A Simulation Study of Cell Separation in Microfluidic Channel Based on Hydrodynamic Principle

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***Abstract*— Separation micro-particles based on physical characteristics is important in numerous applications such as diagnostics, biological analyses, food industries and chemical processing. Microfluidic devices have emerged as a multi-functional and powerful platform for separation ranging from nano-micro sized particles to biological cells. This paper presents a simulation study for microparticle separation in a microfluidic channel based on hydrodynamic technique. By exploiting the hydrodynamic properties of the fluid flow and physical characteristics of microparticles, effective size-based separation is demonstrated. The objectives of the simulations are to obtain the appropriate channels' angle to separate micro-particle. The analysis of effects of taper angle for microparticle separation was carried out using numerical solutions from the finite element ABAQUS-FEA software. The taper angles 20º and 25º are successfully separate the mixture of 1000 kgm^{-3} and 10000 kgm^{-3} density microparticle.**

Keywords— ***Hydrodynamic; finite element; cell separation; microfluidic.***

I. INTRODUCTION

Separation process is essential for a wide range of technologies in both industries as well as research. It can be defined as a process to select or removal of specific impurities from heterogeneous mixture. In medical diagnostic, physical properties of cells will be investigated for example size, type, density and stiffness to classify the specific population of interest. Several lines of evidence suggested that cancerous cells tend to be softer than healthy cells [1], while malaria infected red blood cells will become stiffer and more rigid [2]. The efficiency of separation process can be evaluated by using several indicators like sample purity, enrichment and throughput [3]. High purity relay information regarding concentration of samples. Enrichment is the enhancement of target sample as compared to the background sample indicates selectivity of separation process. Throughput relates the separation speed typically reported in number of samples per minute or volumetric flow rate.

Recent trends towards label-free separation approach is widely accepted enabling the birth of microfluidic technology. Microfluidic devices have emerged as multi-functional and powerful platform for separation ranging from nano-micro sized particles to biological cells [4,5]. Microfluidic is proven to more remarkable to the conventional bench-top equipment's, because of more benefit offered from microfluidic such as reduced reagents usage, reduced power requirement and reduced samples volume [6-8]. For instance, microfluidic applications include sensing/detection [9,10], micromanipulation and microseparation [11]. Microfluidic separation device can be categories into two group, which are active and passive separation.

Label free techniques which require external force also known as active separations are driven either by electrical, magnetic, acoustic or optical. Dielectrophoresis (DEP) is derived from principle of electrokinetic whereby the separation is based on polarizability and size [12-15]. However, device which is prone to electrolysis and joule heating can cause permanent damage to the electrodes. Magnetic activated cell separator (MACS) was designed using integration of high gradient magnetic fields and FACS [16,17]. Although magnetic sorters may produce high specificity results, the application is limited to only magnetizable particles/cells and successful separation requires non-homogeneous magnetic field creation. Optical separation also has been used to sort waterborne colloidal particle using an array of holographic optical tweezer (HOT) [18,19]. This method has been tested for separations applications, however the constraints are quite demanding.

Passive techniques do not rely on labels instead utilize the manipulation between the flow field, channel structure and particles. In general, some of the famous techniques are microfiltration [20], microvortex manipulation (MVM) [21], pinched flow fractionation (PFF) [22] and deterministic lateral displacement (DLD) [23]. The hydrodynamic based separation can be seen as the most fundamental technique has been widely adopted for passive separation due to its simple and nondestructive nature. Hydrodynamic separation principle lies on the stream manipulation and interaction of particle with fluid or walls. Moreover, hydrodynamic separation can either utilized continuous wall or discrete wall because of the interaction between particle and wall. This technique was capable to separate blood, plasma and micro particle based on their size, shape and density [24]. The hydrodynamic device for separation is usually limited in term of efficiency. One group has demonstrated the CTC cell can achieved 90% separation by utilized centrifugal force technique based on curved microchannel [25]. However, ability to depleting a small particle was the limitation of this technique. Another group has utilized the effect of gravity in amplifying sedimentation of multi-sized polystyrene particles to enhance separation capability by >99% [26]. Although the sample purity has been greatly improved, the small fluid flow velocities (~1 mL/hour) produced in the device can be disadvantageous for preparative samples preparation [26].

