Continuous detection of micro-particles by fiber Bragg grating Fabry-Pérot flow cytometer

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Abstract: A novel method to detect different sizes of micro-particles using a fiber Bragg grating Fabry-Pérot (FBG-FP) flow cytometer is presented. The chip is composed of a FBG-FP cavity integrated in a microfluidic channel. Solution with three different sizes of polystyrene particles flowing through the channel induces variations in the transmission spectrum of the FBG-FP cavity. Theoretical and experimental data show that different sizes of particles reveal different resonant wavelengths with a good resonance shift sensitivity of 10⁻⁵. Additionally, the chip is easy to fabricate and features with non-contact and label-free operation. This study demonstrates a promising potential of the FBG-FP flow cytometer in medical and biological sensing.

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References and links


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1. Introduction

The detection of protein molecules’ structure [1], living cells’ size [2] and organic nanospheres’ shape [3] is an important topic in biomedical and chemical studies. For example, the size of tumor cell is larger than that of normal cell. Therefore, the reorganization of cell size is an effective way to distinguish different kinds of cancers. Actually, fundamental dynamical processes of a single cell or particle is often covered up in complex systems filled with different kinds of cells or microparticles. In the past decades, there have been significant efforts to improve the detection precision and efficiency. Researchers are driven to develop new methods to distinguish and analyze particle/cell size, shape and structure [4] for biomedicine [5], environtology [6] and many other disciplines.

Recently, analysis of particle/cell size using optofluidic micro-systems (lab on a chip) is a hot topic, which integrates various functions of a traditional laboratory, such as sampling, dilution, reaction, separation, and detection. Compared with traditional optical devices, optofluidic chips feature advantages of high integration and reconfigurability [7]. Therefore, the optofluidic chip is becoming a new research platform for particle study and even single-cell analysis and detection [8]. W. Z. Song et al. designed a microfluidic chip integrated with a fiber-based Fabry-Pérot (FP) cavity [9]. They used spectral shift feedback to determine the cell’s refractive index (RI) and size at 0.1% accuracy. Niyom Lue et al. used Hilbert phase microscopy to measure living cells’ average RI [10]. H. Shao et al. differentiated polystyrene spheres, Y cells, human RBCs, and WBCs by studying their transmission spectra [11,12]. Although above-mentioned optofluidic chips have been demonstrated in these technologies, there are unfortunately several inadequacies to overcome. The observation process usually involves procedures of cell capture, where intense laser may lead to cell damages. In addition, complicated manufacturing method usually requires great quantity of precision components and expensive instruments, making the detection inefficient and costly. A compact and quick detection device is more competitive to simplify the distinguishing process. And undamaged and label-free methods should be adapted for more precise measurement.

Flow cytometry is a rapid way to quantitatively analyze tens of thousands of particles and cells, and to sort the specific group of them in a fast-flowing fluid simultaneously [13–16]. At present, there are several methods to detect particle/cell, such as using fluorescence labelling...
cells [17], capturing particles by laser trapping [18], applying magnetic field [19], parallel electrodes [20] or surface acoustic waves [21]. However, some fluorescent dyes used in biochemical analysis are detrimental or harmful. The detection method of using laser trapping usually accompanies with photochemical reaction. And, the preparation process of chips integrated with magnetic field, electric field or surface acoustic wave generation devices is complicated and these methods are only suitable for certain kinds of particles/cells. Therefore, it is especially important to fabricate a device that can meet all these requirements.

In this study, we present a non-contact, label-free, and real-time monitoring flow cytometer to realize continuous particles recognition based on an FP cavity embedded in a microchannel, which is fabricated in a Polydimethylsiloxane (PDMS) microfluidic chip. The Fabry-Pérot cavity is composed of a pair of aligned fiber Bragg gratings (FBGs). Compared with conventional fiber based FP cavity [9], the fiber Bragg grating based FP cavity (FBG-FP) is more attractive for the particle detection due to its higher reflectivity, sensitivity and Q factor [22,23]. In the FBG-FP cavity, the optofluidic channel serves as a defect to the FBG, leading to a phase shift when light propagates from the input fiber to the output fiber. The resonant wavelength (or the defect mode) is critically dependent on the phase shift when the particles are presented in the cavity. In our experiment, the solution containing different polystyrene micro-spheres is injected into the microchannel and the resonant wavelength shift is observed. Since the refractive indices (RIs) of particles are the same, the phase shift is just influenced by their sizes. We can distinguish the size of particles through different resonant wavelength shifts. Not only could it be used to detect single particle rapidly, but also the non-contact and label-free manipulations can avoid damages to the sample. Such a device might contribute to complex separation and mixture of particles/cells recognition in medical, chemical and clinical researches.

