

Vertical Cavity Laser and Passive Fabry Perot Interferometer Based Microfluidic Biosensors

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Abstract: Passive and active microfluidic Fabry-Perot vertical cavity based biosensors were designed and fabricated for the detection of biological cells. Transmission spectra of single polystyrene spheres, yeast cells, and blood cells inside optical cavities are reported.

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1. Introduction

Rapid detection of chemical and biological samples is of great interest in a variety of fields, including biology, health, environmental monitoring, and homeland security. Laser based biosensors, such as Raman optical tweezers [1] and biocavity lasers [2] have been used for the detection of human blood cells. In this work, we have combined microfluidic and optical sensing techniques to realize real-time, label free detection of single biological cells. The detection and differentiation are based on the modulation of an actively or a passively excited Fabry-Perot (FP) cavity's transmission spectrum due to changes in refractive index of a sample inside the microfluidic cavity.

Both active and passive versions were developed in this work. The active biosensor was constructed by integrating a microfluidic sample area to the laser cavity of an electrically pumped vertical external cavity surface emitting laser diode (VECSEL). The resulting device is termed a fluidic intracavity laser diode (FIL) sensor. The passive biosensor, referred to as an optofluidic intracavity spectrometer (OFIS) sensor, was constructed by etching a 10~30 μm deep fluid filled FP cavity on glass substrates. It utilizes an external broadband LED as the excitation source. Both the active and the passive biosensors excite longitudinal and transverse modes through the biological cells in their respective FP cavities. The transmission spectra of both the sensors were used to detect and identify different biological cells placed in their respective sample areas. This paper presents preliminary results obtained from the active VECSEL based biosensor, showing significant modulation of laser spectra due to prototype 10 μm diameter polystyrene spheres. Transmission spectra of single biological cells including yeast and human blood cells using the passive biosensor are also reported in this work. Preliminary results on correlation analysis of the transmission spectra prove the concept of biosensor's functionality.

2. Biosensor structures and fabrication

Fig. 1 shows the structures of the FIL and the passive interferometer based biosensors. The detailed information about the fabrication of FIL and OFIS biosensors can be found in references [3] and [4] respectively.

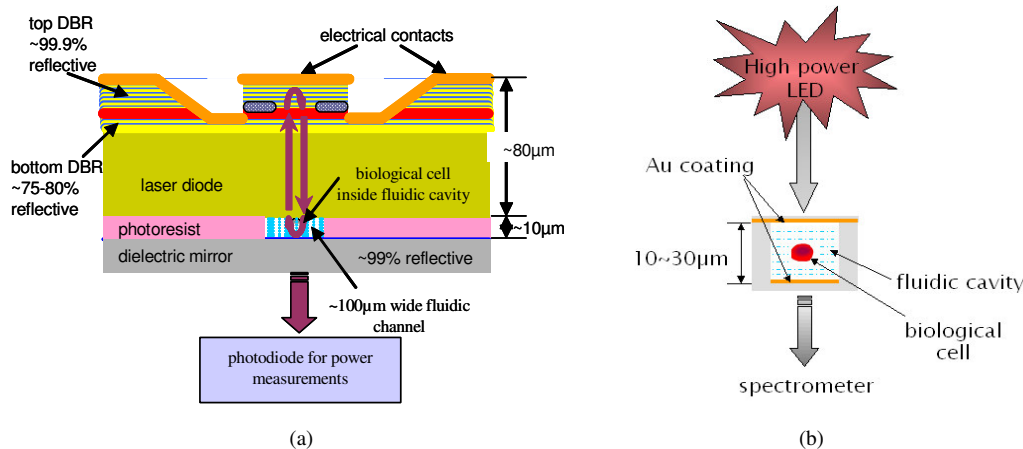


Fig. 1. Structures of (a) active VECSEL based biosensor and (b) passive Fabry-Perot interferometer based biosensor.

3. Sensing mechanism and experimental results

Both the sensors share the same sensing mechanism, which is based on the modulation of transverse mode spectra by a biological cell. Different biological cells have different shapes and refractive index profiles. When placed inside an actively or passively excited Fabry-Perot cavity, these cells uniquely modulate the transmission spectra of the resonator. Single cell spectra obtained using this method qualitatively appear to have characteristics such as the number of modes and mode spacing that can be used to differentiate cells. Fig. 2 (a)-(c) shows the measured transmission spectra of single cells obtained by using a passive biosensor. Fig. 2 (d) shows the transmission spectra of an active VECSEL based biosensor modulated by a prototype 10mm diameter polystyrene sphere.

