# A Compact Optofluidic Cytometer for Detection and Enumeration of Tumor Cells

Jinhong Guo, Xiuhong Liu, Kai Kang, Ye Ai, Zhiming Wang, and Yuejun Kang

***Abstract*—Biophotonics has emerged as a powerful technology, which can reveal very important physiological information for healthcare applications. Nowadays, with the development of advanced micro/nano fabrication technology, the interdisciplinary optofluidic technology by integrating the polymer-based microfluidic chip with the optical fiber provides a convenient and powerful platform for point of care diagnosis. In this paper, we demonstrate a low cost and compact optofluidic cytometer, which is able to characterize the biological cells by analyzing multiple phenoltypical and biochemical parameters. This device includes the microfluidic focusing and optical detection components on a glass substrate made with Poly(dimethylsiloxane) (PDMS). Multiple optical parameters such as fluorescence, side scatter, and forward scatter are obtained to provide 3-D plots for determination of cell types and subpopulations. As a specific biomedical application, the proposed compact optofluidic cytometer is able to provide a rapid and low-cost platform for detection of tumor cells.**

***Index Terms*—Biophotonics, circulating tumor cell, microfluidic chip, optical fiber, optofluidic cytometer, point of care.**

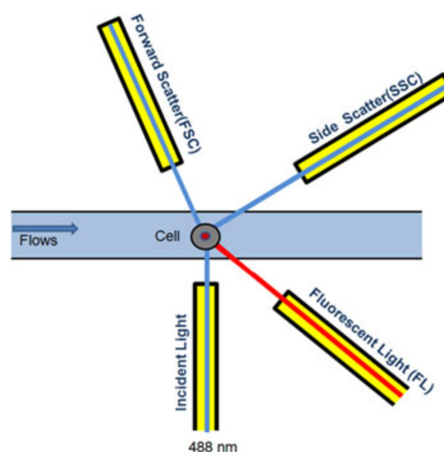


Fig. 1. Schematic illustration of the major optical parameters (FL, FSC, SSC) in flow cytometry.

## I. Introduction

FLOW cytometry has successfully demonstrated its powerful ability to characterize and analyze biological cells for clinical diagnostics of hematological disorders [1]–[5]. As illustrated in Fig. 1, when cells transport through a detection region, where an incident light beam is active, optical signals such as forward scattering (FSC), side scattering (SSC), fluorescent light (FL) emission are simultaneously measured to provide important biological information of cells. FSC signal measured at a small angle (0.5°–20°) is able to provide the information such as cell size and viability. SSC signal measured at large angle (15°–150°) reveals the information such as cellular granularity. Fluorescence signal is measured from the same angle as SSC and can provide the specific biological information which is determined by the type of labeled molecules. Once these three optical parameters are measured simultaneously, multi-dimensional analyses of critical parameters can be achieved to sort all the detected cell events into different phenoltypical groups. Conventional flow cytometry, such as Beckman–Coulter FC500, has a very high price tag of about US$100 000 for a basic configuration. The daunting cost of the conventional flow cytometry seriously limitations access and availability for low-income patients in most developing countries. In addition, the bulky size of the conventional flow cytometer restricts its portability for point of care diagnostics. In recent years, the advanced micro/nano fabrication technique combined with microfluidics-based lab-on-a-chip technology enables the development of compact optofluidic cytometry, which is believed to be an innovative and promising platform for analyzing the chemical and biological samples in a rapid, reliable, and portable fashion [6]–[9].

In addition to hematological assay, flow cytometry has gradually been applied for diagnosis of other major diseases, e.g., cancer. Cervical cancerranks the third in the common malignant tumors that leads to women death after breast and colorectal cancer in developing countries [10], [11]. HeLa cells are the circulating tumor cells (CTCs) shed from the primary cervical tumors, causing metastases in the cancer patients [12]. Detection of these extremely low-abundance CTCs is critical for clinical diagnosis and treatment of cervical cancer. However this task

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remains challenging under current clinical practices. Although the recent concept of a compact Coulter counter may provide a potential solution to analyze the electrical properties of biological cells [13], however it cannot realize comprehensive and reliable biochemical assays using the abundant biomarkers available for optical detection. Therefore it is highly desirable to develop a compact optofluidic cytometer, which enables low cost, reliable, and rapid clinical detection for the CTCs due to cervical cancer.

