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Finite Element Simulation of Microfluidic Biochip for High Throughput Hydrodynamic Single Cell Trapping

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Abstract

In this paper, a microfluidic device capable of trapping a single cell in a high throughput manner and at high trapping efficiency is designed simply through a concept of hydrodynamic manipulation. The microfluidic device is designed with a series of trap and bypass microchannel structures for trapping individual cells without the need for microwell, robotic equipment, external electric force or surface modification. In order to investigate the single cell trapping efficiency, a finite element model of the proposed design has been developed using ABAQUS-FEA software. Based on the simulation, the geometrical parameters and fluid velocity which affect the single cell trapping are extensively optimized. After optimization of the trap and bypass microchannel structures via simulations, a single cell can be trapped at a desired location efficiently.

Keywords*: single cell trapping, high throughput, finite element simulation, hydrodynamic, microfluidic*

1. Introduction

Microfluidics is a rapidly developing area of research, and scientists in the biotechnology, pharmaceutical and life science industries are continually discovering the wide range of possibilities the technology can provide. Microfluidics plays important roles in various emerging biological research and application development, including cellular biology [1,2], lab-on-a-chip [3-6], organ-on-a-chip [7,8] and synthetic biology [9,10] just to name a few. Recently, single cell analysis has become increasingly important in the field of cellular biology and medical research. Conventional cellular analysis usually measures the average response from a whole cell group. However, bulk measurements may cause misleading interpretations due to cell heterogeneity [11]. Therefore, the analysis of single cell is required to obtain accurate information regarding the properties, conditions or functional responses of individual cells.

For analyzing a single cell, the scale of the system must be miniaturized to the single cell level i.e. the physical dimensions of the systems are in the microscale range. In this light, microfluidics emerges as a powerful technology in providing an accurate individual cell manipulation. For achieving single cell analysis in microfluidic devices, trapping of a single cell is necessary. Currently, various techniques have been employed to trap an individual cell in microfluidic devices. These techniques include dielectrophoresis (DEP) [12-14], optical tweezers (OT) [15-16], microwell [17-19], and hydrodynamic trapping [20-23]. Dielectrophoresis uses a nonuniform electric field to exert a force on a dielectric particle [24] and can be used to manipulate different types of particles [25]. Although it is a very versatile technique, it requires polarization of the manipulated object. Moreover, to design the system correctly, the frequency at which the object will experience positive or negative dielectrophoresis must also be known. There is also a risk of cell damage from the stress induced by the electrical field or joule heating if care is not taken when designing the system [26]. Optical tweezers are capable of mobilizing and trapping cells using a gradient force produced by a focused laser beam [27]. The trapped cell can be moved freely by the manipulator. Although optical tweezers are a high-precision technique, it can only be used on a limited number of cells, and the position of the cell needs to be known in advance. Care must also be taken to avoid absorption of laser light by trapped cells, since cell may be heated during manipulation due to photothermal effects from the laser irradiation and this may result in cell damage [28]. Microwell arrays allow random capture of thousands of cells by gravity forces. Although the throughput of such devices is high and many

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cells can be trapped in an array-based format, precise geometrical optimizations are required in designing the microwells to achieve a high trapping efficiency [17]. In this method cells are not actively held inside the traps and the following chemical rinsing step may remove the cells from the bottom of the microwells. Hydrodynamic trapping systems are based on the use of differential fluidic resistances, where fluidic streamlines transport single cells into each trap. Once a cell is captured by a trap, the cell body diverts the streamlines to exclude subsequent cells. In comparison to other methods, hydrodynamic trapping has shown advantages of ease of operation, high biocompatibility, and high trapping efficiency without the need for surface modifications or external forces. Although hydrodynamic technique has recorded success in trapping cells, further parameter investigation and optimization on cellular trapping efficiencies are still requested [29].

In this study, a proof of concept demonstration for a cell positioning platform using hydrodynamic manipulation to trap a single cell is presented. The proposed microfluidic device consists of a series of trap and bypass microchannel structures for efficient and reliable cell trapping. Selecting appropriate geometrical parameters and obtaining the fluid velocity are helpful to ensure efficient trapping of cells. By using the optimal design parameter selection of the device, individual cells could be trapped efficiently without the need for surface modification, external electric force, or robotic equipment. To fulfill this requirement, a finite element simulation model to study the hydrodynamic trapping of cells in the microfluidic device is created. Then, the simulations are conducted to evaluate the cells trapping efficiencies for various geometrical parameters. The results obtained from the finite element simulation model show a very good agreement with the previously published experimental results by Tan and Takeuchi [21], which highlighted the value of finite element simulations in predicting and investigating the movement of cells in the microfluidic device. The simulation set-up discussed in this paper can provide some significant guidelines for new biochip design and optimization.

