Magnetophoretic separation of blood cells at the microscale

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Abstract

We present a method and model for the direct and continuous separation of red and white blood cells in plasma. The method is implemented at the microscale using a microfluidic system that consists of an array of integrated soft-magnetic elements embedded adjacent to a microfluidic channel. The microsystem is passive and is activated via application of a bias field that magnetizes the elements. Once magnetized, the elements produce a nonuniform magnetic field distribution in the microchannel, which gives rise to a force on blood cells as they pass through the microsystem. In whole blood, white blood cells behave as diamagnetic microparticles while red blood cells exhibit diamagnetic or paramagnetic behaviour depending on the oxygenation of their haemoglobin. We develop a mathematical model for predicting the motion of blood cells in the microsystem that takes into account the dominant magnetic, fluidic and buoyant forces on the cells. We use the model to study red/white blood cell transport, and our analysis indicates that the microsystem is capable of rapid and efficient red/white blood cell separation.

1. Introduction

Magnetophoresis involves the manipulation of magnetic particles in a viscous medium using an applied magnetic field [1]. Research in this area has intensified recently, with an emphasis on applications in microbiology and biomedicine. Much of this work has focused on the development of microfluidic systems with magnetic functionality that can process magnetically tagged biomaterials such as cells, enzymes, antigens and DNA [2, 3]. Magnetophoretic microsystems are well suited for bioapplications because they enable (i) fast reaction times, (ii) the analysis and monitoring of small samples (picoliters) and (iii) the integration of ‘micro total analysis systems’ (µTAS). However, while numerous microsystems have been developed for processing magnetically tagged biomaterial, relatively little work has been done on the direct magnetophoretic separation of blood cells at the microscale. Indeed, few such microsystems have been reported, despite the substantial need for fast, accurate and inexpensive blood cell analysis [4]. One such microsystem has been developed by Han and Frazier [5]. In this device, direct blood cell separation is achieved using the magnetic field due to a single magnetized soft-magnetic wire, which is in proximity to a microfluidic channel through which the cells flow. Han and Frazier have modelled, fabricated and characterized their device and have demonstrated that efficient blood cell separation can be achieved in practice.

In whole blood, white blood cells (WBCs) behave as diamagnetic microparticles, while red blood cells (RBCs) exhibit diamagnetic or paramagnetic behaviour depending on whether they are oxygenated or deoxygenated, respectively [6]. Thus, the magnetic force on WBCs is opposite to that on deoxygenated RBCs.

In this paper we present a novel method and a mathematical model for the direct and continuous separation of red and white blood cells in plasma. The method involves the use of a passive magnetophoretic microsystem that consists of an array of integrated soft-magnetic elements embedded adjacent to a microfluidic channel. The magnetic elements, which are magnetized by a bias field, produce a nonuniform field distribution that gives rise to a magnetic force on blood cells as they flow through the microchannel (figure 1). The microsystem is oriented with the fluid flow parallel to the gravitational force, and the cells are separated perpendicular to the flow. The reason for this orientation is that the fluidic and gravitational forces are stronger than the magnetic force and
should be orthogonal to it so as not to interfere with efficient magnetic separation (figure 1(c)).

We develop a mathematical model to predict the motion of blood cells in the microsystem. The model takes into account the magnetization of the soft-magnetic elements, and the dominant magnetic, fluidic and buoyant forces on the cells. We use it to study the motion of WBCs and deoxygenated RBCs and our analysis indicates that the magnetic force is sufficient to separate the two types of cells as they flow through the microchannel.

The cell separation method presented here has significant and distinct advantages over competing techniques such as centrifuging or magnetophoresis that involves magnetically labelled materials. First, blood cells can be continuously separated in their native state, without the need for magnetic tagging. Second, small sample volumes can be processed, with efficient cell separation completed within minutes. Third, a high degree of system integration is possible, which enables the potential for a comprehensive total analysis microsystem with a microfluidic channel showing the bias field, magnetic elements and forces on red and white blood cells (RBC and WBC).

The reason for this is that the magnetic elements span the width of the flow channel, and therefore the magnetic field and force are essentially invariant in this direction, which enables efficient separation along the entire width of the channel. This is in contrast to the separation method developed by Han and Frazier in which a single magnetic element projects a magnetic field and force that decay with distance into the flow channel, thereby limiting the region of efficient separation [5]. For these reasons, the method and model presented in this paper should stimulate and enable the development of novel microsystems for processing blood cells for a variety of research and diagnostic applications.