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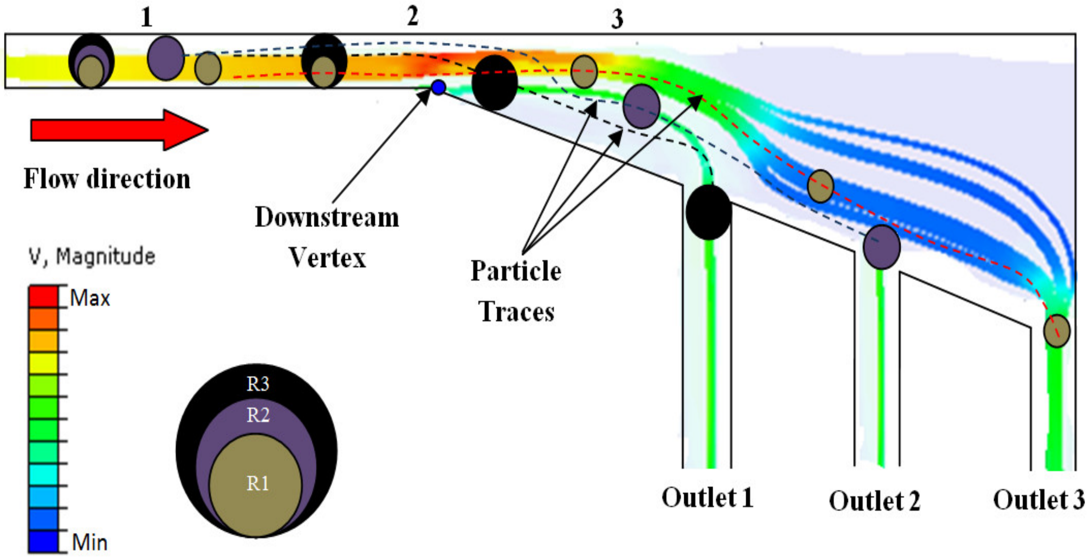

Fig. 1. Illustration of working principle for tapered microfluidic device. Particle radius R3>R2>R2.

Another group was demonstrated the three-dimensional microchannel was improved separation efficiency [27]. However, this complex fabrication and tedious bonding alignment procedure are major limitation of this device.

For that reason, an alternative separation method to provide high purity samples using low complexity device is needed. This study presents development of a simple passive separation device to meet with the requirements intended for high purity hydrodynamic based separation. The microfluidic finite element model based on hydrodynamic principle has been proposed in this paper.

II. THE IDEA AND CONCEPT OF THE MODEL

Micro-object hydrodynamic based separation involved manipulation of hydrodynamic spreading produced by tapered device design. Tapered microchannel is defined as a microchannel with an increasing channel width. This unique design enables faster velocity distribution in order to create a pressure gradient between main channel and the three outlets. Moreover, the widening of tapered microchannel width generates widening streamlines which is divided into carrier flow and original sample flow. Higher velocities signify lower hydrodynamic resistance property which is needed to ensure successful particle trapping towards the desired outlets.

The microparticle separation microfluidic device and the concept for microparticle separation are schematically illustrated in Fig. 1. A passive continuous flow microfluidic separation device was designed and implemented. The goal of the tapered microchannel was to passively separate multi-particles with different intrinsic properties (size and density) into three different outlet channels. The fluid velocity distributions were depicted after flow rate is applied to the device inlet. Cells will be introduced into the device through the inlet with appropriate flow rate. This widening of microchannels affected the velocity distributions and particles start to travel using their own path or trajectory [28,29]. Determination of particle path lines normally is dictated by the particle size. As a result, this situation triggers the sedimentation of particles. Sedimentation velocity experienced by denser and larger particles are greater than smaller one as indicated by (1).

$$U_{sed} = \frac{2r^2 g\Delta p}{9\mu} \tag{1}$$

Thus, denser and larger particles tend to sediment faster as compared to smaller particles. Particles distributed to outlet 1 tend to have the largest diameter. Particles collected by outlet 3 have the smallest diameter. Finally, particles with an intermediate diameter resulted in outlet 2.

III. SIMULATION SETUP

The channel was designed with consists of a single inlet, and three side outlets. The finite element ABAQUS-FEA analysis software has been utilized perform the analysis. ABAQUS-FEA is capable to execute multi-physics analysis. At first, a 3D finite element models have been developed for biological cell representing human cervical epithelial carcinoma (HeLa), polystyrene microbeads and to simulate the multi-particles separation using different taper sizes. The required parameters such as radius, density and Young Modulus were obtained from [18,19] and were defined at material assignment. Water micro-channel was modeled as 3D Eulerian explicit EC3DR and an 8-node linear Eulerian brick element was used [30,31]. Properties of water were assigned with density and viscosity where the value are 1000 kg/m^3 and 0.001 Pa.s respectively.

