1.33. Figure 2 shows the simulation results of the optimized structure, which has a cavity width of 2.2 μm and a silver thickness of 8 nm. The differential value has a

linear change with a slope of 30.743/RIU (refractive index unit) in the refractive index range of 1.32 and 1.345 ($\Delta_{\text{diff}} = 0.025$). We defined the dynamic range (Δ) as the refractive index range where the measured or calculated quantity is changing linearly. Compared to the slope and the dynamic range of the differential value, the efficiencies of 780 nm and 850 nm have smaller slopes (17.241/RIU and 18.028/RIU, respectively) in the smaller dynamic ranges of 1.336–1.354 ($\Delta_{780} = 0.018$) and 1.316–1.334 ($\Delta_{850} = 0.018$), respectively. Therefore, the differential detection method results in a larger responsivity and a larger dynamic range than the efficiency of an individual wavelength.

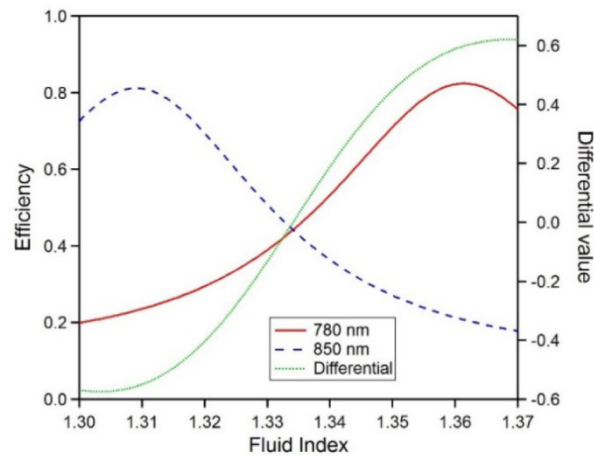


Fig. 2. Efficiencies of 780 nm and 850 nm and the differential value of the optimized optical cavity structure for the two-laser system in the refractive index range of 1.3–1.37 (red solid line: efficiencies of 780 nm, blue dashed line: efficiencies of 850 nm, and green dotted line: differential values).

3.2 The refractive index measurement results

To fabricate the optical cavity structure, a thin silver layer was deposited on both 4-inch glass wafers. The SU8 layers were then patterned on top of the silver layers and manually bonded together through a wafer level SU8-to-SU8 bonding technique [13]. Once a refractive index fluid filled the fabricated optical cavity, we collected 170 CMOS images for about one minute for 780 nm laser diode and calculated the average intensity over an area of 150 x 150 pixel array near the center of the beam. Then, we repeated this process for 850 nm. The differential value was calculated using average intensities of 780 nm and 850 nm. This procedure was repeated for different refractive index fluids until the measurement was completed. Figure 3 shows the measured intensities of both laser diodes and calculated differential values as a function of the refractive index of liquids. As the refractive index is changing from 1.315 to 1.35, the intensity of 780 nm is increasing while the intensity of 850 nm is decreasing, which is consistent with the simulation results. The calculated differential value has a linear region between the refractive index of 1.32 and 1.345 with a slope of 32.943/RIU. These measurement results match very well with simulation results. The results shown in Fig. 3 include error bars with $\pm$ standard deviation from collected 170 CMOS images, but it is too small to appear.

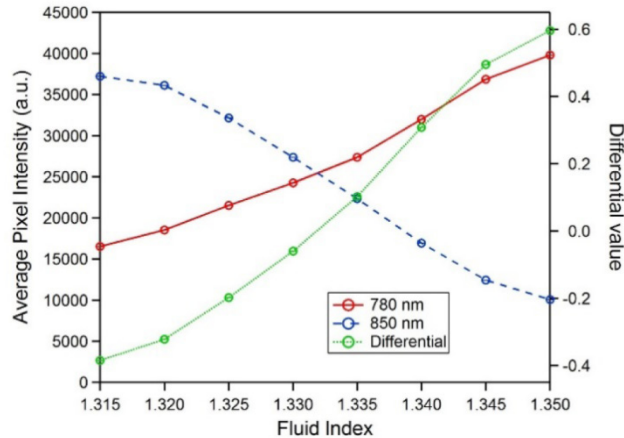


Fig. 3. Measured results of the optical cavity sensor with the two-laser system as a function of refractive index from 1.315 to 1.35 (red solid line: 780 nm, blue dashed line: 850 nm, and green dotted line: differential value).

