

# Design of MEMS-based Magnetophoresis micro-Separator

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**Design and investigation of a micro-Electro-Mechanical System (MEMS) based fluidic separator for high gradient magnetophoresis cell separation (HGMCs) is the main goal of our study. The HGMC separation effect is achieved by using ferromagnetic materials in the mechanical structure. We proposed a standard lithography process with SU8 spin coating on a quartz substrate for fabrication process. In our study we chose new layout of soft irons which increases the gradient of magnetic field. This effect provides highly efficient magnetic field patterns at the separation zone and as a result effective magnetic force on magnetic beads. Our numerical study reveals that the proposed technique is able to separate T+CD4 cells from blood components and eases the final numeration process. Rapid separation and low cost are the main advantages of our design. Our introduced MEMS based magnetophoresis separator, has an external applied magnetic field with a magnetic flux density of 0.23 T, separation time of under 14s, and 100% separation of target cells.**

**Keywords---** MEMS; separator; magnetophoresis; T+CD4 cells;

## I. INTRODUCTION

The advent of micro-electromechanical systems (MEMS) that their base are miniaturization of mechanical components and integration with electrical systems, has created the potential to fabricate a variety of structures and devices in the micrometer size range. In recent years, miniaturization and integration of biochemical analysis systems to MEMS devices has been of great interest which has led to invention of Micro Total Analysis Systems ( $\mu$ -TAS) or Lab-on-a-Chip (LOC) systems. Since the majority of chemical reactions occur in liquid environments, the development of  $\mu$ -TAS is essentially connected to the design of liquid handling micro-devices (e.g., micro-separators and micro-mixers). Recently, several studies of micro-sized devices has been reported that are capable to sorting and separation of cells in microfluidics. This kind of systems that are able to isolate the cells in a microfluidic medium at microscale have been named micro-separators which one of the important components on Lab-on-a-chip systems. Till now many micro-separators have been devised that are based on the use of fluorescent labels [1-4], physics of electrophoresis [5], Di-electrophoresis [6-8], and magnetophoresis [9-11]. Among them, the magnetophoresis

cell separator does not require any optical instruments and equipments (like laser flow cytometry) or current source and the electrodes (like electrophoresis and Di-electrophoresis). In this method by using a permanent magnet or electromagnet, the magnetic force exerted on the micro-fluid with micro-particles in the channel and leads to completely controlled movement of the magnetic cells inside the channel. In fact, there are two types of magnetophoretic cell separator systems. In the first type solution contains particles or cells which they have intrinsic magnetic properties. These types of particles or cells, are super-paramagnetic particles (particles with relative permeability coefficient higher than 1) and or diamagnetic particles (particles with lower relative permeability lower than 1). Thus the magnetic force applied to the particles directly and affects them. In the second type, the system consists of particles that do not respond to magnetic force and are not affected by magnetic fields. These particles are non-magnetic particles that their relative permeability is equal to 1. In cases where we need to influence these particles by magnetic fields, we are required to use magnetic labels [12,13]. Magnetic labels are a series of smaller super paramagnetic particles which have antibodies on their surface that adapted to bind to antigens on the surface of non-magnetic target cells, like fig.1. These super paramagnetic particles are known as Dynabeads. This Dynabeads enter into solution which have non-magnetic target cells and is stick to these cells by binding affinity of their antibodies and target cells antigens. Thus the non-magnetic target cells are labeled by Dynabeads. Finally, in the presence of a magnetic field, the combination of non-magnetic target particles and Dynabeads reacts. In this paper, because the separation of certain types of white blood cells (T helper lymphocytes) is considered and their relative permeability is 1, thus the super paramagnetic bead is used as magnetic labels.

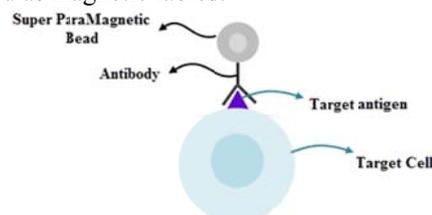


Fig. 1. binding of super paramagnetic particles to cells by binding affinity between antibodies and antigens.