In order to develop miniature flow cytometer, compact lab-on-chip systems have been introduced recently [14]–[20]. Compared to the conventional methods, on-chip diagnostic devices offer many advantages, such as they only require the handling of extremely small sample volumes with low density of particles of interest. These devices also make it possible to integrate sophisticated sample handling and detection components on a single chip, which enables the development of compact and standalone platform for real clinical applications. Miniaturization of flow cytometer was first attempted by Kamentsky in the mid-1960s [3]. In the last decade, micro-cytometry mostly based upon optical detection has been developed. Some of the early devices demonstrated the feasibility of miniaturization of flow cytometer. Wang *et al.* integrated optical fibers with microfluidic channels to build a miniature optofluidic cytometry capable of FSC and SSC measurements [6]. The developed optofluidic cytometer was demonstrated to differentiate microspheres of different sizes. Fluorescence detection capability was later implemented in the optofluidic cytometer for the detection of nucleic acid labeled fungus [7] and DNA fragment analysis [8]. However, they suffered from lower sensitivity and screening throughput, which limited their functionality for practical biological or clinical applications. The performance of the optofluidic micro-cytometry mainly depends on the precise integration of the optical detection components into the on-chip devices. In most applications, the optical fiber or integrated waveguide is employed to deliver and collect the optical signals. It is still a challenge to design an optofluidic chip with low coupling loss, while maintaining focus of light.

In this paper, we present a PDMS-based microfluidic chip with integrated optical fibers for detection of CTCs using both light scattering and fluorescence measurement. Biological cells were hydrodynamically focused by sheath flows to pass through the laser light one-by-one. We have developed a numerical model to predict the hydrodynamic focusing, which can help optimize the cell positioning when passing through the detecting fibers. The optical signals (FL, SSC and FSC) were collected by the embedded optical fibers for cell characterization. Compared with existing studies [6]–[8], the on-chip lens design was optimized to maximize the sensitivity and meanwhile minimize the coupling loss. To demonstrate its application in cancer diagnosis, the developed compact optofluidic cytometer was applied to differentiate HeLa cells from mixed microspheres. The results were compared to those from a commercial flow cytometer. It was demonstrated that the proposed optofluidic cytometer was able to provide a low cost and compact platform for point of care diagnostics to characterize and analyze the CTCs accurately and reliably.

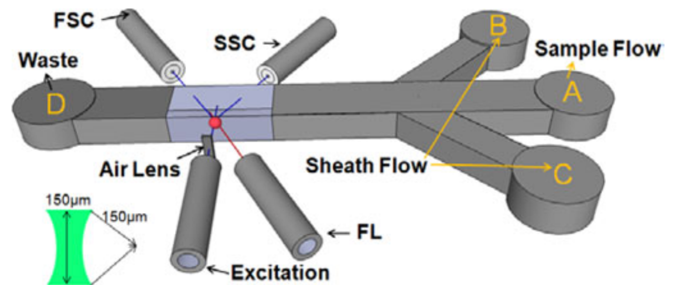



Fig. 2. Schematic view of the proposed optofluidic cytometer, inserted fig indicates the geometry properties of the air lens.

## II. Method and Fabrication

The schematic configuration of the compact optofluidic cytometers shown in Fig. 2. The device consists of a flow component (hydrodynamic sheath flows) and a detection component (optical fibers detection). Inlet A is used to introduce the biological samples, while B and C are used to convey the sheath flow to keep the sample from inlet A focused at the center of the microfluidic channel. In the detection region, the excitation fiber is used to deliver the 488 nm laser to the center of the optofluidic chip. A hollow chamber filled with air is designed to work as a lens and focus the laser light on the detection spot where the biological sample passes through. Three detection fibers are used to measure three optical parameters, including FL, FSC light and SSC light, respectively.

