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A Numerical Study on Motion of Malaria-Infected Red Blood Cells under Electromagnetic Field in Microfluidic Chip

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Abstract

Nowadays, malaria infection is still a major problem in countries located in tropical climate zone, and more than one million patients have died in each year around the world. The malaria parasite transmitted by infected mosquito lives by feeding off the hemoglobin in human blood cell, and then hemoglobin turns into crystal called Hemozoin that exhibits paramagnetic property. This study aims to design a new microfluidic chip for detecting infected red blood cell from patient's blood. To design the chip the numerical analysis of the motion of infected and healthy red blood cells as well as white blood cells, which are effected by different magnitude of magnetic force, is performed under various flow rates. The design is to laterally separate the infected red blood cells from a main stream, and manipulate them into a specific outlet port of the microfluidic chip. From the numerical results, the proper magnitude of electromagnetic force on infected red blood cells should be higher than 0.1 pN and suitable volume flow rate should not exceed 0.15 μL/min. The data is necessary to develop a prototype of microfluidic chip later.

Keywords*:* Malaria, Microfluidics, Cell sorting, Electromagnetic field, Red blood cell, Numerical method

1. Introduction

Malaria is always a serious disease and may be a deadly illness. In Thailand, the highly seasonal spreading rate of Malaria in the rural forested areas that border between Myanmar, Cambodia and Laos is often reported. To prevent its serious spreading, the illness diagnosis by sampling blood cells from a patient should be quickly and precisely performed. However, the high precision blood cell analyzer is still expensive and that limits accessibility of patients especially in such rural area. Therefore, the common diagnosis technique in that rural area is counting infected red blood cells using human eyes through a microscope which often causes fault diagnosis, taking a lot of time and failure in preventing the spread of Malaria illness even though it is performed with more than 100 camera angles by an expertise[1-2]. The fault diagnosis is due to an inability to detect a low concentration of infected red blood cells. To resolve this problem, an alternative and yet practical technology that can separate infected cell out might help the

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expertise in performing diagnosis with better accuracy and reducing the fault diagnosis.

Among various Malaria-infected blood cells' characteristics, Hemozoin [6] or often called Malaria pigment recently becomes an important diagnosis target for Malaria infection. Hemozoin is a disposal product formed from the digestion of blood by Malaria parasites. This is due to free heme is toxic to cells so the parasites convert it into an insoluble crystalline form, called Hemozoin, which exhibits paramagnetic property.

In the last decade, many techniques have been developed for separating Malaria parasite based on bio marker [4], electric impedence microscopy [5], and magnetophoresis method [7-10]. Most recently, Nam et al. (2013) developed a microfluidic chip for the sorting of Malaria-infected blood cell using magnetic forces[11]. However, the study in this related field is still rare although it is significantly valuable probably due to the costliness and complexity of the chip fabrication. Therefore, this study aims to develop an alternative and yet practical microfluidic chip for sorting of healthy and infected red blood cells.

In this paper, a motion of red and white blood cells modeled as solid particles in a microchannel are simulated under various conditions of magnetic force and volume flow rate. In the future, the effects of each parameter will be optimized in a design of microfluidic chip. The overall schematic system, with a channel height and width of 50 and 100 μm, respectively, is shown in Fig.1.

2. Principle

2.1 Magnetophoresis Force

The magnetophoresis force exerts on a cell exhibiting magnetic properties when the cell is dispersed in liquid medium under inhomogeneous magnetic field. Magnetic force due to this

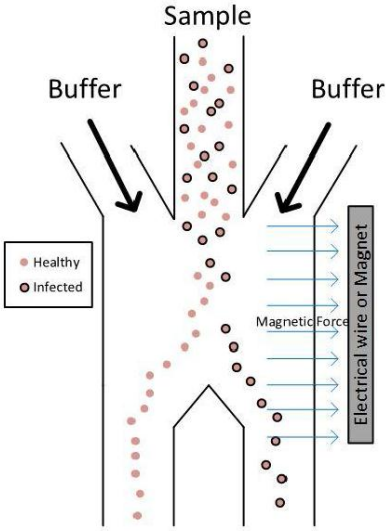

Fig. 1 The overall schematic microfluidic system studied in this work using an external magnetic-force generating source.