On the other hand, generally, there are two sources of magnetic field that can be integrated into MEMS devices, namely permanent magnets and current-fed conductors. Permanent magnets can generate strong fields on the order of tesla compared to the field generated by conductors, which is in the range of mili-tesla. One advantage in exploiting permanent magnets over conductors is that the actuation is not involved in the Joule heating, which is a serious challenge in Bio-MEMS applications. Various magnetic materials (e.g., NdFeB films) have been reported by some researchers which can be fabricated in micro-scale as a permanent magnet [14,15]. In this paper we use of the NdFeB material such as permanent magnet to create the magnetic field. Recently, numerous researches of magnetophoresis separators have been reported that are pertaining to use ferromagnetic material in the presence of an external applied magnetic field to increase the magnetic field gradient [16-18]. Magnetic materials such as permalloy, micro fabricated NiFe layers, steel wood and soft irons, used in magnetophoresis separators, to increase the gradient of the magnetic field. For example in a designe[19] an array of soft irons in symmetrical shape either sides of the channel is used to separate diamagnetic cells from the channel walls and focus them in the Midline line of the channel. In this paper we used an array of the soft irons in one side of the channel to separate the paramagnetic or non-magnetic cells (with magnetic lable). In addition We have developed a new layout of the soft irons to eliminate the areas with reverse direction of the magnetic force that generated by the soft irons.

The number of CD4 + T lymphocytes per milliliter of blood, is used to determine infection HIV. In medical laboratories, these information achieved by the laser flow cytometry. conventional flow cytometry techniques demand heavy instrumentation and are not applicable on the micro-scale. This work focuses on design of the magnetophoretic micro-separator chip with new layout of soft irons, for rapid and low cost separation micro-device of CD4+T lymphocytes from whole blood.

## II. THEORY

### A. forces on the cells or beads in magnetophoresis separation

Fig.2 shows a schematic image of a magnetically labeled cell travel trajectory through a microfluidic channel. In this case, the set of cell and dynabead (lable), regardless of gravitational force ( $F_g$ ), experience two forces: the hydrodynamic drag force ( $F_d$ ), the and the magnetic force ( $F_{mag}$ ).

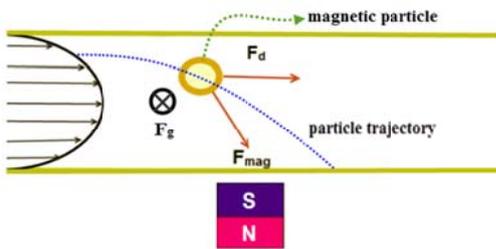


Fig. 2. Magnetic labeled cell travel trajectory in microfluidic channel when an external magnetic field is applied.

The gravitational force is perpendicular to the two other force and has no role in the diversion of particles to the left or right.

#### 1) Drag force

Assuming that the magnetically labeled cell is spherical, the hydrodynamic drag force obtained from Stokes' law

$$\vec{F}_d = 6\pi\eta R_p(\vec{V}_p - \vec{V}_f) \quad (1)$$

where  $\eta$  is the viscosity of the medium,  $R_p$  is the particle radius, and  $\vec{V}_p$  and  $\vec{V}_f$  are the velocities of the particle and fluid, respectively.

In fact, when the composition of cell and dynabead floating in the fluid, it rotates and moves in the fluid like Fig.3. In this mode hydrodynamic drag force exerted on cell that it's size is larger than the size of dynabead, Then it leads to movement of cell and Dynabeads attached to it.



Fig. 3. Drag force on cell and particle attached to it

#### 2) Magnetophoresis force

The magnetic force acting on a magnetic particle (here on dynabeads) at non-magnetic nature medium in the presence of an applied external magnetic field is given by

$$F_m = 2\pi\mu_0 R_{m.b}^3 \frac{\mu_r - 1}{\mu_r + 2} \nabla H_0^2 \quad (3)$$

Where  $\mu_0$  is the permeability of free space,  $\mu_r$  is the relative permeability of dynabead,  $R_{m.b}$  is radius of magnetic bead and  $H_0$  is the intensity of the external magnetic field.

As shown in fig.4, here the magnetic force is applied only to the super paramagnetic particles (Dynabeads). Then with the orientation of the dynabeads in the direction of magnetic field, the cell also moves in this direction.

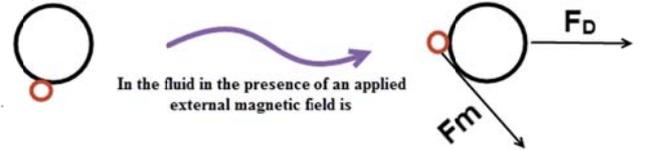


Fig. 4. Magnetophoresis and drag force on cell and Dynabead attached to it

Since, in practice, a large number of super paramagnetic beads will be connected to a cell, the resultant magnetic force on the particles attached to the cells increases and the magnetic attraction of target cell, is easier and faster.

