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Simulation of Magnetophoretic Blood Cells Sorter Platform

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ABSTRACT

Analysis of cells is important for medical research and pharmaceutical industry. This paper presents a new technique for sorting blood cells on a bio-analysis platform that combines the magnetophoretic force and hydrodynamic force as the means of cell manipulation. The integration of these two techniques can improve on-chip sorting ability which could result in high throughput compared to microfluidic system that uses hydrodynamic method alone. Here, studies on the magnetic density that profiled the actual magnetophoretic force and the hydrodynamic force analysis were conducted using COMSOL Multiphysics v4.2 software. These simulations are important in order to assess magnetophoresis performance during experiments. The suggested model is capable of separating target cells from a heterogeneous population which can be applied for detection purpose particularly in cell biology, immunology, stem cell research, and other clinical applications.

Keywords: Simulation, Magnetophoresis, Hydrodynamics, Bio-Analysis Platform, Sorting Cell, Microfluidic.

1. Introduction

The technology of handling small particles using microfluidics is rapidly growing in the field of Biomedical Microelectroechanical-systems or Bio-MEMS. Amongst the applications of Bio-MEMS, specific biological cells arrangement in suspension is very important particularly in the process of preparing samples for diagnostic reasons. While, large and general laboratory devices for cell sorting are being normally used, micro-sized sorting or separation devices are in a state of research globally due to its cost effectiveness (Seo et al., 2010).
Blood separation has a vital role in medical diagnostics activities. This is because; the human blood is composed of 55% plasma and 45% blood cells in which 98% of the blood cells are red blood cells (RBCs). Thus, removing the RBCs completely from a composition of blood sample would significantly aid the purification of a clinical sample for downstream microanalysis. Moreover, an immediate diagnosis can be done within seconds using micro scale analysis system specifically designed to separate certain different type of cells. However, the accuracy of result during the detection of the targeted cells can be questioned due to the physiological changes of the biological cells during the separation process (Seo et al., 2011). Separation process can also help with the execution of functions for analyzing particular nucleated cells or proteins on a solitary biochip (Han et al., 2006).
Recently, hydrodynamic based biochip has attracted large interest for rapid-continuous separation of blood compositions. The advantage of using fluid flow during separation is that cellś viability could be improved. This technique is usually has simple design compared to other cell manipulation techniques, and hence it is easily integrated on a single biochip and also more robust (Yamada and Seki, 2005). One way of moving cells and accurately manipulate the direction of cells on the miniature biochip is by using microfluidic channels. These channels can help in regulating the cell movements and transporting the cells to the required location accurately.
Meanwhile, Magnetophoresis (MAP) is a technique to separate cells on biochip. MAP functions by using the magnetic property of biochemical substances. Mainly, RBCs are paramagnetic while all the other cells including white blood cells (WBC) are diamagnetic (Zborowski and Chalmers, 2008). Therefore, cell separation using MAP consists of steps for separating RBCs from the WBCs, and other types of cells such as cancer cells and affected cells (Gijs et al., 2010).The use of magnetic fields to separate particles has a long history, especially in the application of high-gradient-magnetic separation and the most widely used magnetic separation methods especially those for biological applications are by means of paramagnetic or super-paramagnetic beads (Lee et al., 2013) . Contemporary researches used free-flow MAP for continuous separation of magnetized biological (Wu et al., 2013).

Here, a new cell sorter technique for bio-analysis platform is presented. Numerical analysis of the MAP, hydrodynamic and particle flow are simulated using finite element software, COMSOL Multiphysics v4.2. The new design has a U-shape in which the ferromagnetic wire lie in the internal boundary of the microchannel. The concept of the proposed design is based on the intrinsic paramagnetic property of RBCs which allow separation of RBCs and WBCs without the use of magnetic beads. Two types of magnetic materials were used; a ferromagnetic wire inside the microchannel and a neodymium permanent magnet outside the microchannel. The ferromagnetic wire will create a magnetophoretic force on a large area of the microchannel which improves the separation efficiency. On the other hand, the permanent magnet magnetizes the ferromagnetic wire placed upon the channel which provides a non-homogeneous magnetic field by which the magnetic field direction is controlled and it is basically perpendicular to the direction of the flow (Chen, 2012). With this design, the mixture of RBCs and WBCs are deflected more or less from their original paths next to the internal wall of the microchannel depending on their size and intrinsic magnetic properties.

The RBCs are forced away from the internal wall near the ferromagnetic line of the channel when the magnetic field is generated and the WBCs and other cells (diamagnetic particles) are forced toward the internal side of the channel. For an external magnetic field of 1T generated by a neodymium permanent magnet placed near the microchannel and perpendicular to the ferromagnetic wire, the flow of the hydrogenous blood in the microchannel needs to be tightly controlled to ensure an effective separation.