2. Modeling principle of FBG-FP cavity

The formulation for the forward and backward wave amplitudes, $a$ and $b$, is given by the matrix method based on the coupled-mode theory [24, 25]:

$$\begin{pmatrix}
a_{\text{out}} \\
b_{\text{out}}
\end{pmatrix} = \begin{pmatrix}
A & B \\
C & D
\end{pmatrix}^M \begin{pmatrix}
\exp(ih) & 0 \\
0 & \exp(-ikd)
\end{pmatrix} \begin{pmatrix}
A & B \\
C & D
\end{pmatrix}^N \begin{pmatrix}
a_{\text{in}} \\
b_{\text{in}}
\end{pmatrix},$$

where $A = (1-r^2)^{-1} \left[ \exp(iqh) - r^2 \exp(-iqh) \right]$, $C = -B = (1-r^2)^{-1} r[\exp(iqh) - \exp(-iqh)]$, $D = (1-r^2)^{-1} \left[ \exp(-iqh) - r^2 \exp(iqh) \right]$. Here $h$ is the cavity length, $q = \pm \left[ 2\pi \left( \lambda^{-1} - \lambda_g^{-1} \right) \right]^{-1/2}$, and $r = \left[ q - 2\pi \left( \lambda^{-1} - \lambda_g^{-1} \right) \right]/\kappa$ is the effective reflection coefficient of the grating, $\kappa = \pi \delta n / \lambda_g$ is the grating coupling constant. $\lambda_g = 2n_{\text{eff}} \Lambda$, where $n_{\text{eff}}$ is the effective refractive index of the optical mode, $\Lambda$ is grating period and $\delta n$ is the depth of index modulation. $M$ and $N$ are the period number of the left and right FBG, respectively. The phase discontinuities is accounted by the shift of $\Delta \phi = k_l l$, where $k_l = n l \omega / c$, $n_l$ is the cavity RI. $l = n_i (h - d) + n_d d$ and $d$ is the particle diameter, $n_i$ is the particle RI. The transmission spectrum can be calculated by $T = |A \cdot (B - C) / D|^2$.

In our configuration, the cavity length and location are fixed. With the above formulism, we can go on calculating the $l$ value, which simply corresponds to the particle size and particle RI. The transmission spectrum is modified by the various particles passing through the cavity.
3. Fabrication and experimental setup

Figure 1(a) presents the schematic diagram of the designed optofluidic chip based on FBG-FP cavity. The optofluidic chip is fabricated in PDMS via conventional soft lithography methods. The chip consists of one cruciform fluidic channel and two FBGs with a refractive index contrast of $10^{-3}$ and a period of 535.5 nm. The FBGs are inserted into the fiber channel as the input and output fiber, as shown in Fig. 1(b). The Bragg wavelength is 1549 nm. As part of the system, the inlet and outlet channels are 125 μm in width. Since the FBG outer diameter is 125 μm (Corning SMF-28e), the fiber channels are designed to have a width of 150 μm and aligned with each other to reduce the coupling loss between the FBG-FP cavity and input light. Two ends of the inlet channel are the injection slot and select slot, respectively. An amplified spontaneous emission (ASE) source with wavelength from 1528 nm to 1573 nm is coupled into the input fiber. The output signal is detected by an optical spectral analyzer (OSA, AQ6370C) with a resolution of 0.01 nm. Since the optofluidic channel is much larger than particle size and the particle flows in the channel is not always at the center, we cannot judge the particle only on the resonant wavelength. Thus, the chip is put under an inverted microscope (IX51, Olympus) in order to get a clear observation of the FBG-FP cavity during the measurement process. As the coupled light propagates through the FBG-FP cavity, a significant resonance peak can be observed as a result of phase shift occurring in the FBG-FP cavity. The position of the resonance peak is very sensitive to the phase shift variation in the FBG-FP cavity, i.e. the particle size. Therefore, injecting the solution with different particles into the channel will modify the position of the resonance peak, resulting in variations in the transmission spectrum. As a result, a change of the particle size in the solution can be transferred to a corresponding variation of transmission spectrum. By monitoring the position of the resonance peak, the particles in the solution can be accurately defined. In order to avoid interference of measurement error, the measurement and observation are simultaneously. That is to say, when we see the particle flowing through the center of the channel, the transmission spectrum is recorded. The chip has the advantages of low cost and easy fabrication which make the FBG-FP flow cytometer suitable for a fast and efficient detection.

![Schematic of the optofluidic chip](image1)

Fig. 1. (a) Schematic of the optofluidic chip. (b) Top view of the cruciform fluidic channel with two FBGs. (c) Photograph of the 15 μm and 25 μm particles flowing through the FBG-FP cavity.