If we apply Newton's second law of motion to a magnetic particle flowing through the channel, we can write:

$$m_p \frac{d\vec{V}_c}{dt} = \vec{F}_m + \vec{F}_g + \vec{F}_d \quad (4)$$

where  $m_p$  is the mass of the particle,  $\vec{V}c$  is the velocities of the cell,  $\vec{F}_m$  is the magnetic force,  $\vec{F}_g$  is the gravitational force, and  $\vec{F}_d$  is the viscous drag force.

### III. DEVICE PHYSICS AND DESIGN

Our work focus on the separation of T+CD4 cells with a novel array layout of soft irons. To understand the new idea of the project, first we placed an array of soft irons adjacent to the channel wall and apply an external magnetic field by a permanent magnet, like what ever designed [19], fig.5 .

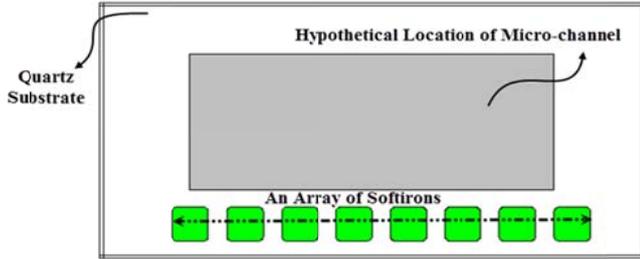


Fig. 5. Initial pattern of an array with 8 soft iron in adjacent to channel wall

Magnetic flux density diagrams seen in the figure below in two cases of applying an external magnetic field: 1.in absence of soft irons 2.in the presence of soft irons,. This diagrams shows that the magnetic flux density is constant in the first case and the latter case is variable. Therefore, the use of soft iron in the structure leads to creation of the magnetic field gradient.

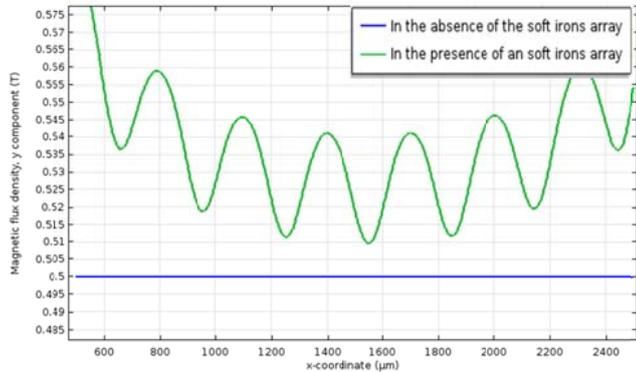


Fig. 6. Comparison of the magnetic flux density diagrams in the absence and presence of soft iron

It is clear from fig.6, how both the magnetic field magnitude and its variations contribute to the magnetic force as from expression(4).

To simulate the direction of the magnetic force we are required to provide characteristics of the super paramagnetic particle [20]. Table I summarizes the properties of FlowCamp+CD4 dynabeads that commercially available beads manufactured by Invitrogen Corporation[21].

TABLE I. characteristics of the FlowCamp+CD4 dynabeads

Dimeter(um)	Saturation magnetization ( $A \cdot m^2 / Kg$ )	Magnetic susceptibility ( $m^3 / Kg$ )	Density ( $g / cm^3$ )
2.8	13	$6 \times 10^{-4}$	1.6

Due to these properties, the magnetic force acting on the super paramagnetic particle can be obtained as follows,

$$F_m = 2 \times 4\pi \times 10^{-7} \times 3.14 \times (1.4 \times 10^{-6})^3 \times \frac{1.9 - 1}{1.9 + 2} \times \nabla H_0^2 = 4.9 \times 10^{-24} \times \nabla H_0^2 \quad (5)$$

As a result, by given characteristics of the super paramagnetic particle, the magnetic force is directly dependent on the gradient of square the magnetic field strength.

Fig.7 shows that the magnetic field direction is symmetrical along the microchannel, this means that, in the first half of microchannel above the soft irons, the magnetic force backward and in the second half, it is forward and it is not desirable, because if a magnetic particle placed at a point where is have backward field direction, this partile also moves backward.