In the proposed design in Fig.1 the main area of separation is the band near the internal surface of the microchannel where the ferromagnetic wire is placed. This region is where hydrodynamic and magnetophoresis combine to separate the blood component as it has low velocity which increases the probability of interaction between cells and the magnetic field. Accordingly, the highest portion of RBCs is collected in the first and the second outlets while the majority of WBCs flow the ferromagnetic line until they reach the third outlet and therefore, these blood cells can be arranged and sorted. The proposed design gives promising results and it has successfully combined the two techniques.

2. Theoretical Background

The key component of the hydrodynamic separation is the microfluidic channel in which a laminar flow is generated in x-direction by an inlet and outlet channels. The paramagnetic particles or RBCs will flow straight through following the direction of the major detraction of pumped liquid as they interact with the magnetic field aligned by the ferromagnetic layer. However,

WBCs will be dragged into the magnetic field and thus forced toward the ferromagnetic line and slowly pumped out from the end of the channel. The total velocity vector U (in ms^{-1}) of a magnetic particle can be explicated as the sum of the magnetically induced flow on the particle U_{mag},and the applied hydrodynamic flow U_{hyd}:

$$U = U_{hyd} + U_{mag} \tag{1}$$

At excessively high flow rates, the hydrodynamic flow vector, U_{hyd}, outweighs the magnetically induced flow vector, U_{mag}. On the other hand, at slow flow rates, the magnetically induced flow in y-direction dominates over the applied flow in x-direction and hence, particles would be expected to follow the microchannel shape in the separation area. When the external magnetic field generated by a permanent magnet, the MAP force on a blood cell placed in the plasma solution, F_{mag} can be calculated as (Pamme et al., 2006)

$$F_{mag} = \Delta\chi \frac{V_{cell}\ (\nabla.B)\, B}{\mu_0} \tag{2}$$

The magnetically induced flow vector, U_{mag}, is the ratio of the magnetic force, F_{mag}, exerted on the particle by the magnetic field over the viscous drag force:

$$U_{mag} = \frac{F_{mag}}{6\pi\eta r} = \frac{\Delta\chi\ V_{cell}\ (\nabla.B)\, B/\mu_0}{6\pi\eta r} \tag{3}$$

where $\Delta\chi$ is the difference in susceptibility between the cell and medium (χ_{cell}-χ_{plasma}), η is the liquid viscosity (kg m^{-1} s^{-1}), V_{cell} is the volume of a blood cell (m^3), B the externally applied flux density (T) and $\nabla.B$ its gradient (T m^{-1}),μ_0 is the permeability of a vacuum (H m^{-1}), and r the particle radius (m).

On closer inspection of Eq. (3), it can be seen that, for a given magnetic field and a given viscosity, the magnetic flow vector, U_{mag}, is dependent only on the size and the magnetic characteristics of the particle.

$$U_{mag} \propto\ r^2\chi_p \tag{4}$$

When cells are placed on the detraction of the flow, the ferromagnetic wire helps to create high magnetic gradient which force the cells to slightly change their direction (Moore et al., 2013). In the case of WBCs, $\Delta\chi$ is negative as diamagnetic and they will be attracted toward the ferromagnetic line. Meanwhile, $\Delta\chi$ is positive for the paramagnetic particles or RBCs and they will be forced away from the ferromagnetic wire. The permanent magnet has to be placed in close region to create a strong external magnetic field. The hydrodynamic velocity flow vector U_{hyd} can be determined by solving the Stokes equation for

laminar flow in the microchannel given by (Henrik, 2008).

$$\left(\frac{\partial^2}{\partial x^2}+\frac{\partial^2}{\partial x^2}\right)U_{hyd}=-\frac{\Delta p}{\delta L}\quad \text{for}\quad -\frac{w}{2}<y<\frac{w}{2}\quad \text{and}\quad 0<z<h \tag{5}$$

$$\textit{and } U_{hyd}=0,\ \textit{at the boundary}$$

Where $\Delta p$is the pressure difference, $\delta$is the fluid viscosity, w,h,L are the channel diameters, and x,y,z the coordinate which define the position of particles.The solution for the velocity along the micro-channel is given by Fourier series expansion

$$U_{hyd}=\frac{4w^2\Delta p}{\pi^3\delta L}\sum_0^\infty\frac{1}{n^3}\left[1-\frac{\cosh\left(n\pi\frac{x}{w}\right)}{\cosh\left(n\pi\frac{h}{2w}\right)}\right]\sin\left(n\pi\frac{y}{w}\right) \tag{6}$$

When the particles are injected through the microfluidic channel the large particles or WBCs follow the low velocity flow. Conversely, small particles or RBCs follow the high velocity flow. To maximize the separation we design the ferromagnetic line to be in the internal boundary of the microchannel where the hydrodynamic velocity is low which enhance the magnetic separation in that area. The U-shape design which combine hydrodynamic and MAP improve the control of particle movement on biochip because the interactions of both WBCs and RBCs are not conflicting. So, the separation force of each particle is the summation of both forces; the MAP force and the hydrodynamic force.