2. Research Method

2.1. Hydrodynamic Trapping Mechanism

The proposed device employs fluidic resistance engineering to perform hydrodynamic trapping of single cell. To explain this mechanism, the possible flow paths of a single cell are schematically presented in Figure 1. In Figure 1A the arrow is going to the trapping path and in Figure 1B the arrow is going to the bypassing path. Here trapping is defined as a single cell flowing into the trap, and bypassing is defined as the flow of subsequent cell through the channels next to the trap.

In order to trap the cell as shown in Figure 1, the trap array geometry should be designed so that the trapping path for an empty trap has a lower flow resistance than the bypassing path. Then during the loading process, a cell in the fluid is most likely to move into an empty trap (Figure 1A). However, once the trap is loaded by a cell, the flow resistance in trapping path dramatically increases and is much larger than that in bypassing path, and thus subsequent cell bypass the filled trap as shown in Figure 1B.

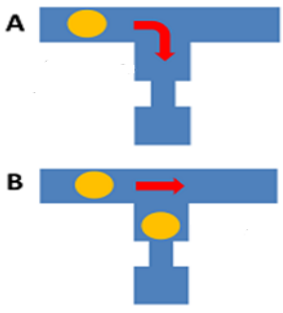


Figure 1. Schematic illustration of the flow hydrodynamic resistance in the microchannel for two different conditions (A) empty trap channel (before cell trapping occurs); (B) after cell has been trapped.

The flow within a microfluidic device is determined by the pressure drop across the two ends of the microchannel, as defined by the following Equation:

$$\Delta P = Q \times R_h = Q \times \left(\frac{12\mu L}{WH^3}\right) \quad (1)$$

where ΔP is the pressure drop, Rh is the hydrodynamic flow resistance of the rectangular microchannels, μ is the fluid viscosity, L, H and W are length, height and width of the channel respectively. By using a relationship of A = W × H and P = 2(W + H), the hydrodynamic flow resistance can be formulated in the following equation:

$$R_h = \frac{C\mu LP^2}{A^3} \quad (2)$$

where C denotes a constant that depends on the aspect ratio (H/W), A is the cross-sectional area and P is the perimeter of the channel. The flow rate ratio between trap path and main path can be modelled as given in the following equation:

$$\frac{Q_{Trap}}{Q_{Main}} = \left(\frac{L_M}{L_T}\right) \cdot \left(\frac{W_M + H_M}{W_T + H_T}\right)^2 \cdot \left(\frac{W_T H_T}{W_M H_M}\right)^3 \quad (3)$$

For the trap to work, the flow rate along trap path must be greater than that of main path (QTrap>QMain).

In this section, it is explained the results of research and at the same time is given the comprehensive discussion. Results can be presented in figures, graphs, tables and others that make the reader understand easily [2],[5]. The discussion can be made in several sub-chapters.

2.2. Simulation Setup

The analysis is carried out using finite element ABAQUS-FEA analysis software which can perform multiphysics analysis. The single cell trapping model consists of two different parts; Eulerian part as the fluid channel and a three dimension (3D) deformable part as the sphere-shaped elastic cell model as shown in Figure 2A-2B. The fluid consists of two microchannels, the main channel and trap channel with a rectangular trap hole is placed in the center, at the edge of the trap channel. The microchannel is modelled as 3D Eulerian explicit EC3DR and an 8-node linear Eulerian brick element part assigned with water properties (density, equation of state, and viscosity). A sphere-shaped cell (5 μm in diameter) is modelled as an elastic 3D standard solid deformable C3D8R and an 8-node linear brick 3D part.

Figure 2C shows the assembly setup with a cell positioned in the main channel, near the channel's inlet (left). The parts are assembled to develop the finite element model for the proposed system as shown in Figure 2C. The initial position of cell is fixed to the same position (distance between cell and trap channel) for all the models used. Interaction between objects and water are set as general contact with rough tangential behaviour and the interaction between cell surface and channel's wall is set as frictionless. The fluid channel and cell is meshed using hexahedron and tetrahedron mesh types, respectively. Total mesh elements for the cell trapping model ranged from 10627 to 22485 elements. No-inflow and non-reflecting outflow Eulerian boundary conditions are applied to the channel's wall. Constant inflow velocity of 0.5 μms-1 is applied to the inlet and atmosphere pressure is applied to the outlet of the channel for all the models analyzed.

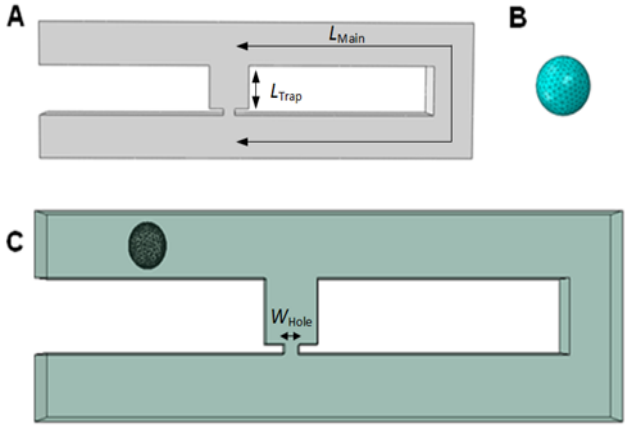


Figure 2. Construction of the finite element model of single cell trapping system and parts involved (A) Eulerian part (fluid channel's top view) Lmain represents the main channel's length and Ltrap represents the trap channel's length; (B) 3D deformable part (cell model); (C) Simulation's assembly setup (cell is positioned between inlet and trap channel as initial position) Whole represents trap hole's width.