3.3 Repeatability test

We performed a repeatability test for this optimized design for the refractive index measurements. Three more samples are fabricated with the exactly same process. Figure 4 shows the measurement results of these three new samples compared to the sample we measured for Fig. 3 (1st sample). The slopes of differential values for 1st, 2nd, 3rd, and 4th samples are similar to one another, which are 32.943/RIU, 28.11/RIU, 29.449/RIU, and 32.002/RIU, respectively. In addition, they show good linearity in the dynamic range of 0.025 with the coefficients of determination (R^2) of 0.9907, 0.9977, 0.9831, and 0.9946, respectively. However, despite the similarities, the differential values have shifted slightly and each sample has a dynamic range in a different refractive index region. For example, the 1st sample has the dynamic range in between the refractive index of 1.32–1.345. However, the 2nd sample, which is shifted the most from the 1st sample, has the dynamic range in between 1.3 and 1.325. The horizontal shift of the differential value is mainly due to cavity width variations among samples. Based on the simulation, we found that the 2nd sample has a cavity width larger than the 1st sample by 33 nm while the 4th sample's cavity width is larger by 8 nm. Further simulations show that a 50 nm deviation (about 2.3% from the designed width of 2.2 μm) in the cavity width shifts the dynamic range by 0.03 in the refractive index. This result also implies our design for the two-laser system has a very tight fabrication tolerance to maintain the dynamic range around 1.33. This is problematic because the optical cavity structure is mainly proposed for biosensing applications. In other words, if these four samples are used for biosensing applications, the 2nd and 3rd samples won't show the response change upon the adsorption of target biomarkers because their dynamic ranges don't include 1.33.

The cavity width of the optical cavity sensor is determined by the SU8 thicknesses on both substrates and the manual bonding process. It is not an easy task to fabricate consistent samples with this tight fabrication tolerance, and it will eventually increase the cost of sample fabrications. One way to improve this fabrication tolerance is to increase the dynamic range. With a large dynamic range, it is possible for any sample to have a dynamic range including 1.33, even with some fabrication errors. To increase the dynamic range and improve the fabrication tolerance, we propose a three-laser system with a chained differential detection method.

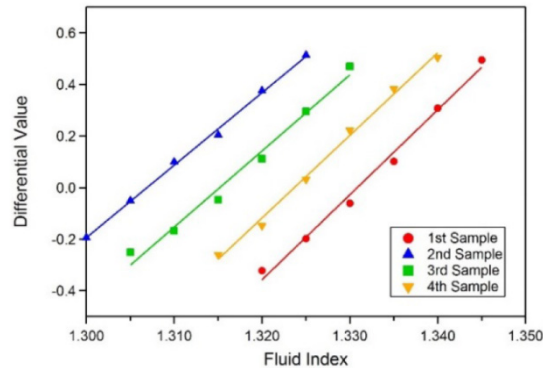


Fig. 4. The repeatability test results. The 1st sample data is from Fig. 3.

3. Three-laser system

A schematic of the three-laser system is shown in Fig. 5. Again, we optimized the optical cavity structure for the available low-cost off-the-shelf laser diodes. The final wavelengths used for the optimized structure are 780 nm, 808 nm, and 904 nm wavelengths. Two beam splitters combine the collimated light waves from three different laser diodes. The light waves propagate through the optical cavity along the same path, and the CMOS camera captures each laser beam profile to measure the average intensities of the three laser diodes sequentially.

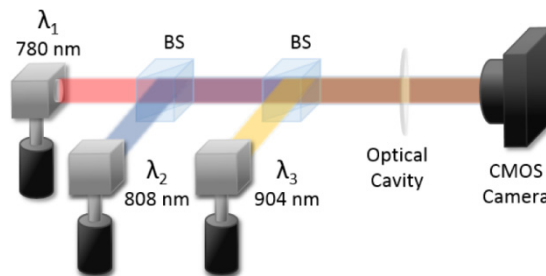


Fig. 5. Schematic diagram of three-laser system using low-cost laser diodes at 780 nm, 808 nm, and 904 nm wavelengths.