### A. Hydrodynamic Focusing Design and Simulation

The flow component employs the hydrodynamic sheath flows to focus the micro-particles along the axis of the microfluidic channel. By optimizing the ratio between the sample flow rate and the sheath flow rate, the biological cells can be focused in a thin stream of 20 $\mu$m in width along the axis of the microfluidic channel for accurate detection. The simulation and optimization is performed by a commercial Finite Element Method package (COMSOL, Mathworks, MA, USA). The COMSOL computational fluids dynamics module can compute the flow field by solving the Navier–Stokes equation:

$$\rho\left[\frac{\partial\vec{u}}{\partial t}+\vec{u}\cdot\nabla\vec{u}\right]=-\nabla p+\mu\nabla^2\vec{u} \tag{1}$$

where $\rho$ is the fluid density, $\vec{u}$ is the fluid velocity, $p$ is the pressure, and $\mu$ is the fluid viscosity. The diffusion equation is

$$\frac{\partial c}{\partial t}+\nabla\cdot(-D\nabla c)=R-\vec{u}\cdot\nabla c \tag{2}$$

where $c$ is the concentration, $D$ is the diffusion coefficient, and $R$ is the reaction rate. During this simulation, $D=10^{-10}\mathrm{m}^2/\mathrm{s}$, and $R=0$ since there is no chemical reaction that affect the concentration of the reagents. The focusing width can be evaluated through the concentration profile of the aqueous phosphate buffered saline (PBS) solution.

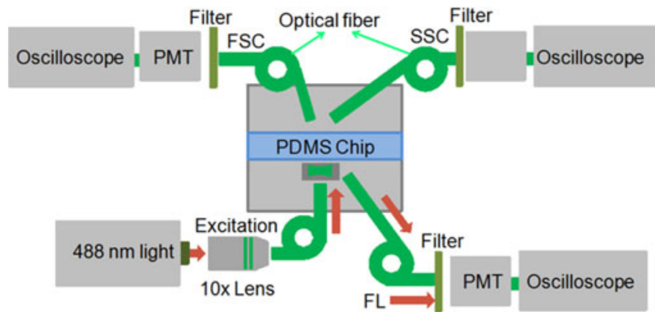


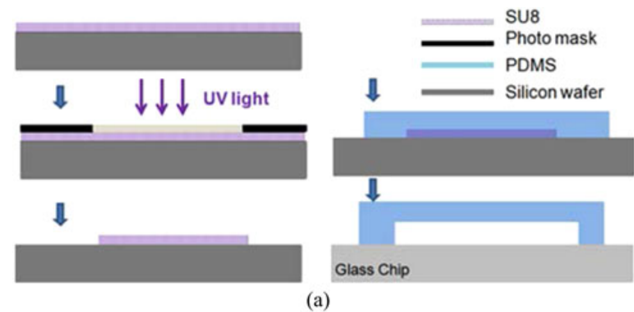

Fig. 3. Schematic configuration of the optical detection components.

### B. Optical Design and Detection

As illustrated in Fig. 3, the detection component includes four optical fibers, one incident and three detection fibers. The incident fiber (single-mode, core diameter: 50 $\mu$m, cladding diameter: 125 $\mu$m, and $\mathrm{NA} = 1.4$) is with smaller numerical aperture (NA) and is able to guide the excitation light of 488 nm to the sample flow stream, which is achieved by focusing using the air lens. The design of the on-chip air lens was optimized by commercial optical design software ZEMAX (Radiant Zemax, America). In the optimization, the refractive index of PDMS was set as 1.412 [21], and the refractive index of the PBS buffer was approximately set as 1.333 [21]. In order to form the beam spot that could cover the micro-particle located at the center of microfluidic channel, the radius of curvature of the air lens was optimized as 155 $\mu$m, the original beam width without lens is larger than 100 $\mu$m, and around 50 $\mu$m with lens at the center of the microfluidic channel. The other three detection fibers (multiple-mode, core diameter: 105 $\mu$m, cladding diameter: 125 $\mu$m, and $\mathrm{NA} = 0.22$) with relatively larger NA were used to collect the scattered light and FL. The fibers for FL and SSC light were buried with receiving angles of 60° and 120°, respectively (see Fig. 2). The fiber for FSC light was arranged with a receiving angle of 20°. The height of the optofluidic chamber was designed as 128 $\mu$m so that the optical fibers with outer diameter of 125 $\mu$m could fit in appropriately. Band-pass filters with central wavelength 488nmwere applied for FSC and SSC signal; and a band-pass filter with central wavelength 588 nm was used for FL signal. Finally, all the filtered optical signals were amplified by photomultipliers and displayed subsequently by a digital oscilloscope. The data were collected by a data acquisition board and was imported in MATLAB (Mathworks, America) for further processing.