3. Results and Analysis

3.1. Single Loop Microchannel

From the simulation result, RhMain/RhTrap ratio of 3.5 is found to be able to trap single cell via hydrodynamic trapping concept. The analysis is carried out to investigate the movement of subsequent cells after trapping occurred. Results obtained show that the first cell moved into the trap channel as shown in Figure 3B and subsequent cells bypassed the trap channel as shown in Figure 3C. The velocity streamlines plots illustrate how the fluid stream is directed to the trap channel during cell trapping as shown in Figure 3B, but then the direction changed to the main channel after the cell trapping as shown in Figure 3C.

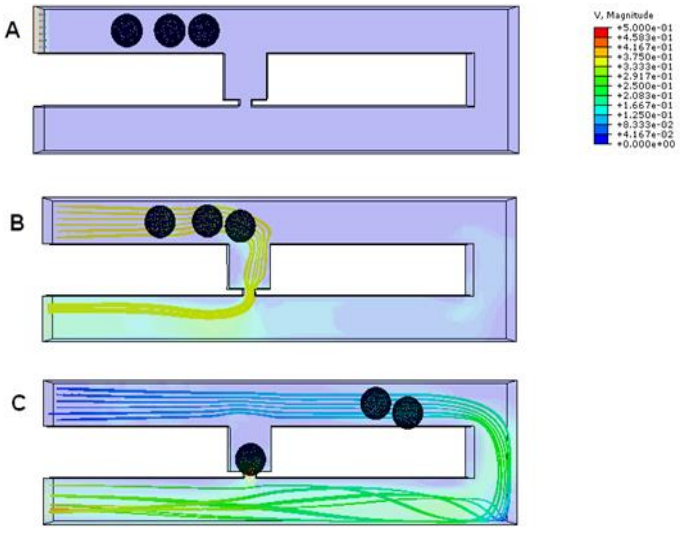
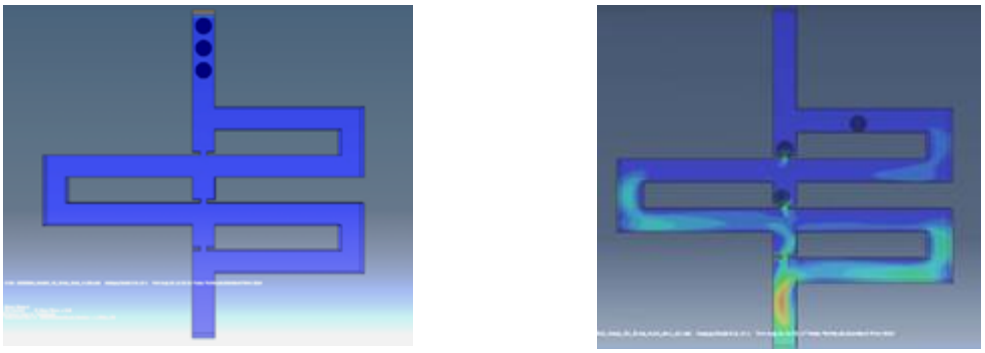


Figure 3. Simulation findings of fluid's velocity streamline plots for single loop microchannel with RhMain/RhTrap ratio of 3.5 during (A) the initial position of cells; (B) cell trapping; and (C) after cell trapping.

3.2. High Throughput Microchannel

The simulation results show that high throughput microchannel with RhMain/RhTrap ratio of 3.5 is able to trap single cells using the hydrodynamic trapping concept. Results obtained show that the first cell moved into the first trap channel and subsequent cells bypassed the first trap channel to be trapped into the following trap channel as shown in Figure 4B.



A B

Figure 4. Simulation findings of fluid's velocity streamline plots for high throughput microchannel with Rh_{Main}/Rh_{Trap} ratio of 3.5 during (A) the initial position of cells; (B) cell trapping.

4. Conclusion

In this study, a proof of concept demonstration for a cell positioning platform using hydrodynamic manipulation to trap single cells in high throughput manner is presented. Selecting appropriate geometrical parameters and obtaining the fluid velocity are helpful to ensure efficient trapping of cells. By using the optimal design parameter selection of the device, individual cells could be trapped efficiently. A finite element simulation model to study the hydrodynamic trapping of cells in the microfluidic device is created. The results obtained from the finite element simulation model show a very good agreement with the previously published experimental results which highlighted the value of finite element simulations in predicting and investigating the movement of cells in the microfluidic device.

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