3.1 Simulation results

The optimized optical cavity structure for the three-laser system has a cavity width of $3.5 \mu\text{m}$ and a silver thickness of 8 nm. The simulation results are shown in Fig. 6. Figure 6(a) shows the efficiency changes for the three wavelengths between the refractive index of 1.3 and 1.45. The resonant response curves overlap one another to create repeated patterns in which at least two of the three wavelengths are changing their intensities in opposite directions throughout the entire range of the refractive index. We selectively chose those two wavelengths at different index ranges to calculate the differential values. For example, between the refractive index of 1.314 and 1.337, efficiencies of 780 nm and 808 nm are changing the most in the opposite directions while the efficiency of 904 nm doesn't change much. Therefore, those two wavelengths are used to obtain the differential values in that range. Similarly, the differential values are calculated using 780 nm and 904 nm wavelengths from 1.337 to 1.351 index. In the range of 1.351–1.371, we used 808 nm and 904 nm wavelengths to calculate the differential values. Figure 6(b) shows the calculated differential values in these different ranges with different sets of wavelengths that are used. This mechanism is named the chained differential detection method. By utilizing it, we can obtain seven linear regions of

differential values between the refractive index of 1.314 and 1.45. Figure 6(c) shows the concatenated differential values, which have a slope of 35.724/RIU with a coefficient of determination of 0.998. The dynamic range obtained by the chaining action is 1.314–1.45 ($\Delta n = 0.136$), which is more than five times greater than the dynamic range of the two-laser system ($\Delta n = 0.025$).

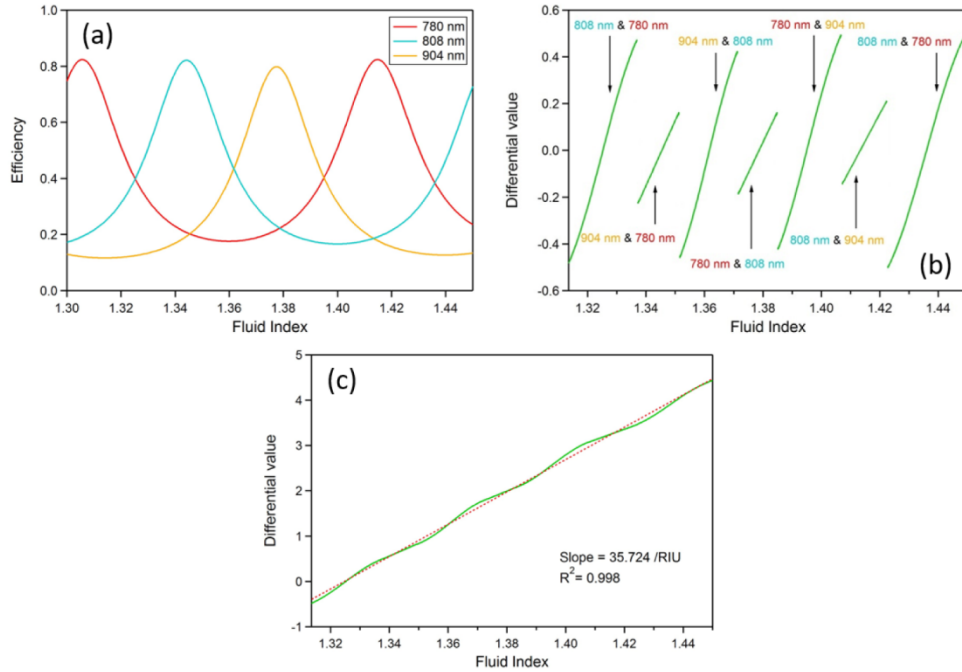


Fig. 6. Simulation results for the optimized optical cavity structure for the three-laser system. (a) Efficiencies of 780 nm (red), 808 nm (sky blue), and 904 nm (yellow) as a function of the refractive index from 1.3 to 1.45. (b) Calculated differential values with different sets of two wavelengths in seven different sections. (c) Concatenated differential values.