magnetophoresis principle is proportional to the size of the cell and the gradient of magnetic field, and the force is defined as

$$F_m = 2\pi\mu_{medium}(R)^3\left(\frac{\mu_{cell}-\mu_{medium}}{\mu_{cell}+2\mu_{medium}}\right)\nabla\left|\vec{H}\right|^2 \quad (1)$$

where F_m is magnetic force (N), μ_{medium} is permeability of medium (N/A^2), μ_{cell} is permeability of cell (N/A^2), R is a diameter of the cell (m) and H is magnetic field strength (A/m). From the equation, it shows that the magnetic force is considerably created with a large amount of magnetic field gradient in order to properly manipulate a motion of cells. The other factor affecting the magnitude of magnetic force is the difference between permeability of medium and cell, which is defined as

$$\mu = \mu_0(1+\chi) \quad (2)$$

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where μ is permeability of a matter (N/A^2), μ_0 is vacuum permeability and χ is volume magnetic susceptibility of a matter. The difference between permeability of medium and cell can be considered in the other way as the relative magnetic susceptibility of blood-cell components as shown in Table 1. The relative magnetic susceptibility, or $\Delta\chi = \Delta\chi_{cell}-\Delta\chi_{medium}$, can be rewritten as

$$\mu_0(\Delta\chi) = \mu_{cell} - \mu_{medium} \qquad (3)$$

From the Eqs. (1) and (3), it is figured out that the magnitude of magnetic force is proportional to the relative magnetic susceptibility.

2.2 Other Fluidic Forces

2.2.1 Drag Force

In a microfluidic system, the device is in a micrometer scale where, generally, Reynolds number is very small (Re<<1) and the flow is considered to be laminar flow. The cell dispersed in a liquid medium moves along the fluid flow due to drag force which is written as

$$F_D = C_D \frac{1}{2}\rho V^2 A \qquad (4)$$

where F_D is drag force (N), C_D is drag coefficient, ρ is density of fluid (kg/m^3), V is a relative velocity of cell to the flow (m/s) and A is the cross-sectional area (m^2) of the cell to the flow direction. From Stoke's law for viscous incompressible flow, the force that exerts on the spherical cell at low Reynolds number is written as

$$F_D = 6\pi\eta RV \qquad (5)$$

where η is the viscosity of medium liquid (N.s/m^2).

2.2.2 Buoyancy and Lift Forces

The cells suspended in liquid always are exerted by buoyancy force which is defined as

$$F_B = \rho \forall g \qquad (6)$$

where F_B is buoyancy force (N), $\forall$ is volume of a cell sinking in the fluid (m^3) and g is gravitational acceleration (m/s^2). In addition, they are also under the effect of lift force resulting from the unequal shear force acting on the cell due to the non-uniform flow velocity. The lift force is a function of lift coefficient C_L and the shear rate of fluid given by $G = U_{max}/D_h$, where U_{max} is the maximum velocity of the flow at a given cross-section and D_h is hydraulic diameter of the channel. The relationship is defined as

$$F_L = C_L \rho G^2 R^4 \qquad (7)$$

Table 1 Magnetic properties of blood components and liquid medium.