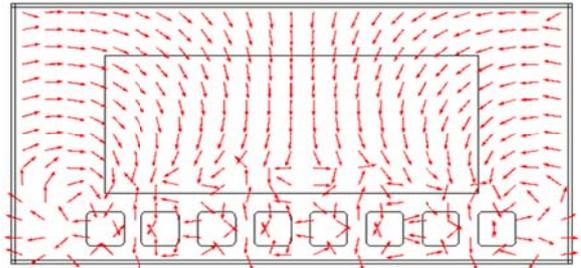


Fig. 7. The simulation of the magnetic force caused by an external applied magnetic field in presence of soft irons

This figure also contains two basic result: 1.For separation application, place of micro-channel should not include field turbulent regions, 2.This arrangement of soft irons is preventing of forward moves of magnetic particles.

#### A. Our new idea to solve the problem

In fact, The previous problem was due to the same dimensions of soft irons. We consider an array of soft irons without being identical dimensions. Their dimensions increases with a constant ratio. Now we can shift the unfavorable directions of the magnetic field directions in the areas that are not used in microchannel section. With this design we have a wide part with the uniform forward force direction. It causes that the magnetic particle moves forward in areas where is the magnetic force bigger than drag force (where the magnetic force is dominant).

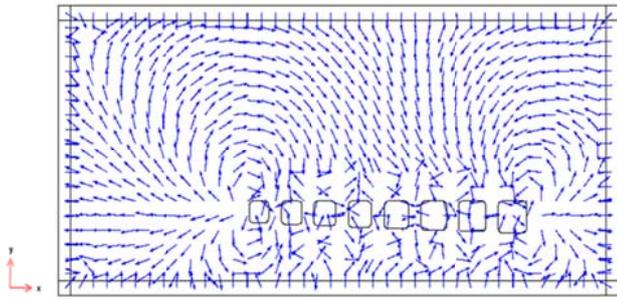


Fig. 8. New design of soft irons and direction of magnetophoresis force vectors in this design

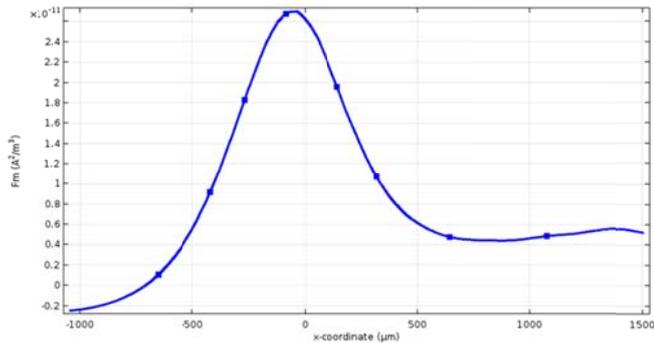


Fig. 9. Diagram of magnetophoresis force

With this simulation of the proposed arrangement of soft irons we can offer the best location for the micro-channel, like fig.10.

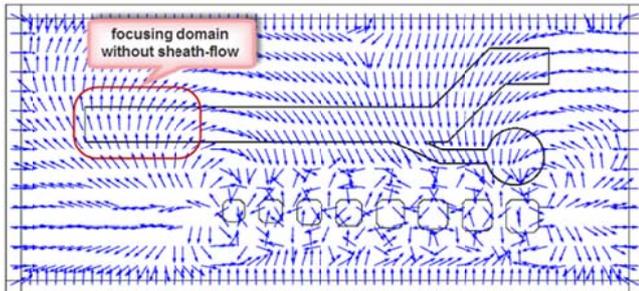


Fig. 10. Best location of micro-channel for separation magnetic particles application

As can be seen in Fig.10 in order to achieve the best magnetic field pattern on microchannel, it is placed where it is shown in Fig. At the beginning of micro-channel we have a fluid focusing area without sheath-flow, where only due to the magnetic force directions. The reason why the target output channel width is 2.5 times smaller than the width of the main channel is to show that even in this difficult condition that fluid velocity in the target output channel is very low, the separator works fine.

3D design of this project will be shown in fig.11, channel dimensions of  $3.2 \times 0.25 \times 0.05 \text{ mm}$ , an external applied

magnetic field of 0.23T and relative permeability of soft irons is 4000.