3.2 The refractive index measurement results

To experimentally demonstrate the optical cavity sensor with a chained differential detection method, we fabricated the optical cavity structure with exactly the same process used for the fabrication of samples for the two-laser system except for thicker SU8 layers on both substrates (slower spin speed) in order to obtain the cavity width of 3.5 μm . The test setup for the three-laser system is also the same, except for the use of three laser diodes and two beam splitters, as shown in Fig. 7. The results of the refractive index measurements using the three-laser system are shown in Fig. 8. Figure 8(a) shows the measured intensities of the 780 nm, 808 nm, and 904 nm wavelengths in the refractive index range of 1.3–1.395. The results are very similar to the simulation results in that the measured intensities of the three wavelengths overlap each other and form a repeating pattern. The differential values are obtained by using different combinations of two wavelengths changing the most in opposite directions. Initially, for the refractive index range of 1.3–1.33, 780 nm and 808 nm are used to calculate the differential value. Then, 780 nm and 904 nm are used for the range of 1.33–1.34 while 808 nm and 904 nm are used for 1.34–1.365. For the index range of 1.365–1.375, 808 nm and 780 nm are used. Lastly, 904 nm and 780 nm are used for the range of 1.375–1.395. The combined differential values in the different refractive index ranges with different sets of wavelengths are shown in Fig. 8(b). Figure 8(c) shows the concatenated differential values that have a slope of 40.548/RIU and a coefficient of determination of 0.994 within the dynamic range of 1.3–1.395 ($\Delta n = 0.095$). This experimentally measured dynamic range is

more than three times greater than that of the two-laser system. Note that this is the measurable dynamic range with the refractive index fluids we used, and the actual dynamic range could be more than five times greater than that of the two-laser system based on the simulations.

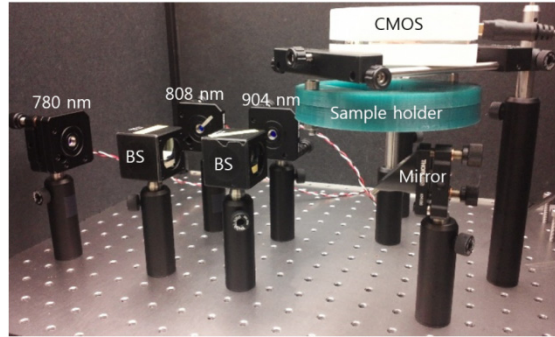


Fig. 7. The measurement setup for the three-laser system.

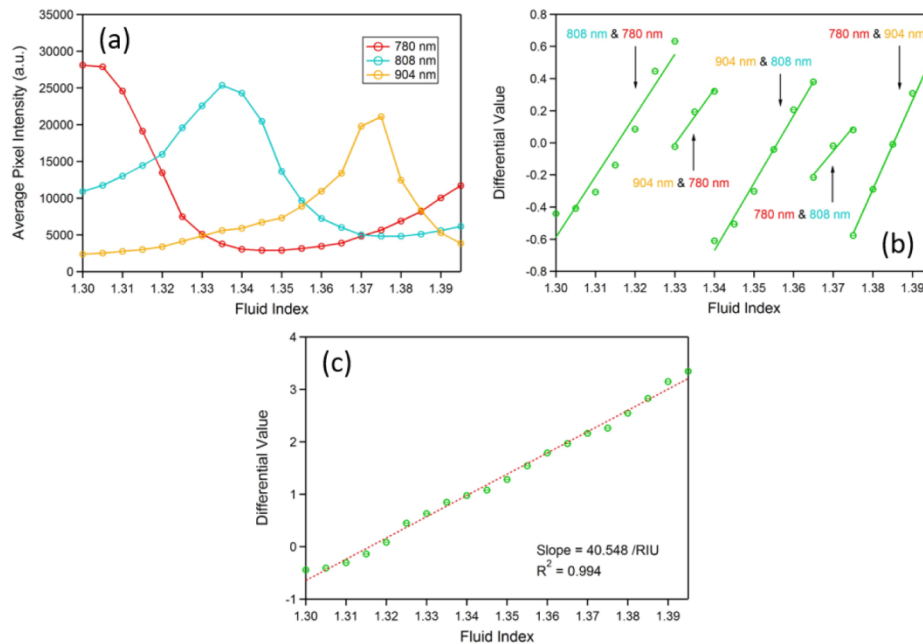


Fig. 8. Measurement results. (a) Intensities of 780 nm (red), 808 nm (sky blue), and 904 nm (yellow) as a function of the refractive index from 1.3 to 1.395. (b) Calculated differential values in five different sections with selected wavelengths. (c) Concatenated differential values.