Blood components & Medium	Magnetic susceptibility (χ)	Relative magnetic susceptibility ($\Delta\chi=\Delta\chi_{cell}-\Delta\chi_{medium}$)
Red blood cell (hRBC)	-9.02× 10 $^{-6}$ [14]	0.01 × 10 $^{-6}$ [11]
Infected-Red blood cell (iRBC)	-7.16 × 10 $^{-6}$ [14]	1.80 × 10 $^{-6}$ [11]
White blood cell (WBC)	-11.6 × 10 $^{-6}$ [15]	-2.57 × 10 $^{-6}$
Water	-9.035 ×10^{-6} [15]	0

2.3 Motion Equation

In this study, the infected red-blood, healthy red-blood and white blood cells are modeled like a spherical particle, and the motion of these blood cells moving in a microchannel under magnetic force field is examined. The goal is to laterally manipulate them by magnetic force resulting from high gradient magnetic field. To simplify the problem, a uniform magnetic force field is

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assumed. The system defined in this study is shown in Fig. 2 while the force system exerting on the particles and their directions are summarized in Fig. 3.

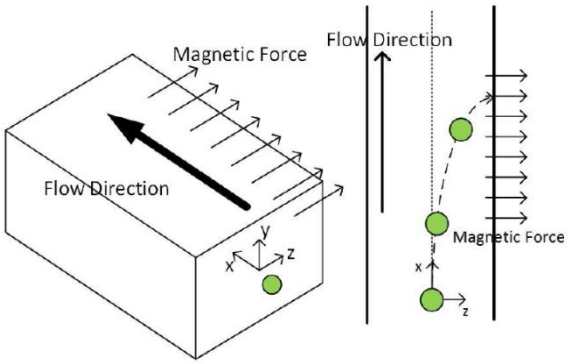
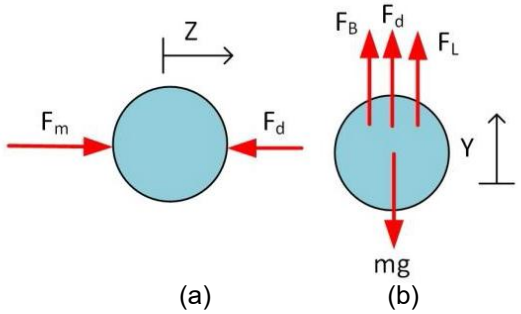


Fig. 2 Flow direction, magnetic force direction in a given coordinate system in a microchannel.



(a) (b)

Fig. 3 Force system on a cell; (a) lateral direction, (b) vertical direction.

From the 2nd law of motion, the motion equations the vertical and lateral directions are derived as

$$\sum \vec{F} = m\vec{a} \quad (8)$$

$$-\rho_{cell}\forall g + 6\pi\eta R\frac{dy}{dt} + C_L\rho R^4\left(\frac{U_{max}}{2wh/(w+h)}\right)^2 + \rho\forall g = \rho_{cell}\forall\frac{d^2y}{dt^2} \quad (9)$$

$$F_{mag} - 6\pi\eta R\frac{dz}{dt} = \rho_{cell}\forall\frac{d^2z}{dt^2} \quad (10)$$

where ρ_{cell} is density of cell (kg/m^3) and the channel width is w and height is h. In a small system, the gravitational force that is predominant causes a cell to move towards a bottom wall of microchannel, and we found from our analysis using Eq. (9) that the cells move towards and reach the bottom floor within a short distance as the results will be explained and discussed later.

In this study, the magnitude of the magnetic force acting on the infected red blood cell will be varied as 0.01, 0.1 and 1 pN while the relative magnetic force on the healthy red blood cell and white blood cell can be approximated from the relationship in Eq. (1) as proportional to the relative susceptibility and they are summarized in Table 2. Other constant parameters for the calculation are given in Table 3.