2. Theory

2.1. Equations of motion

We develop a model for predicting the motion of blood cells in the microsystem and then apply the model to study cell separation. We make several simplifying assumptions in order to render the problem tractable. First, we treat the blood cells as rigid noninteracting microspheres and ignore the fact that they are deformable. We also ignore the complex rheology of blood and use a fixed bulk value for the blood viscosity rather than a more realistic value that would otherwise depend on the shear rate of the flow and the dimensions of the microchannel.

We predict the motion of blood cells using Newton’s law:

$$\frac{dv_c}{dt} = F_m + F_f + F_g,$$  

(1)

where \( m_c \) and \( v_c \) are the mass and velocity of the cell and \( F_m \), \( F_f \) and \( F_g \) are the magnetic, fluidic and gravitational force (including buoyancy), respectively. The magnetic force is obtained using an ‘effective’ dipole moment approach and is given by [7]

$$F_m = \mu_0 V_c (\chi_c - \chi_t) (H_s \cdot \nabla)H_s,$$  

(2)

where \( \chi_c \) and \( V_c \) are the susceptibility and volume of the cell, \( \chi_t \) is the susceptibility of the transport fluid (in this case plasma), \( H_s \) is the applied magnetic field and \( \mu_0 = 4\pi \times 10^{-7} \text{ H m}^{-1} \) is the permeability of free space. The fluidic force is based on Stokes’ law for the drag on a sphere,

$$F_f = -6\pi \eta R_c (v_c - v_t),$$  

(3)

where \( R_c \) is the radius of the cell and \( \eta \) and \( v_t \) are the viscosity and the velocity of the fluid, respectively. The gravitational force is given by

$$F_g = V_c (\rho_c - \rho_t) g \hat{k},$$  

(4)

where \( \rho_c \) and \( \rho_t \) are the densities of the cell and fluid, respectively \((g = 9.8 \text{ m s}^{-2})\). It is important to note that gravity acts in the +x direction, parallel to the flow (see figures 1(c) and 2(b)).

2.2. Magnetic force

The magnetic force on a cell is obtained using an ‘effective’ dipole moment method in which the cell is replaced by an ‘equivalent’ point dipole with a moment \( m_{c,\text{eff}} \) [7]. The force on the dipole (and hence on the cell) is given by

$$F_m = \mu_4 (m_{c,\text{eff}} \cdot \nabla)H_s,$$  

(5)
where \( \mu \) is the permeability of the transport fluid and \( \mathbf{H} \) is the applied magnetic field intensity at the centre of the cell, where the equivalent point dipole is located. We evaluate equation (5) for a cell in a fluid of permeability \( \mu_f \) and obtain

\[
F_m = \mu_i V_c \frac{3(\chi_e - \chi_i)}{[(\chi_e - \chi_i) + 3(\chi_i + 1)]} (\mathbf{H}_i \cdot \nabla) \mathbf{H}_e. \tag{6}
\]

A detailed derivation of equation (6) is given in [7]. For blood cell separation, |\( \chi_e - \chi_i | \ll 1 \) and \( \mu_e \approx \mu_0 \), and therefore equation (6) reduces to equation (2).

### 2.3. Magnetic field of the magnetized elements

To evaluate the magnetic force, we need an expression for the applied field. This is a superposition of two distinct fields, the bias field \( \mathbf{H}_{\text{bias}} \) and the field \( \mathbf{H}_e \), due to the array of magnetized elements,

\[
\mathbf{H}_k = \mathbf{H}_{\text{bias}} + \mathbf{H}_e = \mathbf{H}_{\text{bias}}, \hat{x} + (\mathbf{H}_{\text{bias}},y + \mathbf{H}_{e}), \hat{y}. \tag{7}
\]

However, \( \mathbf{H}_{\text{bias}} \) and \( \mathbf{H}_e \) are not both independent. Specifically, \( \mathbf{H}_e \) depends on \( \mathbf{H}_{\text{bias}} \) as it is the bias field that magnetizes the elements. Therefore, \( \mathbf{H}_{\text{bias}} \) induces \( \mathbf{H}_e \). The bias field can be optimized using an analytical formula as described by Furlani [8, 9]. Once the bias field is known, we can determine \( \mathbf{H}_e \), but for this we need a magnetization model for the magnetic elements, which we assume are noninteracting (i.e. the field of one does not influence the magnetization of another).