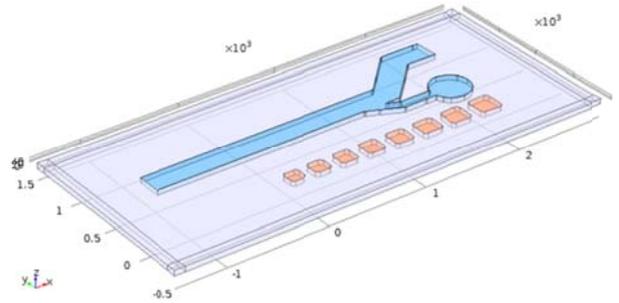


Fig.11. 3D design of a magnetophoresis micro-separator

### B. Results

With this design we were able to separate a kind of white blood cells from other blood components. The focusing and separation is shown in fig.12 and fig.13 respectively.

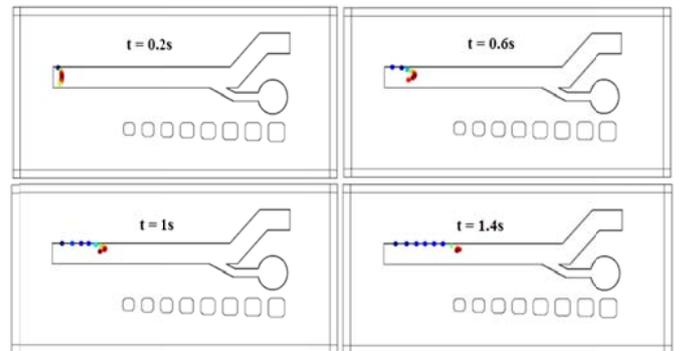


Fig. 12. Focusing magnetic particles without sheath flow in the design presented.

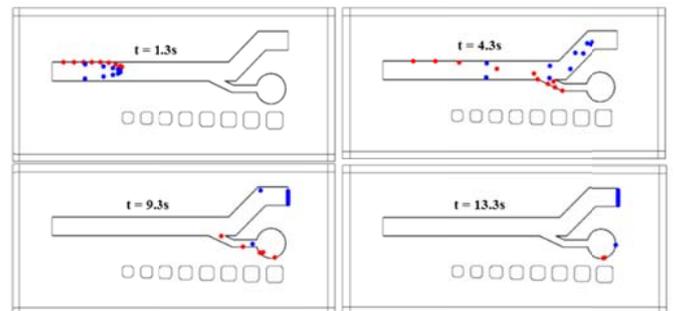


Fig. 13. Separation of magnetic particles in the design presented. The red particles are target cells and the blue particles show other blood component

As can be seen in the fig.12 and fig.13 at first stage all target cells are focusing on the left side of inlet wall. Then the magnetic force attracts all these target cells to the front wall and so separation is performed.

Displacements both cell types were investigated and the results shown in the diagrams of fig.14.

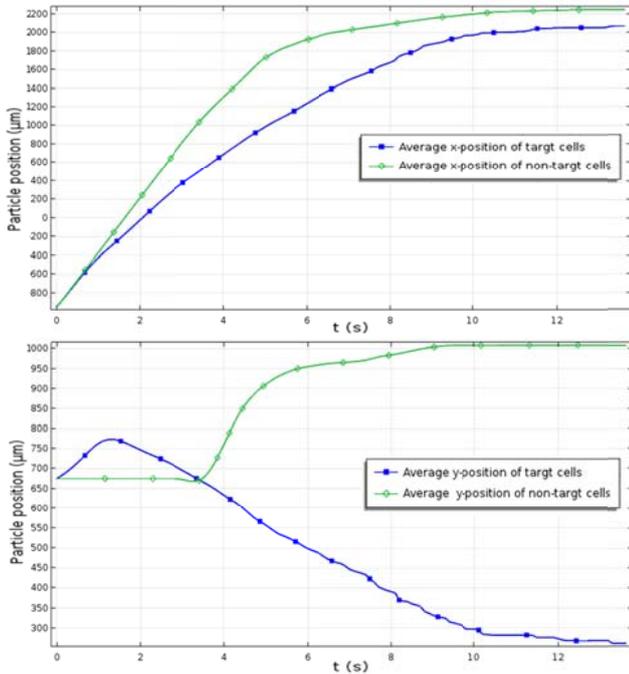


Fig. 14. Average x and y- position of both cell types in presented micro-separator

Fig.15 shows results of the fluid velocity profile as expected from modelling.