### C. Device Fabrication

Soft-lithography rapid prototyping was used to fabricate the microfluidic chip. Negative photoresist SU-8(SU-8 2050, Microchem, MA, USA) was spin-coated on a silicon wafer under speed of 1500 r/min and subsequently soft baked (65 °C for 5 min, 95 °C for 20 min). After UV light exposure for 20 s and post-baking (65 °C for 5 min, 95 °C for 10 min), the coated wafer was submerged in SU-8 developer for 10–15 min. Finally, the patterned SU-8 mold was created on the silicon wafer with height of 128 $\mu$m. The PDMS (Sylgard 184, Dow Corning, MI, USA) and curing agent were mixed with a volumetric ratio of 10:1 and then cast on the SU-8 mold. After degassing for 30 min, the PDMS was cured in an oven box for 4 h at temperature 75°. The solidified PDMS chip was peeled off from the mold. The optical fibers were carefully inserted into the fiber groove manually. Finally the chip with embedded optical fibers was plasma-treated and bonded with a clean glass substrate. The fabrication procedures and the final chip with installed tubing are shown in Fig. 4.



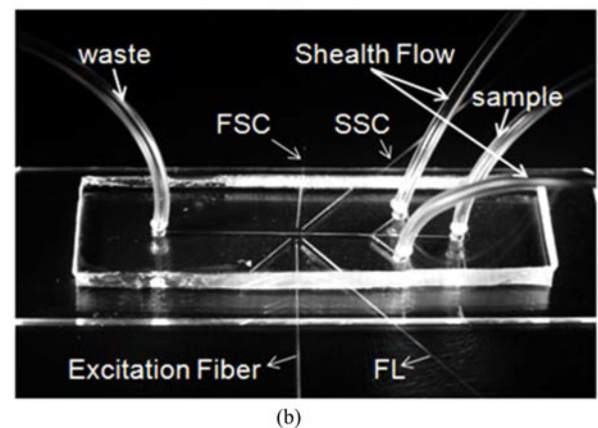




Fig. 4. (a) Soft-lithography fabrication of the microchannel. (b) Final assembly of the optofluidic cytometer.

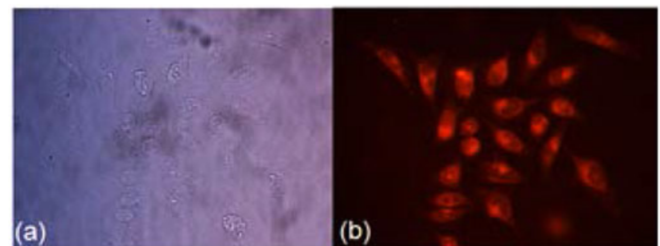



Fig. 5. (a) HeLa cells under the bright field. (b) Stained HeLa cells under a fluorescence microscope.