We use a linear magnetization model with saturation to predict the magnetization of the soft-magnetic elements. Specifically, below saturation,

\[
M_e = x_e H_{\text{bias}}, \tag{8}
\]

where \( x_e = \mu_e/\mu_0 - 1 \), and \( \mu_e \) is the susceptibility and permeability of each element. Above saturation \( M_e = M_{es} \), where \( M_{es} \) is the saturation magnetization of the element. In equation (8) \( H_{\text{bias}} + H_{\text{demag}} \) is the field inside the element. Specifically, \( H_{\text{demag}} = -N_d M_e \), where \( N_d \) is the demagnetization factor, which is geometry dependent [10]. Thus from equation (8) we have \( M_e = \chi_e (H_{\text{bias}} - N_d M_e) \), which can be rewritten as

\[
M_e = \frac{x_e}{1 + N_d \chi_e} H_{\text{bias}}. \tag{9}
\]

For a soft-magnetic element, \( \chi_e \gg 1 \) and equation (9) reduces to

\[
M_e = \frac{H_{\text{bias}}}{N_d} \tag{10}
\]

The demagnetization factor for a highly permeable (\( \chi_e \approx \infty \)) long rectangular element of width \( 2w \) and height \( 2h \) that is magnetized parallel to its height can be obtained using analytical formulae (see figure 2(b)). Specifically, both the demagnetization factor \( N_d \) and the aspect ratio of the element \( p = h/w \) can be defined parametrically as a function of a variable \( k \) over the domain \( 0 < k < 1 \) as follows [11]:

\[
N_d = \frac{4}{\pi} \frac{[E(k) - k^2 K(k)] [E(k') - k^2 K(k')] - K(k')}{k^2}, \tag{11}
\]

\[
h = \frac{E(k') - k^2 K(k')}{E(k) - k^2 K(k)} \tag{12}
\]

where \( k' = \sqrt{1 - k^2} \) and \( K(k) \) and \( E(k) \) are the complete elliptic integrals of the first and second kind, respectively,

\[
K(k) = \int_0^{\frac{\pi}{2}} \frac{1}{\sqrt{1 - k^2 \sin^2(\phi)}} \, d\phi,
\]

\[
E(k) = \int_0^{\frac{\pi}{2}} \sqrt{1 - k^2 \sin^2(\phi)} \, d\phi. \tag{13}
\]

### Figure 2. Magnetophoretic microsystem: (a) microfluidic channel and (b) cross section of microsystem showing array of magnetized elements.
To determine the magnetization $M_e$ of the elements, we first use equations (11) and (12) to obtain $N_d$ for a given aspect ratio $p$ (see p 191, table A.2 in [11]). Next, we evaluate equation (10), taking saturation into account. Specifically, the magnetization of an element is obtained using

$$M_e = \begin{cases} H_{\text{bias}}/N_d & H_{\text{bias}} < N_d M_{\text{es}}, \\ M_{\text{es}} & H_{\text{bias}} \geq N_d M_{\text{es}}. \end{cases} \quad (14)$$

Once $M_e$ is known, $H_e$ is easily determined. Specifically, the field solution for a long rectangular element of width $2w$ and height $2h$ that is centred with respect to the origin in the $x$–$y$ plane, and magnetized parallel to its height (along the $y$-axis as shown in figure 2(b)) is well known (pp 210–211 in [10]). The field components are

$$H_{ex}^{(0)}(x, y) = \frac{M_e}{4\pi} \ln \left[ \frac{(x + w)^2 + (y - h)^2}{(x + w)^2 + (y + h)^2} \right] - \ln \left[ \frac{(x - w)^2 + (y - h)^2}{(x - w)^2 + (y + h)^2} \right] \quad (15)$$

and

$$H_{ey}^{(0)}(x, y) = \frac{M_e}{2\pi} \left\{ \tan^{-1} \left[ \frac{2h(x + w)}{(x + w)^2 + y^2 - h^2} \right] - \tan^{-1} \left[ \frac{2h(x - w)}{(x - w)^2 + y^2 - h^2} \right] \right\}. \quad (16)$$

In these equations, $M_e$ is determined using equation (14).