3.3 Repeatability test

A repeatability test is also performed on the three-laser system. We fabricated two more samples with exactly the same process used for the sample for Fig. 8 and conducted refractive index measurements. Figure 9 shows the concatenated differential values of all three samples as a function of the refractive index between 1.3 and 1.385. All of them are changing linearly with the slope of 39.407/RIU (1st sample used for Fig. 8), 40.488/RIU (2nd sample), and 39.726/RIU (3rd sample). The coefficients of determination are 0.994 (1st sample), 0.995 (2nd sample), and 0.99 (3rd sample). As expected from the two-laser system repeatability

test, the cavity width variations among three samples cause the resonant response curve shifts. However, because of its large dynamic range, the differential values still have linear changes near the refractive index of 1.33. This means the optical cavity sensor with a chained differential detection method using the three-laser system has not only a larger dynamic range but also a larger fabrication tolerance. Because of the large dynamic range, this optical cavity sensor can measure a wide range of refractive index of fluids. And because of its large fabrication tolerance, the optical cavity sensor with some fabrication errors can still be used for biosensing.

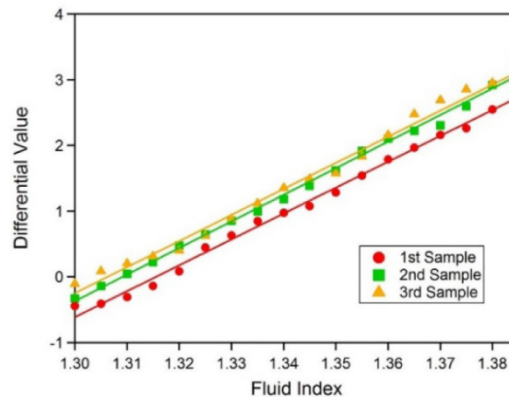


Fig. 9. The concatenated differential values of three samples using the three-laser system.

4. Conclusions

The optical cavity based biosensor has been proposed and experimentally demonstrated through refractive index measurements. The optical cavity structure for the two-laser system is designed to have a cavity width of $2.2\ \mu\text{m}$ and a silver thickness of $8\ \text{nm}$. By employing the differential detection method, the responsivity and dynamic range are improved compared to the intensity change of individual wavelength. The measurement results match very well with the simulation results. However, the repeatability test shows that small fabrication errors such as $33\ \text{nm}$ in the cavity width makes the sensor unusable for biosensing. This tight fabrication tolerance is mainly due to the small dynamic range of the sensor ($0.025\ \text{RIU}$). To improve the fabrication tolerance by increasing the dynamic range, we have proposed to employ a three-laser system using laser diodes with wavelengths of $780\ \text{nm}$, $808\ \text{nm}$, and $904\ \text{nm}$. The optimized optical cavity structure for the three-laser system has a cavity width of $3.5\ \mu\text{m}$ and a silver thickness of $8\ \text{nm}$. We properly select different sets of wavelengths that change in opposite directions for different refractive index ranges. The differential values in different refractive index ranges are calculated using those selected wavelengths. We obtained the concatenated differential values by properly combining them. The measurement results match very well with the simulation results again for the three-laser system. The concatenated differential values with the three-laser system has the responsivity of $40.548/\text{RIU}$ with a dynamic range of 0.095 , which is more than three times greater than that of the two-laser system. The repeatability test using the three-laser system shows that the increased dynamic range effectively improves the fabrication tolerance. Note that the responsivity reported in this paper is not necessarily the best responsivity of the proposed optical cavity based sensor. We focused more on demonstrating the optical cavity sensor with the chained differential detection method using the standard refractive index fluids. Therefore, the slope of the differential values can be increased by properly redesigning the optical cavity structure for more sensitive biosensing applications.

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