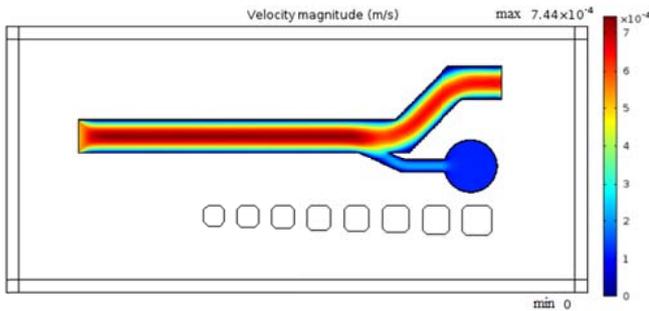


Fig. 15. Plot of fluid velocity. At the inlet of micro-channel, velocity of the fluid (containing blood components and the target cells with Dynabeads attached to them) is 0.5mm/s that can be set by an electrokinetic or piezoelectric pump [22].

### C. Microfabrication process

The manufacturing process consists of two main steps:

1. Production of permalloys on glass slides substrate by electroplating the soft iron elements.
2. Creation of microchannel on the same glass slides substrate by photolithography employing the negative photoresist SU8-50 to pattern the structures.

Sealing is achieved by covering the whole device with another wafer with SU8 spun on it.

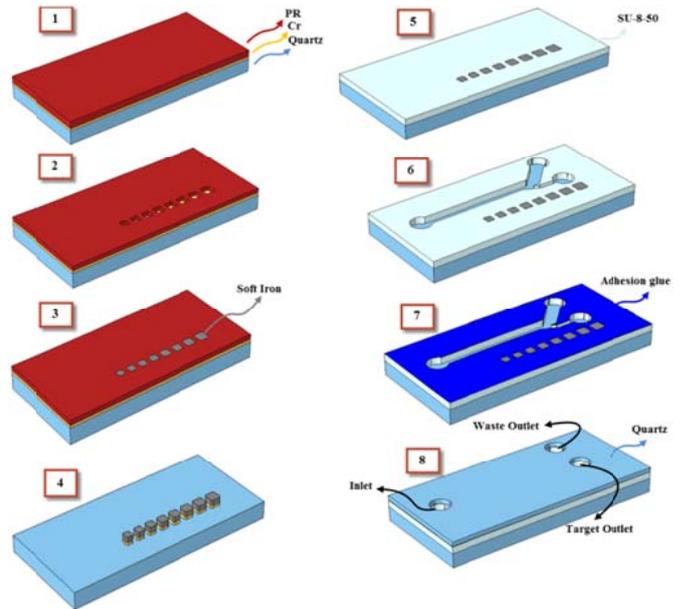


Fig. 16. Fabrication process. 1-4: Deposition of Cr layer and photolithography to pattern the soft irons structure, then electroplating the soft irons elements, remove the PR layer and etch the Cr layer. 5-6: photolithography employing the negative photoresist SU8-50 to pattern the structures and etch the micro-channel. 7: spin coat of a very thin layer of adhesion glue for bondind this wafer to another wafer with SU8 spun on it and the inlet and outlets is specified on it with diamond drilling.

## IV. CONCLUSIONS

In this paper, a continuous magnetophoretic microseparator were designed by the HGMS method, and successfully demonstrated for directly separating a type of WBCs from whole blood, thanks to antibody-conjugated magnetic beads. Comparison of simulated magnetic forces between the new layout of soft irons and previous designs verified that the new layout was useful for creating the best magnetic force pattern of blood cells in our microseparator. The desine have an array of the soft irons that the first iron with dimensions of 150um to 150um and increasing the dimensions with the fixed ratio for the rest of the soft irons and 50 um in thick for all. Also the microseparator with a microchannel length and width and height of  $3.2 \times 0.25 \times 0.05$  mm respectively. A permanent magnet was used to create an external magnetic flux of 0.23T for the microseparator. Simulation results indicated that our microseparator accumulates the WBCs(T+CD4 cells) with the external applied magnetic field within 13.3s, and showed that it could separate out 100% of this cells from outlet #2 at 0.5 mm/s flow velocity. As future work, we will optimize this microseparator and will use it to separate cells in less external magnetic field. To achieve this, the PMC microseparator could be further improved by increase the number of soft irons or incorporating ferromagnetic permalloys with a higher permeability, using a lower flow rates, and increasing the microchannel length. Therefore, this microseparator provides a promising platform for stem cell research and Diagnosis of AIDS.