### D. Cells Preparation

Hela cells (American Type Culture Collection, MD, USA) were cultured in Dulbecco's modified eagle medium supplemented with 10% fetal bovine serum, 1 mM sodium pyruvate, 0.1 mM MEM nonessential amino acids. The cells were grown at 37 °C under 5% $CO_2$ atmosphere in a T75 flask. Fig. 5 shows their images of the HeLa cells under the bright field and the dark field, respectively. The HeLa cells are stained with

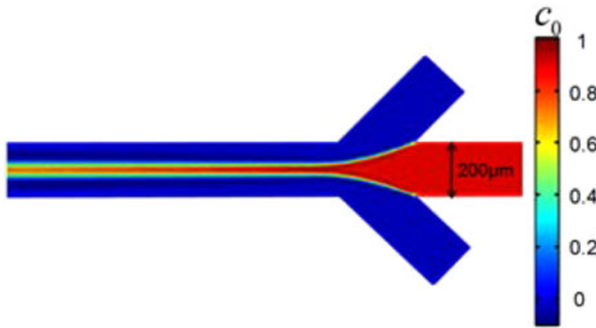



Fig. 6. Numerical simulation of the hydrodynamic focusing, which shows the concentration profile of the aqueous solution diffusing in water. The flow rate ratio is set to be $\mathrm{FRR} = 3$. The focusing width is about 20 $\mu$m.

4′ 6-diamidino-2-phenylindole (Calbiochem, America) with 488 nm excitation/588 nm emission.

## III. Result and Discussion

### A. Simulation of Hydrodynamic Focusing

In order to achieve the Laminar flows for hydrodynamic focusing in the micro-scale channel, it requires to keep Reynolds number ($Re = \rho \mathrm{vL}/\mu$ low for the flows [22]. This results from the necessity to generate a reliable focusing effect along the flow path, guaranteeing that the biological samples can transport in line until they reach the detection region. The ratio of liquid flow rates between focusing streams and sample flows should be set to meet this requirement. In the simulation, the ratio of the flow rates between hydrodynamic focusing liquids and central liquids is set 1:3. The simulated result of hydrodynamic focusing is shown in Fig. 6, indicating the concentration profile of an aqueous solution diffusing in DI water along the microfluidic channel. In such case, the simulated width of the aqueous solution is within about 20 $\mu$m, which can enclose the HeLa cells.

### B. Performance Test Using HeLa Cells

In order to evaluate the accuracy of the device for enumeration of CTCs, specific concentrations (500 units/50 $\mu$L, 1000 units/50 $\mu$L and 2000 units/50 $\mu$L) of Hela cells were prepared as shown in Fig. 7(a)–(c) under fluorescence microscope. Each sample was tested by both the optofluidic chip and a commercial flow cytometer (FC500, Beckman–Coulter, America). The HeLa cell suspension of each concentration was injected from inlet A (see Fig. 2) with a flow rate of 20 $\mu$L/min. PBS solution was introduced from inlets B and C as sheath flow at a flow rate of 60 $\mu$L/min using a syringe pump. For the optofluidic chip, only FL optical fiber was activated to record the fluorescence signals from the stained HeLa cells. The total number of the fluorescent cell events recorded by the optofluidic chip was compared with the data obtained from the commercial flow cytometer, as shown in Fig. 7(d), indicating a good agreement between the proposed device and the commercial flow cytometer. From Fig. 7(d), there are still some differences in the comparison. We speculate that one possible reason is the limitation

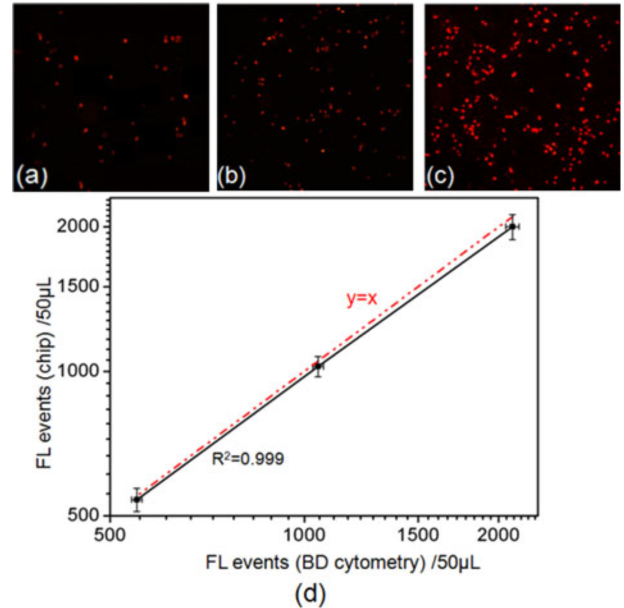



Fig. 7. (a)–(c). PBS diluted HeLa cells with dilution x1, dilution x2 and dilution x3, respectively; (d) quantitative comparison of the events obtained from the optofluidic cytometry and commercial cytometry.