4. Result and discussion

To characterize the particle size detecting performance of the FBG-FP flow cytometer, our experiment was performed using de-ionized (DI) water (RI = 1.333) and DI water contains three kinds of polystyrene particles as the injected solutions. The diameters of particles are 15, 20 and 25 μm, and RI is 1.59. We injected the solution via a programmable syringe pump and the injection speed was controlled at 5 μL hr⁻¹. DI water was first injected into the channel as the blank solution. After the whole cavity is filled with DI water and the transmission spectrum is stable, the DI water contains three kinds of polystyrene particles was then injected into the channel. The transmission spectrum was synchronously recorded by an OSA. The photograph of the channel for particle detection is shown in Fig. 1(c). The particles are flowing in the
channel. Figures 2(a)-2(d) show the experimental transmission spectra. In Fig. 2(a), the wavelength of the phase-shift peak is 1549.08 nm when the channel cavity is filled with pure DI water. In Fig. 2(b), the spectrum shows a new phase-shift peak wavelength of 1548.70 nm when a 15 μm particle passes through the cavity. The resonance shift is −0.38 nm. Analogously, in Fig. 2(c), the phase-shift peak exhibits an obvious red shift to 1549.18 nm when a 20 μm particle passes through, and the peak becomes weaker with the resonance shift of 0.1 nm. As a 25 μm particle flows through the FBG-FP cavity which is shown in Fig. 2(d), the phase-shift peak changes to 1549.56 nm with the resonance shift of 0.48 nm, and the peak is the strongest. As a comparison, Figs. 2(e)-2(h) show the simulated transmission spectra. Figure 2(e) shows the resonant wavelength is 1549.08 nm when the \( n_r \) and \( d \) are set as 0. As \( n_r = 1.59 \), Fig. 2(f) shows the case of \( d = 15 \) μm, the resonant wavelength is 1548.45 nm and the resonance shift is −0.63 nm. Figure 2(g) shows the resonant wavelength is 1549.36 nm with a resonance shift of 0.28 nm in the case of \( d = 20 \) μm. When \( d = 25 \) μm, the resonant wavelength is 1549.75 nm with a resonance shift of 0.67 nm. The theoretical resonant wavelengths are basically consistent with the above experimental results. Figure 3 Shows the resonant wavelength as a function of the particle size. It can be seen that the detection sensitivity of \(-10^{-3}\) is obtained.

![Fig. 2. Measured and simulated transmission spectra in response to different particles' sizes.](image)

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![Fig. 3. Linear relationship between the resonance shift and particle size for theoretical result (solid line) and experimental result (dashed line) with a slope of 10^{-3}.](image)
To show the movement process of the particles in the FBG-FP cavity intuitively, we used a laser with a center wavelength of 1549 nm as an input source. The output fiber was directly connected to an oscilloscope as Fig. 4(b) shows. We used the solution with all three kinds of particles (15, 25 and 20 μm) as the injected solution and the flowing rate is fixed at 5 μL hr⁻¹. Stable triangle waveform was formed, as shown in Fig. 4(d). It presents a critical waveform when a 25 μm particle followed a 15 or 20 μm particle into the cavity, the valley value of the optofluidic signal develop to deeper. The changing of particle size will lead to a signal value variation, which indicates the monitoring detection system are reliable, stable operation and excellent compatibility. Simple requirement of equipment and convenient manufacture ensure the particle can be determined rapidly. Meanwhile, low solution consumption and real-time measurement are realized in the detection process.

Fig. 4. Illustration of various light signal generation. (a) Triangle signal generation when a 15 μm particle flows through the cavity. (b) Deeper triangle signal generation when a 25 μm particle flows through the cavity. (c) Schematic illustration of the experimental setup. The black arrows indicate the directions of light propagation. (d) Experiment result of light signal by injecting the solution contained 15, 20 and 25 μm particles at the flowing rate of 5μL hr⁻¹.

5. Conclusion

An easy fabricated, simple control and label-free micro-detection system was demonstrated in a PDMS chip and a new method to distinguish different sizes of particles in a FBG-FP cavity was exhibited (see Visualization 1). Experimentally, as particles with different sizes (15, 20 and 25 μm) flowing through the cavity, three different resonant wavelengths were observed. The results show that the particle size can be correlated with the resonance shift. The simulated and experimental results fit well. In addition, a particle detection flow cytometer may be expected to have great potentials in medical and biological sensing. It would provide a novel method to improve detection efficiency because of its easy fabrication and operation. Furthermore, the merit of recyclable can significantly reduce the waste of resources.

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