The field and force for an array of elements can be obtained from (15) and (16) [8, 9]. Specifically, let $N_e$ denote the number of elements in the array, and let $n = (0, 1, 2, 3, 4, \ldots, N_e - 1)$ label the individual elements (figure 2(b)). Now, $H_{ex}^{(0)}(x, y)$ and $H_{ey}^{(0)}(x, y)$ denote the field components due to the first element ($n = 0$). The $n$th element is centred at $x = x_n$, and its field components can be written as $H_{ex}^{(0)}(x, y) = H_{ex}^{(0)}(x - x_n, y)$ and $H_{ey}^{(0)}(x, y) = H_{ey}^{(0)}(x - x_n, y)$. The total field of the array is obtained by summing the contributions from all the elements

$$H_{ex}(x, y) = \sum_{n=0}^{N_e-1} H_{ex}^{(0)}(x - x_n, y),$$
$$H_{ey}(x, y) = \sum_{n=0}^{N_e-1} H_{ey}^{(0)}(x - x_n, y). \quad (17)$$

It follows from equations (2), (7) and (17) that the force components are

$$F_{mx}(x, y) = \mu_0 V_e (X_e = \chi_e) \left[ \sum_{n=0}^{N_e-1} H_{ex}^{(0)}(x - x_n, y) \right] \times \left( \sum_{n=0}^{N_e-1} \frac{\partial H_{ex}^{(0)}}{\partial x}(x - x_n, y) \right) + \left( H_{\text{bias}, y} + \sum_{n=0}^{N_e-1} H_{ey}^{(0)}(x - x_n, y) \right) \times \left( \sum_{n=0}^{N_e-1} \frac{\partial H_{ey}^{(0)}}{\partial y}(x - x_n, y) \right) \quad (18)$$

and

$$F_{my}(x, y) = \mu_0 V_e (X_e = \chi_e) \left[ \left( \sum_{n=0}^{N_e-1} H_{ex}^{(0)}(x - x_n, y) \right) \times \left( \sum_{n=0}^{N_e-1} \frac{\partial H_{ex}^{(0)}}{\partial x}(x - x_n, y) \right) + \left( H_{\text{bias}, y} + \sum_{n=0}^{N_e-1} H_{ey}^{(0)}(x - x_n, y) \right) \times \left( \sum_{n=0}^{N_e-1} \frac{\partial H_{ey}^{(0)}}{\partial y}(x - x_n, y) \right) \right]. \quad (19)$$

In equations (18) and (19) we have assumed that the bias field is constant and in the $y$-direction. Explicit expressions for the field and force for an array of rectangular soft-magnetic elements (equations (17)–(19)) have been derived and verified using finite element analysis (FEA) [8, 9].

2.4. Fluidic force

To evaluate the fluidic force in equation (3) we need an expression for the fluid velocity $v_f$ in the microchannel. Let $h_c$ and $w_c$ denote the half-height and half-width of its rectangular cross section (figure 2(a)). We assume fully developed laminar flow parallel to the $x$-axis and obtain

$$v_f(y) = \frac{3 \bar{v}_f}{2} \left[ 1 - \left( \frac{y - (h + h_c + h_b)}{h_c} \right)^2 \right], \quad (20)$$

where $\bar{v}_f$ is the average flow velocity and $h_b$ is the thickness of the base of the channel (i.e. the distance from the top of the magnetic elements to the lower edge of the fluid) [8, 9]. We substitute equation (20) into equation (3) and obtain the fluidic force components

$$F_{fx} = -6\pi \eta R_c \left[ v_{c,x} - \frac{3 \bar{v}_f}{2} \left[ 1 - \left( \frac{y - (h + h_c + h_b)}{h_c} \right)^2 \right] \right] \quad (21)$$

and

$$F_{fy} = -6\pi \eta R_c v_{c,y}. \quad (22)$$

We use these in the equations of motion below.