Inflow velocity was set to be in the range between 0.5 to 10 μm/s. Moreover, the density variations were in the order 10^3 of magnitude for light and denser particle. Lastly, 3.0 to 5.0 μm represents small particle while 10.0 to 20.0 represents big/large particle. To investigate the sedimentation effect to cell separation, 6°,12°,20° and 25° different angles of microchannel have been designed.

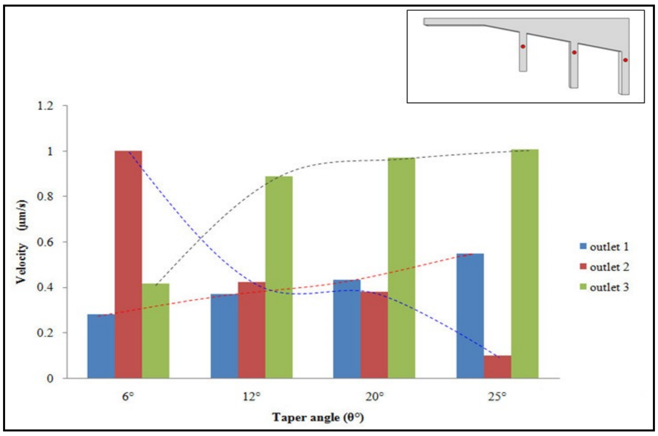

Fig. 2. The velocity trends for 3 different outlets with various taper angles

IV. RESULTS AND DISCUSSIONS

A. *Elurian simulation model verification*

Parametric study was conducted in order to verify hydrodynamic response from fluid distributions once velocity was applied at the inlet. The boundary conditions at all outlets were set to free and the velocity trend produced at all the outlets was being examined. The whole Eulerian part was considered as a shell with enclosed fluid and non-reflecting properties. From Fig. 2, the trends of velocity produced at outlet 1 and outlet 3 is increasing as taper angle increased while velocity at outlet 2 behaved differently.

According to the hydrodynamic principle, the highest velocity outlet will produce the lowest pressure point which will attract suspended particles for successful trapping [32]. However, it can be seen from the tapered. By looking at this phenomenon, the role of Outlet 2 was proven to be insignificant as compared to the Outlet 1 and Outlet 3. Only two outlets were used for separation simulation of two particles.

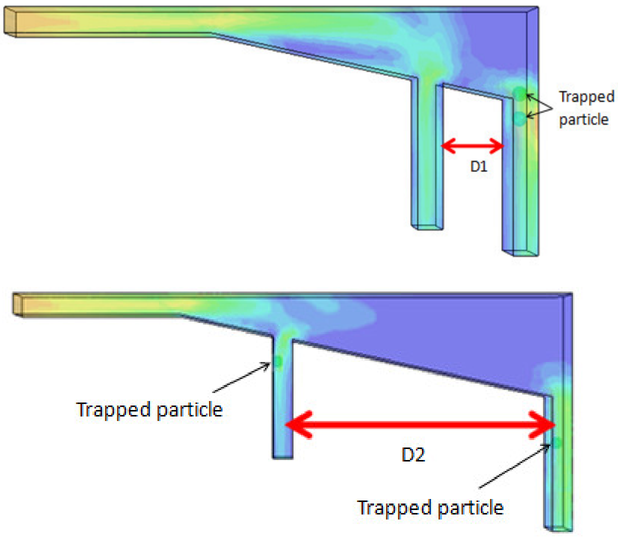

Fig. 3. Side outlets distance optimization simulation using two particles.

B. *Side outlets distance simulation optimazation*

The adequate side outlets distance is crucial in order to achieve successful multi particles separation. According to hydrodynamic trapping concept, successful trapping will occur at the point where the lowest pressure drop is detected which represents lowest hydrodynamic resistance value [33]. Fig. 3 shows the outlets distance optimization simulation for cell separation. D1 was not able to separate the two particles. While, the optimized distance D2 resulted in successful separation between the two particles. It can be seen from Table 1 that the outlets distance (gap) larger than 30 µm can produce successful separation of particles.