3. Materials and Methods

COMSOL Multiphysics is a solver and simulation software for finite element analysis. It implements equations using " physics inter-faces " to solve physics equations and associated boundary conditions. It uses numerous pre-built methods, in which there is complete flexibility to combine and couple pre-built methods with user-defined variables or equations. In order to simulate the suggested design we have used the AC/DC and microfluidic modules. AC/DC module has been used to simulate the MAP force while hydrodynamic flow has been simulated trough the laminar flow study in microfluidic modules. This works suggest a novel prototype in order to study the limitations of flow-rate and separation efficiency of the proposed design. The focus of the study is to separate cells based on the MAP and hydrodynamic forces. Figure 1 illustrates the proposed blood separator with a U-shape microchannel. The design has one inlet and three outlets to separate the WBCs and RBCs. The maximum separation region in the microchannel is the area near where the ferromagnetic wire is placed. In this region, the hydrodynamic and MAP forces

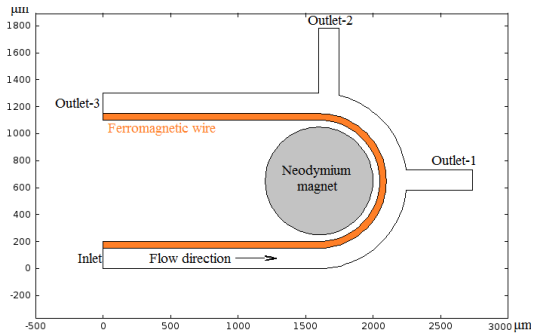

Figure 1: Two dimensions microfluidics hybrid micro-separator.

will separate the blood component due to the velocity of fluid flow. Low fluid velocity for instance, increases the probability of interaction between cells and the magnetic field. Large particles such as WBCs will follow the low velocity flow and moves them to the area near of the ferromagnetic line. At the vicinity of the ferromagnetic line, where the magnetic flux density is high, the MAP force is able to move the WBCs toward outlet-3. Conversely, the RBCs which are relatively smaller than RBCs will follow the high velocity flow toward the outlet-1 and outlet-2.

This novel microfluidic device is simulated using COMSOL Multiphysics software by considering two main parameters; the particles velocity and the magnetic flux density. We assumed that the plasma's relative permeability is 1.05 and the blood cells are spherical with 6μm diameter. The RBCs has a density of 2200 kg/m^3, zero charge and 10^{-6} to 4x10^{-6}permeability (Seo et al., 2011). The ferromagnetic wire permeability sat at 5000 using Ni_3Fe ferromagnetic material and the permanent magnet was sat to give a maximum magnetic flux density of 1 T.

The design of the cells sorter consists of U-shape micro-channel built together with the ferromagnetic line. The design incorporates one inlet and three outlets as shown in Fig.1. The diameter of each channel is 100μm. Meanwhile, a ferromagnetic line with 20μm diameter and aligned along the internal wall of the micro-channel. The magnetic flux density used in all simulation is 1T and the magnetic field gradient is 1.6 T/m.

4. Results and Discussion

The cell sorting simulation was performed using COMSOL Multiphysics V4.2 by combining two physics at the same time; the magnetic fields and

creeping flow. We have used the AC/DC and fluidics flow models in this study. The calculation was based on the equations mentioned in the second section of this paper and the study focused on the fluid flow velocity, pressure magnetic flux density, magnetic gradient and other fluid properties. In all simulations, we assumed RBCs are spheres with 6μm diameter and the microchannels are extra fine meshed with standard boundary conditions. The obtained results are summarized in two figures and one table as illustrated next.

The U-shaped channel generates a secondary flow which is basically named hydrodynamics force which accumulates with MAP force to control the particles velocity.

The impact of external magnetic field on the ferromagnetic which gives a positive control on RBCs as they come near to the first outlet (Fig.3,separation region A.) which double the chance of moving the higher fraction of cells toward the outlet-1.

