Fluid dynamic simulation of single cell sorting by fiber laser in microfluidics

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Abstract. Optofluidic devices have immense potential for single cell manipulation, including trapping, sorting, counting and stretching. Commercially available devices remain costly and technical. Embedded optical fibers within the microfluidic device simplify the construction and supply stable, sensitive, high throughput scattering measurements for particles and cells. We present numerical simulations on flow field in micro channels embedded with an optical fiber, which are able to provide optical sorting and controlled movement of single particles. We simulate the displacement and deflection of micro particles by single laser with different optical forces. We believe that this simulation method can be used to emulate the process of optical trapping and sorting for cells at constriction channels of different cross-sectional areas.

1. Introduction
Single cell manipulation in microfluidics usually requires external force on targeted cells. Optical cell manipulation allows employing to gradient or scattering forces and pulling a cell or particle on condition of its permittivity higher than the surrounding medium [1-2]. A family of emerging technologies, such as single beam laser, diode laser bar, femtosecond laser, optical tweezer, is frequently used in cells sorting, trapping and manipulation [3-7]. For example, Francesca Bragheri et al. [8] proposed a hydrodynamic focusing microfluidic channels by femtosecond laser micromachining. Their device incorporated an optical waveguides to lift the sample for optofluidic cell separation. Liberale et al.[9] have presented a new approach to the development of microfluidic devices for lab-on-chip applications integrating optical trapping and manipulation capabilities. The design and development of miniaturized optical tweezers enabling on-chip manipulation, Raman and fluorescence spectroscopy of single cells lead to their achievement. More recently, A. Priezzhev et al. [10] demonstrated the use of laser tweezers to drive the particle from the equilibrium location. Christopher Probst et al.[11]safely relocated a filamentous Escherichia coli WT (MG1655) from its growing microcolony by laser manipulations. After trapping the cells the researchers calibrated the external forces in the range of 0.1-100pN[12-13]. Another type of optical single cell sorting was called “cross-type optical particle separation” technique [14]. Cells are lifted or pushed from flowing position to the channel portion using, which was proved to require less laser power than the traditional gradient force. Instead of directly using optical force, a striking example of “3D pulsed laser triggered fluorescence activated cell sorter” has been presented by Chen et al [15]. XIN Hongbao et al.[16] realized the arrangement of escherichia coli by using the effect of the restoring moment of the larger light gradient force generated by the large cone angle optical tweeters, which provided an easily realized method for maintaining cell-cell contact and an effective way for studying cell-cell
communication and signal communication. Focusing on generating a micro bubble near the junction of the device, high power pulse laser was applied to push a targeted cell into the collection channel.

Although optical methods are easy to operate and integrated with microfluidic system with a higher degree of freedom, single cell sorting has so far been limited by trial to error approaches and inefficient. Therefore, there is a need for development of dynamic simulation for high-throughput single cell sorting and manipulation. On the COMSOL website, we can see people using dielectrophoresis to separate red blood cells and platelets. Dielectrophoretic forces are closely related to the size, shape, and dielectric properties of the particles, and by controlling these properties, the various cells can be separated from the mixture (see in Figure 1). Here, we report a simulation method for fluid dynamics of single cell sorting by optically induced mechanical forces, to optimize the efficiency of sorting with variable cells.

![Figure 1. Red blood cell separation simulation using dielectrophoresis.](image)

2. Materials and methods
The light force that induces particle motion consists of two parts: the scattering force that acts on the direction of laser beam propagation and the gradient force that acts on the direction of laser beam intensity gradient (see Figure 2). When the gradient force is higher than the scattering force, the light force is shown as binding particles to the strongest light field. When the scattering force is greater than the gradient force, the light force is shown as pushing particles away from the beam direction.

![Figure 2. Schematic diagram of particle motion driven by optical fiber [17].](image)
Simulations were performed to observe the effect of streamlines generated by both laser beam and constriction channel for sorting cells. To simplify the model, the gravity of cells in micro-fluid was not considered in this condition. Similarly, the buoyancy and other external forces were not included here. The forces of operating cells or particles in microfluidics were modeled as the combination of drag force of a microflow to a cell and the laser force, and can be described as

$$\frac{d(mV_m)}{dt} = F_D + F$$

where $m$ is the quality of the targeted cells, $F_D$ is the drag force of the targeted cells, and $F$ is the laser force. $V_m$ is the velocity of the targeted cells in the flow. This model of drag force was integrated with the cell’s diameter to obtain the following description of different cells’ drag force.

$$F_d = \frac{18\mu}{\rho_m d_m^2}$$

where $\mu$ is the dynamic viscosity coefficient of the liquid, $d_m$ is the diameter of the targeted cells, and $\rho_m$ is the density of cells.