2.5. Blood cell properties

We need the magnetic properties of white and red blood cells to complete the mathematical model. WBCs comprise five different kinds of cells that are classified into two groups: agranulocytes (lymphocyte and monocyte) and granulocytes (neutrophil, eosinophil and basophil) [12, 13]. The five different cells have different sizes, with diameters that range from 6 to 15 $\mu$m. We account for the different types of WBCs by using average WBC properties: $\rho_{wbc} = 1070$ kg m$^{-3}$, $K_{wbc} = 5$ $\mu$m and $V_{wbc} = 524$ $\mu$m$^3$ [12]. WBCs exhibit a diamagnetic behaviour in plasma, but their magnetic susceptibility is not well known [13]. In order to determine the feasibility of WBC separation we use a lower bound estimate for the WBC susceptibility as suggested by Takayasu et al., specifically we use the susceptibility of water $\chi_{wbc} = -9.2 \times 10^{-10}$ (SI) [13]. This value is consistent with measurements made by Han and Frazier in which a value of $\chi_{wbc} \approx -9.9 \times 10^{-10}$ was obtained for WBCs 5 $\mu$m in diameter (see table 1
p. Thus, the WBC susceptibility that we use provides a conservative lower-bound estimate of the force and enables us to determine the feasibility of WBC separation.

RBCs, when unperturbed, have a well-defined biconcave discoid shape with a diameter of 8.5 $\pm$ 0.4 $\mu$m and a thickness of 2.3 $\pm$ 0.1 $\mu$m. These cells account for approximately 99% of the particulate matter in blood, and the percentage by volume (hematocrit) of packed RBCs in a given sample of blood is normally 40–45%. For red blood cells, we use $R_{bc}$ = 3.64 $\mu$m (hydrodynamic radius), $V_{bc}$ = 88.4 $\mu$m$^3$ and $\rho_{bc}$ = 1100 kg m$^{-3}$ [14]. The susceptibility of a RBC depends on the oxygenation of its haemoglobin. We use $\chi_{bc,oxy} = -9.22 \times 10^{-6}$ (SI) and $\chi_{bc,deoxy} = -3.9 \times 10^{-6}$ (SI) for oxygenated and deoxygenated RBCs, respectively [13–15]. The transport fluid is plasma, which has the following properties: $\eta = 0.001$ kg s$^{-1}$, $\rho_l = 1000$ kg m$^{-3}$ and $\chi_l = -7.7 \times 10^{-6}$ (SI) [13–15].

2.6. Equations of motion

The equations of motion for blood cell transport through the microsystem can be written in component form by substituting equations (18), (19), (21) and (22) into equation (1),

$$m \frac{d\mathbf{v}_{c,x}}{dt} = F_{mx}(x, y) + V_c(\rho_c - \rho_l)g - 6\pi \eta R_c \left[ \frac{3}{2} \mathbf{v}_c - \frac{1}{ \eta} \left( \frac{y - (h + R_c + b_h)}{h_c} \right)^2 \right],$$

(23)

$$m \frac{d\mathbf{v}_{c,y}}{dt} = F_{my}(x, y) - 6\pi \eta R_c v_{c,y},$$

(24)

$$v_{c,x}(t) = \frac{dx}{dt}, \quad v_{c,y}(t) = \frac{dy}{dt}. \quad (25)$$

Equations (23)–(25) constitute a coupled system of first-order ordinary differential equations (ODEs) that are solved subject to initial conditions for $x(0)$, $y(0)$, $v_{c,x}(0)$ and $v_{c,y}(0)$. These equations can be solved numerically using various techniques such as the Runge–Kutta method.

3. Results

We use the model developed above to study blood cell motion in the microsystem. As a first step, we compute the field due to an array of three magnetized permalloy (78% Ni 22% Fe, $M_s = 8.6 \times 10^5$ A m$^{-1}$ [10]) elements (figure 3). Each element is 300 mm high, 300 mm wide, and they are spaced 300 mm apart (edge to edge). Thus, $w = h = 150 \mu$m, and these elements have an aspect ratio $p = h/w = 1$. From equations (11) and (12) we compute a demagnetization factor of $N_2 = 0.456$ (p 191, table A.2 in [11]). The bias field is set to $H_{bias} = 3.9 \times 10^3$ A m$^{-1}$, which from equation (14) is sufficient to saturate the elements, i.e. $H_{bias} = N_2 M_s \rightarrow M_s = M_s$. This bias field intensity corresponds to a flux density of 5000 G, which can be obtained by positioning rare earth permanent magnets on either side of the microsystem as shown in figure 1.