## REFERENCES

- [1] Fu, A.Y., Spence, C., Scherer, A., Arnold, F.H. & Quake, S.R. "A microfabricated fluorescence-activated cell sorter," *Nat. Biotechnol.* **17**, 1109-1111 (1999).
- [2] Krüger<sup>1</sup>, J. *et al.* "Development of a microfluidic device for fluorescence activated cell sorting," *J. Micromech. Microeng.* **12**, 486-494 (2002).
- [3] Yao, B. "A microfluidic device based on gravity and electric force driving for flow cytometry and fluorescence activated cell sorting," *Lab Chip* **4**, 603-607.
- [4] Yang, S.Y. *et al.* "A cell counting/sorting system incorporated with a microfabricated flow cytometer chip," *Meas. Sci. Technol.* **17**, 2001-2009 (2006).
- [5] Xuan, X. & Li, D. "Focused electrophoretic motion and selected electrokinetic dispensing of particles and cells in cross-microchannels," *Electrophoresis* **26**, 3552-3560 (2005).
- [6] Hu, X. *et al.* "Marker-specific sorting of rare cells using dielectrophoresis," *PNAS* **102**, 15757-15761 (2005).
- [7] Doh, I. & Cho, Y.H. "A continuous cell separation chip using hydrodynamic dielectrophoresis (DEP) process," *Sensors and Actuators A* **121**, 59-65 (2005).
- [8] Park, J. *et al.* "An efficient cell separation system using 3D-asymmetric microelectrodes," *Lab. Chip* **5**, 1264-1270 (2005).
- [9] Choi, J.W., Ahn, C.H., Bhansali, S. & Henderson, H.T. "A new magnetic bead-based, filterless bio-separator with planar electromagnet surfaces for integrated bio-detection systems," *Sens. Actuator B-Chem.* **68**, 34-39 (2000).
- [10] Kim, H.S. *et al.* "Separation of apoptotic cells using a microfluidic device," *Biotechnol. Lett.* **29**, 1659-1663 (2007).
- [11] Pamme, N. & Wilhelm, C. "Continuous sorting of magnetic cells via on-chip free-flow magnetophoresis," *Lab. Chip* **6**, 974-980 (2006).
- [12] N. Pamme, "Magnetism and microfluidics", *Lab on a Chip*, 2005.
- [13] I. Safarik, M. Safarikova, "Use of magnetic techniques for the isolation of cells", *Journal of Chromatography*, 1999, B, 722, 33-53.
- [14] B. Wagner and W. Benecke, "Microsystem Technologies" 90, Berlin, p. 838, H. Reichl (Ed.), Springer Verlag, 1990.
- [15] Rieger, G., *et al.*, "Nd-Fe-B permanent magnets (thick films) produced by a vacuum-plasma-spraying process," *Journal of Applied Physics*, 2000, 87(9): p. 5329-5331.
- [16] S. Miltenyi, *et al.*, "High Gradient Magnetic Cell Separation With MACS" Wiley-Liss, 1989, 231-238.
- [17] K. Han and A. Bruno Frazier, "Paramagnetic capture mode magnetophoretic microseparator for high efficiency blood cell separations", *Lab on a Chip*, 2005.
- [18] S. Miltenyi, *et al.*, "High Gradient Magnetic Cell Separation With MACS" Wiley-Liss, 1989, 231-238.
- [19] G.Schiavone, *et al.*, "Design and Simulation of a Microscale Magnetophoretic Device for the Separation of Nucleated Fetal Red Blood Cells from Maternal Blood", *COMSOL Conference*, 2009, Milan.
- [20] J. Darabi and C. Guo, "On-chip magnetophoretic isolation of CD4+T cells from blood", *Biomicrofluidics*(2013), 7, 054106
- [21] "Dynabeads® FlowComp™ Human CD4 Isolation from PBMC", *lifetechnologies*, Catalog no. 11361D.
- [22] F.Abhari ,H. Jaafar and N. A. Md Yunus, "A Comprehensive Study of Micropumps Technologies: Review paper," *Int. J. Electrochem. Sci.*, 7 (2012) 9765 – 9780.