The velocity profile of the flow in this study is assumed as shown in Eq. (11)[13]. The origin of coordinate system is located at the center of channel so that $-w \le z \le w$ and $-h \le y \le h$.

$$u(y,z) = U_{max}\frac{\sum_{k=1,3,5,\ldots}^{\infty}\frac{(-1)^{(k-1)/2}}{k^3}\left[1-\frac{\cosh(\frac{k\pi y}{2w})}{\cosh(\frac{k\pi h}{2w})}\right](\cos(k\pi z/2w))}{\sum_{k=1,3,5,\ldots}^{\infty}\frac{(-1)^{(k-1)/2}}{k^3}\left[1-\frac{1}{\cosh(\frac{k\pi h}{2w})}\right]} \quad (11)$$

According to the reason that cells mostly roll on the bottom floor, the vertical and lateral motions will be solved independently in this study regardless the change in its out-of-plane location. For the motion in longitudinal direction, the cell is assumed to move along with the liquid flow so it is calculated by solving Eq. (11) at different y and z locations.

3. Computational Methods

Using Eqs. (9) and (10), the motion equations in y and z directions, which are ordinary differential equation, are independently numerically solved using Runge-Kutta fourth order method with MATLAB programming. In the calculation, the effects of two diameters of cell, i.e. 5 and 10 μm, and two flow rates, i.e. 0.06 and 0.15 μL/min, are examined. A time step is kept at

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5 μs while the data every 10 s is recorded and presented. The initial location of all cell types is at the center of microchannel or at 25 μm above the bottom floor of microchannel.

Table 2 Magnetic force conditions in this study.

Parameters	Healthy-red blood cell (hRBC)	Infected-red blood cell (iRBC)	White blood cell (WBC)
Relative magnetic susceptibility	0.01×10^{6} [11]	1.80×10^{-6} [11]	-2.57×10^{-6}
Magnetic Force (pN)	0.0000556	0.01	0.014
	0.000556	0.1	0.14
	0.00556	1	1.4

Table 3 Constant values used in this study.

Parameters	Value
Viscosity of medium (water)	8.93×10^{-4} Ns/m^2
Density of medium (water)	997 kg/m^3
Density of cells (RBC, WBC)	1100 kg/m^3 [15]
Lift Coefficient (C_L)	0.5 [12]

4. Computational Results

4.1 Vertical Motion

Firstly, the motion of the cells in the vertical direction is examined at the central plane of the microchannel, and the results from calculation are shown in Fig. 4. From the results, at the fastest speed of the flow in this study, i.e. 0.15 μL/min, the 5 μm and 10 μm cells sink towards and contact the bottom floor within the longitudinal distance of approximately 0.5 and 2.5 mm, respectively. Therefore, most of the time during flowing inside the microfluidic chip, the cells roll on the bottom floor.

4.2 Lateral Motion

The results are shown in Figs. 5 a-f for different conditions. For all conditions, the motion of blood components is divided into three patterns. Firstly, the infected red-blood cells are attracted by magnetic force and tend to move towards the magnetic source owing to its positive relative susceptibility. Secondly, the white blood cells are repelled away from the magnetic source owing to its negative relative susceptibility. Lastly, the healthy red-blood cells stay closely to their own original flow direction because of its relatively low positive relative susceptibility comparing to that of infected red-blood cell.

Regarding the cell size, for all conditions, the results show that the smaller cells travel more laterally than the larger cells. The longitudinal distance where the 5-μm cells travel laterally 50 μm is around one-fourth of that for 10-μm cells. As a result of the magnitude of drag force depending on sizes; therefore, the larger cells take time to move laterally more than smaller cells.

At the same flow rate, for example in Figs. 5a, c and e, they show that the magnitude of magnetic force also affects the motion of cells. For instance at 0.06 μL/min, the 5-μm infected red-blood cells travel laterally around 50 μm within the longitudinal distance of 0.2 mm under the magnetic force of 1 pN while the distance increases to over 10 mm under the magnetic force of 0.01 pN. Moreover, at 0.15 μL/min (see Figs. 5b, d and f), the longitudinal distance where the cells travel laterally around 50 μm increases since the time duration that the cells are exposed to the magnetic force is shorter within the same longitudinal distance.

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From the examined conditions, the results suggest that the flow rate and minimal magnetic force should be in an order of 0.06 μL/min and 0.1 pN if the length of the sorting chamber of a microchannel needs to be shorter than 10 mm for a given channel cross-section.