The field components $B_x$ and $B_y$ due to the magnetized elements are computed along a horizontal line 60 $\mu$m above the elements (i.e. at $y = 210 \mu$m) using equations (15)–(17) with $N_2 = 2$ (figure 3). Notice that $B_x$ peaks near the edges of the elements and alternates in sign from one edge to the other, whereas $B_y$ obtains its maximum value at the centre of the elements.

Next, we compute the magnetic force on a deoxygenated RBC along the same horizontal line as above (60 $\mu$m above the elements). The component $F_{mx}$ acts in the flow direction while $F_{my}$ acts perpendicular to the flow and is responsible for cell separation. Note that $F_{mx}$ peaks near the edges of the element and changes sign across the element (figure 4(a)). Thus, a deoxygenated RBC experiences acceleration in the flow direction as it passes the leading edge of an element, followed by deceleration as it passes the trailing edge. $F_{my}$ is downward (negative) immediately above an element, but alternates in direction across an element, upward to the left of an element, downward above an element and upward to the right of an element (figure 4(b)). Therefore, a deoxygenated RBC accelerates upward, then downward, and then upward again as it passes an element. Oxygenated RBC and WBC exhibit a similar behaviour, but in the opposite direction.

Finally, we determine the feasibility of RBC/WBC separation by predicting the motion of deoxygenated RBCs
Figure 4. Magnetic force on a deoxygenated RBC above three magnetized elements (● = FEA): (a) $F_{mx}$ (parallel to flow), (b) $F_{my}$ (perpendicular to flow) and (c) three elements embedded beneath flow channel.

Figure 5. Blood cell trajectories above magnetized elements (upper half of magnetized elements shown for reference): (a) WBC trajectories and (b) RBC trajectories.

and WBCs as they move through the microsystem. The fluid channel is 120 $\mu$m high, 1 mm wide and 30 mm long, and there are 45 permalloy elements embedded immediately beneath it. Each element is 300 $\mu$m high and 300 $\mu$m wide, and they are spaced 300 $\mu$m apart (edge to edge). Thus, the magnetic element array spans a distance of 26.7 mm along the bottom of the microchannel.

The cells enter the microchannel to the left of the first element ($x(0) = -600 \mu$m) at various initial heights: $y(0) = 165 \mu$m, 180 $\mu$m, ..., 255 $\mu$m. The top of the fluidic chamber is 120 $\mu$m above the elements at $y = 270 \mu$m. The average fluid velocity is $\bar{v}_f = 0.25$ mm s$^{-1}$, and the cells enter the channel with this velocity. The WBC and RBC trajectories are shown in figures 5(a) and (b), respectively. The trajectory profiles are irregular due to the spatial variation of the magnetic force as described above. Note that the WBCs and RBCs separate before they reach the end of the array. Specifically, all WBCs move to the top of the channel, while all deoxygenated RBCs move to the bottom. The separation times for the WBCs and RBCs (i.e. the time it takes for all the cells to reach their respective ends of the microchannel) are 60 s and 80 s, respectively (figure 6). It is important to note that cell separation effectively occurs before the cells reach the top or the bottom of the channel. This is because the fluid exits the microchannel at both the top and the bottom of the channel as shown in figure 1(b). Therefore, cells can be considered
separated once they cross the line that defines the two exit flows.

The preceding analysis demonstrates the viability of WBC/RBC separation. The parameters used in the analysis (e.g. the dimensions and spacing of the magnetic elements) were arrived at through an iterative series of simulations and do not represent optimum values. However, the model enables rapid parametric analysis, and there are several variables that can be adjusted to optimize performance including the number, size and spacing of the elements, the dimensions of the microchannel and the flow rate. Thus, the separation method is robust, and the microsystem holds significant potential for numerous biomedical applications.

4. Conclusion

We have presented a novel method for the direct and continuous separation of red and white blood cells in plasma that has numerous advantages over existing cell separation methods. The method is implemented in a passive magnetophoretic microsystem that can be fabricated using established methods [4, 16, 17]. We have also developed a mathematical model for studying blood cell transport at the microscale and have used the model to predict cell separation in the microsystem. Our analysis indicates that deoxygenated RBCs can be separated from WBCs in plasma and that efficient separation can be achieved within a few minutes. The method and model presented here should stimulate further research into magnetophoretic cell separation and lead to the development of novel cell separation microsystems.

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