In Fig.2 the magnetic vector potential is describing the magnetic lines created by the external magnetic field which is well captured by the ferromagnetic accruing a highly magnetize wire in direct contact with the microchannel and apparently the cells. The paramagnetic prosperity of RBCs is well controlled by MAP combined with the hydrodynamics force as it described in Fig.3. The

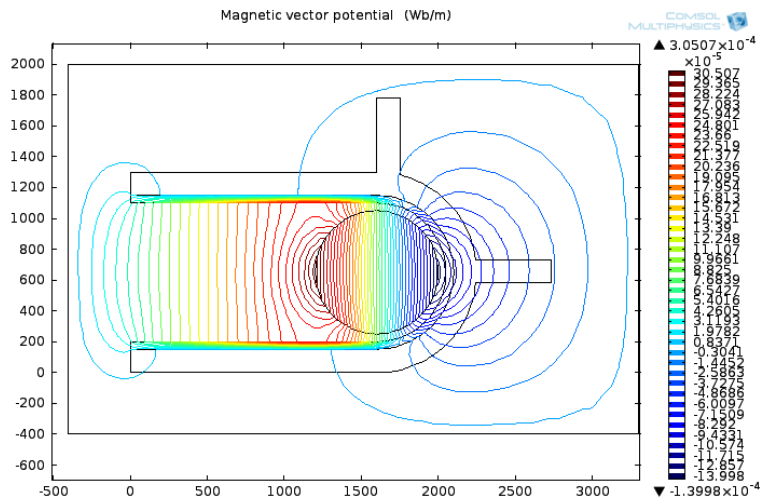

Figure 2: Simulation results describing magnetic potential of the permanent magnet.

simulation results in Fig.3 describe the cells velocity within the microchannel which gives a clear image of the particles movement as they move toward the three outlets.

There are two regions where the separation accrues named A and B. The

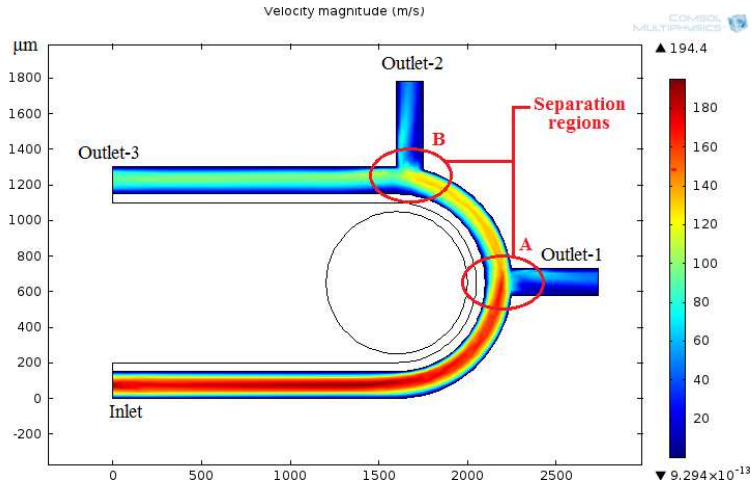

Figure 3: Simulation results indicating the cells velocity magnitude within the microchannel.

average velocity was calculated in an area of 1.8 x10^{-2}mm^{2}from each region by taking 10 points in each direction and the results summary is presented in table 1

Table 1: Simulation results indicating the cells velocity average in two deferent areas across the microchannel

	X (μm)	Y (μm)	Velocity average (m/s)
Separation region-A	2100-2200	610-790	116.408*10^{-13}
Separation region-B	1650-1750	1180-1360	74.873*10^{-13}
Outlet-3	0	1180-1360	53.342*10^{-13}

RBCs follow the high velocity flow as they are injected from the inlet and the MAP caused by the ferromagnet helps in pulling them away from the internal boundary where the hydrodynamic velocity is low where the magnetic field is high. A high velocity average was recorded in the separation region-A where most of particles change their directions toward outlet-1. The rest of particles follow the low velocity flow. Most of these particles are WBCs as they are much larger than RBCs.

Overall, the platform presented in this work may be used to design spiral microchannels for separation of other particles with similar magnetic prosperities. The threshold particle size in this work was 6μm. New design is needed for separations where a change in particle size to have the ability to continuously sort large sample volumes.

5. Conclusion

This paper describes a biochip design which can be used to improve blood cells separation based on their hydrodynamic and magnetic prosperities. The cells movement in the proposed microchannel has been simulated using COMSOL Multiphysics. MAP is useful in blood cells manipulation due to its high magnetic density which benefits the direction of cell movement on bio-analysis platform. We have suggested a numerical analysis to profile the actual MAP, hydrodynamic and cells movements in cell sorting manipulation. The studies are vital to analyze cells movements in fluid and magnetic fields. In this work, the cells experience hydrodynamic drag force and MAP force and the direction of particles can be determined by the total force acting on the cells calculated from these forces. The work on this area is in progress trying to support the simulation results obtained through experimental validation.

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