5. Discussion

In this study, the magnetic force acting on all types and sizes of blood components is assumed to be constant. However, from the Eq. (1), at the

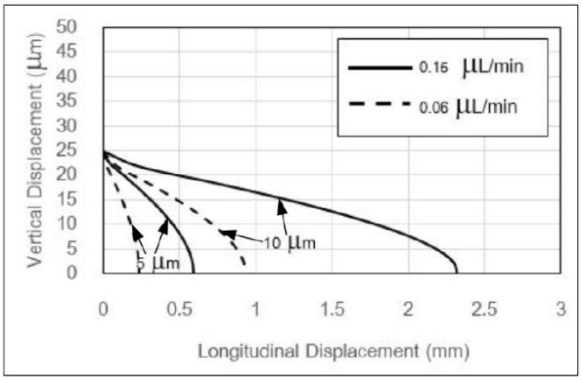
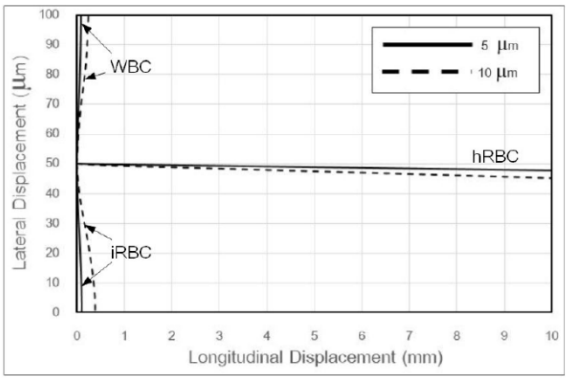
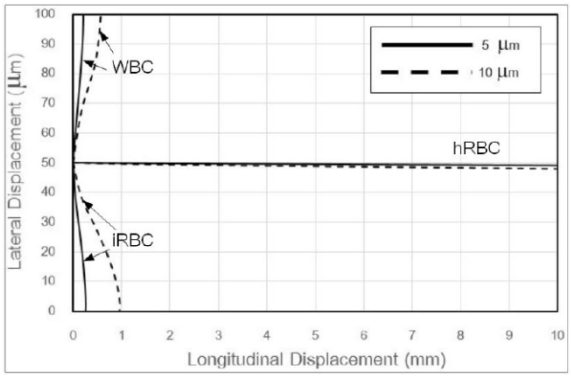


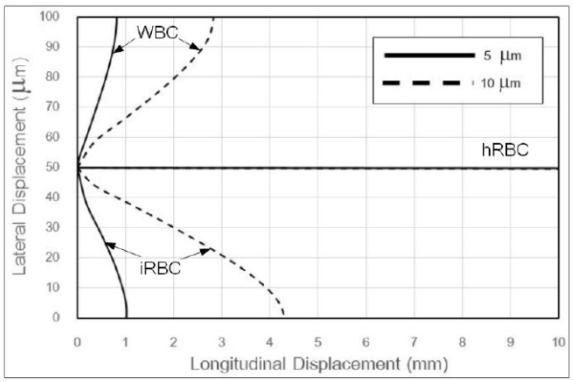
Fig. 4 Motion of cells (RBC & WBC) on the lateral plane at different flow rates.