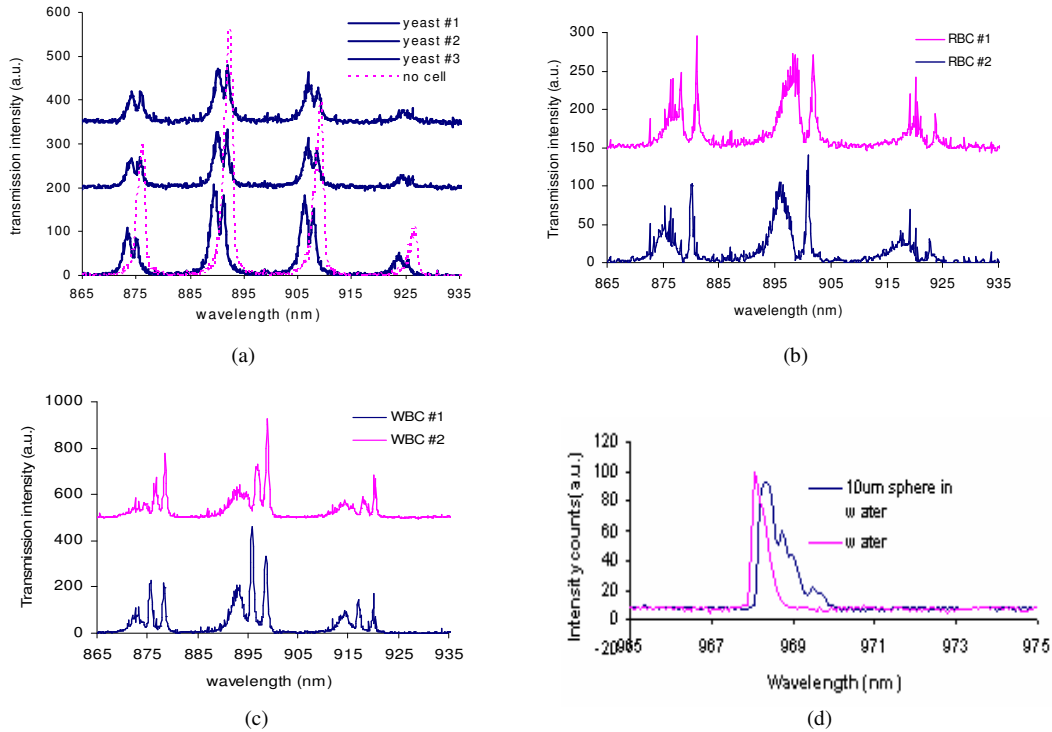


Fig. 2. (a) active device; (b) spectral features of single yeast cells, (c) red blood cells, and (d) white blood cells measured by the passive biosensors.

4. Theoretical analysis

In order to prove the repeatability and reliability of the biosensor to differentiate single biological cells, transmission spectra of multiple cells of each type used in this work have been taken repeatedly. Correlation analysis is a widely used technique in biochemical experiments to recognize specific chemical components [5] and is applied here to cell differentiation. Detailed correlation algorithm has been discussed in reference [6]. Fig. 3 shows an example of the resulting spectra for one red blood cell and one white blood cell.

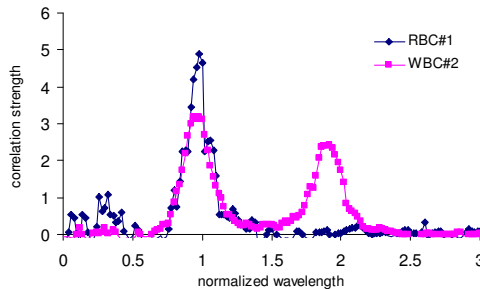


Fig.3. Spectra of a red blood cell and a white blood cell processed according to the steps discussed in reference [6] and ready for a correlation integral.

The correlation coefficients between the transmission spectra of four red blood cells, two white blood cells, and three yeast cells were then computed and recorded in Table 1. The correlation data shows that the red blood cells can be differentiated from white cells based on a correlation coefficient threshold of 0.8, but that the method is not sufficient to differentiate red blood cells from yeast cells. It is also noteworthy that the two white blood cell spectra had a relatively low correlation and may have come from different cell types e.g. neutrophils and lymphocytes. The results presented here were initial correlation studies and better results are expected from more complete studies including the creation of correlation templates or masks that account for the variability of spectra for the same type of cells.

Table 1. Correlation coefficients of spectra for red blood (RBC), white blood (WBC), and yeast (Y) cells.

	RBC1	RBC2	RBC3	RBC4	WBC1	WBC2	Y1	Y2	Y3
RBC1	1	0.84	0.84	0.8721	0.7016	0.6716	0.8430	0.862	0.7993
RBC2	0.84	1	0.9011	0.847	0.757	0.7442	0.820	0.8115	0.8666
RBC3	0.8721	0.9011	1	0.8784	0.7026	0.7241	0.6810	0.7660	0.7314
RBC4	0.9252	0.847	0.8784	1	0.7591	0.7223	0.9068	0.9230	0.8907
WBC1	0.7016	0.757	0.7026	0.7591	1	0.6507	0.6910	0.7690	0.7533
WBC2	0.6716	0.7442	0.7241	0.7223	0.6507	1	0.571	0.6385	0.7465
Y1	0.843	0.820	0.6810	0.9068	0.6910	0.571	1	0.9699	0.8707
Y2	0.862	0.8115	0.7660	0.9230	0.7690	0.6385	0.9699	1	0.9247
Y3	0.7993	0.8666	0.7314	0.8907	0.7533	0.7465	0.8707	0.9247	1

5. Summary

VECSEL and passive Fabry-Perot interferometer based microfluidic cavity biosensors are reported in this work. Transmission spectra of different biological cells from a passive FP interferometer based biosensor are presented. Continuous efforts are being made to improvise the device structure of the active VECSEL based sensor to achieve high finesses transmission spectra, towards the goal of biosensor's functionality. Efforts are also being made towards performing a rigorous correlation analysis that can account for the variability of spectra of the same type of cells. This project was supported in part by DARPA under research contract # E-21-F89-G1.

6. References

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