of current design. The 2-D focusing could not make sure the vertical focusing, which may lead to the acquired signal from the detected tumor cell is weak since its location is not at the center of channel from the vertical axis.

### C. Performance Test Using HeLa Cells Mixed With Fluorescent Particles

We further performed a multi-parametric study using the developed chip on the mixture of HeLa cells with 5 $\mu$m fluorescent particles in order to test its capability of differentiating distinct groups of biological particles using FL, FSC and SSC signals simultaneously. Three samples of different HeLa concentrations were mixed with 5 $\mu$m fluorescent particles. The ratio between fluorescent particles and HeLa cells were pre-determined by the commercial cytometer as around 1:1, 2:1 and 4:1, respectively, for three experiment samples. Using the optofluidic chip, the 3-D plots of all detected cell events based on three optical signals (FL, FSC, and SSC) were correlated to provide critical information about the distribution and distinct groups of the HeLa cells and fluorescent particles as shown in Fig. 8. For the three samples, the ratio between fluorescent particles and HeLa cells measured by the optofluidic chip were 51.8%:48.2% (1.07:1), 68%:32% (2.13:1), and 81.2%:18.8% (4.32:1), showing good agreement with the data obtained by commercial cytometer. From the above experimental results, this optofluidic chip is capable of providing accurate characterization of biological samples containing distinct populations using multi-parametric optical detection.

## IV. Conclusion

This paper presents a compact optofluidic micro-cytometer for detection and enumeration of CTCs toward the point of

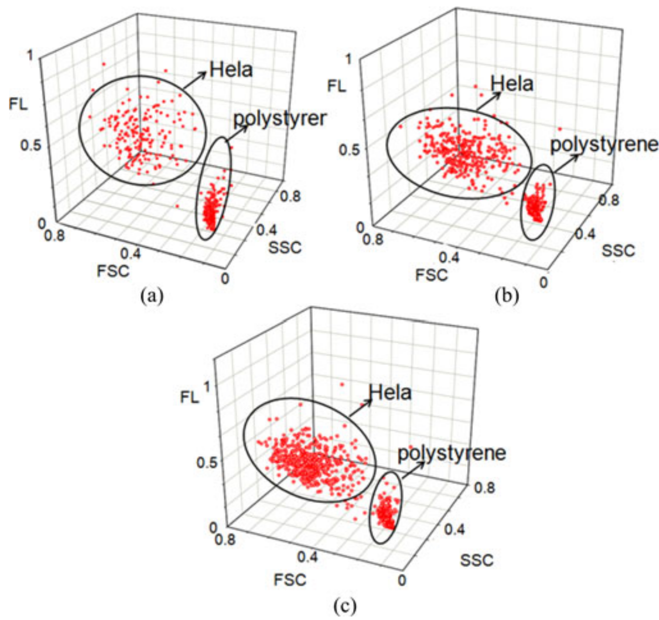



Fig. 8. 3-D plots of all detected cell events (FL+FSC+SSC) for mixed sample of HeLa cells and fluorescent particles with three ratios: (a) 1:1; (b) 2:1; (c) 4:1.

care diagnosis by integrating the hydrodynamic focusing and multi-parametric optical detection components. Simultaneous characterizing the FL, FSC and SSC signals can distinguish the different cell populations in the microfluidic chip. The fabrication cost is very low and the chip is highly portable compared to the bulky and expensive conventional flow cytometers. The cell detection and enumeration is as accurate as the current commercial counterparts. This optofluidic cytometer can provide a cost-effective and reliable platform for rapid point-of-care diagnosis.

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