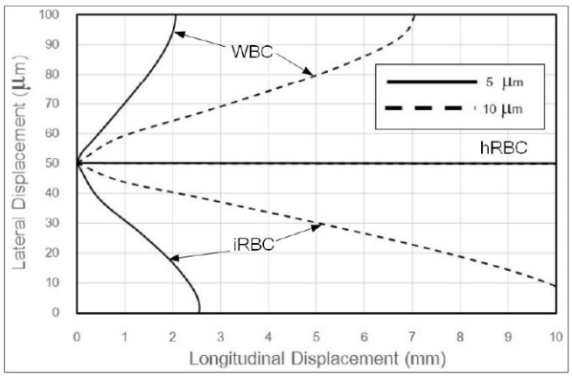
(a) 0.06 μL/min, 1 pN on iRBC



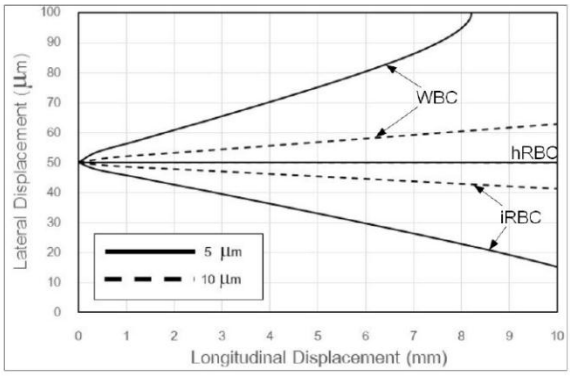
(b) 0.15 μL/min, 1 pN on iRBC



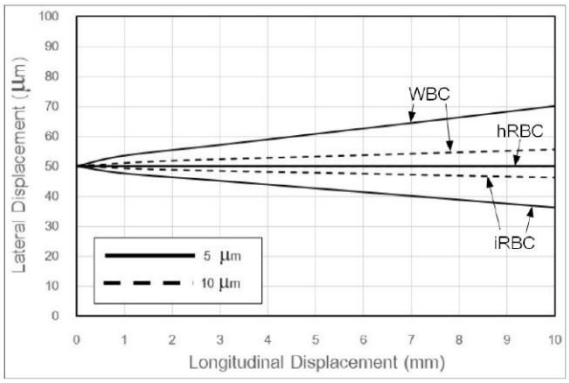
(c) 0.06 μL/min, 0.1 pN on iRBC



(d) 0.15 μL/min, 0.1 pN on iRBC



(e) 0.06 μL/min, 0.01 pN on iRBC



(f) 0.15 μL/min, 0.01 pN on iRBC

Fig. 5 Motion of all cell types on the planar plane at different flow rates and forces.

same gradient of magnetic field, the magnitude of magnetic force also depends on the size of cell so the further analysis is needed in the future.

Regarding the external source to generate high gradient of magnetic field, it is possible in three configurations, i.e. permanent magnet, electromagnet and field-intensifying ferromagnetic component. However, for the permanent magnet, it is hard to locally control the magnetic fields to be intensified in a specific location inside the microchip since the commercialized magnet typically is in a millimeter scale. For the electromagnetic field, it is possible to create high gradient of magnetic field locally; however, it generates Joule heat that might be possibly destroy the cells at the same time. Lastly, the field-intensifying ferromagnetic component is a relatively new option that is potential to create moderate magnetic field gradient. The selection and design of the external source to generate inhomogeneous magnetic field is ongoing.

6. Conclusion

The purpose of this study is to examine the effects of magnitude of magnetic force and volume flow rate on a motion of all blood components, i.e. Malaria infected red blood, healthy red blood and white blood cells, using a numerical method to solve the 2nd law of motion equations. In this analysis, the blood cells are modeled as a solid spherical particle with the size of 5 and 10 μm. Magnetic force exerted on the infected red-blood cell is varied as 0.01, 0.1 and 1 pN while the volume flow rate is varied as 0.06 and 0.15 μL/min. The ultimate goal of this work is to laterally separate the infected red blood cells from a main stream, and manipulate them into a specific outlet port of the microfluidic chip. From the simulated results, for the lateral sorting distance of 50 μm within a longitudinal distance of 10 mm, the flow rate should be in an order of 0.06 μL/min and the magnitude of the force should be higher than 0.1 pN on the infected red-blood cell for the 50 μm x 100 μm rectangular microchannel. In the future, the external source to generate magnetic force field will be chosen, and the prototype of the blood-cell-sorting microfluidic chip will be fabricated and tested.

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