2D simulations were generated using a commercial program, COMSOL Multiphysics for cruciform channel (1000μm width, 1500μm length, and 100μm width for three inlets), as shown in Figure 1. The system consists of main channel (inlet 1), where the cell suspension is introduced, and two sheath flow channels (inlet 2 and inlet 3). At the blue area (see Figure 3), the laser force was assumed to be positive lateral force. The working fluid was assumed to be water in laminar flow module. A constant inflow velocity of $1e^{-4}$m/s is imposed on three inlets, and on the outlet a fixed pressure is also set. In particle tracking module, the cells were assumed to be solid (10μm in diameter, density of 1050kg/m³). And the laser force can be loaded in particle tracking module.

![Figure 3](image)

**Figure 3.** Schematic illustration of flow channels with three inlets. The laser force is loaded in the local area as described.

3. **Results and discussion**

3.1. **Fluid dynamics simulation with laser force**

As a typical sheath flow, the focusing flow is the distribution area of the cells under the action of fluid flow with no laser force, as shown in Figure 4. In the laminar flow, the fluids from three inlets do not
interfere with each other, and the width of the focusing flow is determined to be 22μm, which means the distributions of cells with no action of laser force are ±11μm.

Figure 4. Flow field visualized by streamlines in model.

To study single cell sorting using the laser forces, we simulated 6 different laser forces of 5pN, 10pN, 15pN, 20pN, 25pN, 30 pN, respectively. Cells will gradually deflect away from the fluid flow due to laser forces, as can be seen in Figure 5. The distribution of the cells is from -6μm to 16μm. For example, in the flow profile (Figure 5 A)), cells are deflected upward in the laser action area, and the deflection distance dy is 5 μm by the laser force of 5 pN. Depending on the laser force acted on the cells, some cells may approach into an upper streamline, and other cells may still stay in the focusing flow, with the laser force less than 15pN.

Figure 5. Characterization of hydrodynamic profile of the single cell deflection by laser forces using computational modeling.

Among the six different loaded forces, we determined the force of 35pN to be the sorting force because the cells were all deflected and bonded to the inner wall of the channel. While for the laser force of 15pN, cells were all deflected into the upper streamline, not in the focusing flow. And for 20pN, only a small number of cells at the upstream part of the flow were deflected and bonded to the inner wall as well. We tested the effect of laser force on the cells’ deflection distance as the linear relationship, as shown in Figure 6.
Figure 6. Deflection distance for single cells with different laser forces.

Moreover, as Figure 7 shows the correlation of the deflection distances and the cells’ diameter is not exactly linear, but the deflection distances tend to be smaller when the cells are bigger, which conforms to our understanding and cognition.

4. Computational simulations to predict microfluidic single cell sorting

To investigate how the cells sorting depended on the laser force, we added a collection channel (outlet 2) along the laser transmission direction to receive the sorted cells (Figure 8). As illustrated in Figure 8, with the layout of outlet 2, the streamline pattern was changed and the focusing flow shifted 4 μm along the Y direction consequently. However, under the action of laser force (35 pN), the cells (diameter of 10 μm) were deflected into the channel of outlet 2 (see Figure 9). This indicates that the flow field does not obviously change the cells’ trace, comparing with the laser force. In our simulation screening and sorting of different cells in suspension can be utilized by controlling the velocity of liquid entry and the quantity of laser force.

Figure 7. Deflection distance for variable cells with laser force of 15 pN.

Figure 8. Modified microchannels for single cell sorting.
Figure 9. 2D simulation result of cells (diameter is 10μm) being sorting to collection channel.

5. Conclusion

We used COMSOL software to simulate the flow field of micro channels by shear stress in a liquid flow. To predict active cell sorting, we calculated and optimized the hydrodynamic conditions and the external force to perform single cell’s deflection and its path tracing. The cells of interest were then optically guided into the sorting channel by laser force. Current simulation indicated that the laser force of 35pN could drive the cells (diameter of 10μm) to the collection channel.

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