From the result, the small outlets gaps ranging from 10 µm to 30 µm were not proven suitable to be used on the tapered microchannel design on all taper angle sizes. Hence, outlet gap of higher than 30 µm will satisfy the minimum requirement for successful particle separation by using tapered microchannel.

Table 1: THE RESULT OF SIDE OUTLETS DISTANCE (GAP) IN TAPERED MICROFLUIDIC SEPARATION DEVICE.

Taper Angle (˚)	Gap (µm)	Separation
6 & 12	< 10	No
	< 20	No
	< 30	No
	> 30	No
20 & 25	< 10	No
	< 20	No
	< 30	No
	> 30	Yes

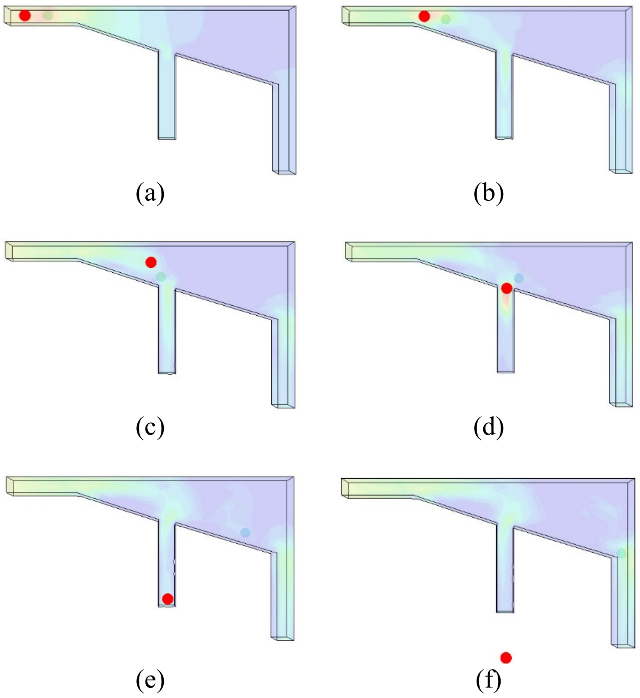

Fig. 4. Successful hydrodynamic separations for tapered microchannel angle 20˚

C. Simulation of particle separation using tapered microchannel

In this simulation, two different types of particles (polydisperse) were added in the simulation assemblies. Both particles have different density which are 1000 kgm^{-3} and 10000 kgm^{-3}. All four taper angle has been designed in this simulation for investigated the capability to separate the different particle density. Fig. 4 illustrated the simulation of microchannel with taped angle 20˚ by using hydrodynamic principle to separate the two microparticle.

As shown in Table 2, the larger taper angles 20° and 25° were successfully separate both denser and lighter particle. While the smaller taper angles 6° and 12° unable to separate the both particle in 1 cycle experiment proses. Denser particle tends to choose the nearest Outlet 1 (O1) while lighter particle will travel further away and collected by Outlet 2 (O2). Widening of streamlines due to tapered design will cause a rapid change in velocity and thus, the particles separations will happen. In real application, this capability is sought after for separation effectiveness due to high sample purity.

Table 2: HYDRODYNAMIC SEPARATION OF TWO PARTICLES INSIDE TAPERED MICROCHANNEL. L = 1000 KGM^{-3} AND D = 10000 KGM^{-3}

Taper Angle (θ˚)	**Particle positioning & Destination outlet**			
	L-D		**D-L**	
6	L=x	D=O1	L=O2	D=x
12	L=x	D=O1	L=O2	D=x
20	L=O2	D=O1	L=O2	D=O1
25	L=O2	D=O1	L=O2	D=O1

** x = unsuccessful trapping

V. CONCLUSION

This study presents the model of tapered microchannel device using finite element software. The simulation has demonstrated the tapered channel capability to separate microparticle by utilized taper angles of 20° and 25° design. This device can over-come previously related hydrodynamic based separation limitations and was proven to be suitable for both particle and cell separation applications. Therefore, this device provides a new perspective for label-free passive separation device which eventually may become a catalyst for development of point of care device (POC).

Acknowledgment

The research was supported by the Ministry of Higher Education of Malaysia (grant Nos. 4L640 and 4F351), and Universiti Teknologi Malaysia (grant Nos. Grants 03E11, 03G47, 4J148, 02G46, 16H38, 03H80 and 19H22); we thank them for funding this project and for their endless support.

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