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High gradient magnetic field microstructures for magnetophoretic cell separation

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ABSTRACT

Microfluidics has advanced magnetic blood fractionation by making integrated miniature devices possible. A ferromagnetic microstructure array that is integrated with a microfluidic channel rearranges an applied magnetic field to create a high gradient magnetic field (HGMF). By leveraging the differential magnetic susceptibilities of cell types contained in a host medium, such as paramagnetic red blood cells (RBCs) and diamagnetic white blood cells (WBCs), the resulting HGMF can be used to continuously separate them without attaching additional labels, such as magnetic beads, to them. We describe the effect of these ferromagnetic microstructure geometries have on the blood separation efficacy by numerically simulating the influence of microstructure height and pitch on the HGMF characteristics and resulting RBC separation. Visualizations of RBC trajectories provide insight into how arrays can be optimized to best separate these cells from a host fluid. Periodic microstructures are shown to moderate the applied field due to magnetic interference between the adjacent teeth of an array. Since continuous microstructures do not similarly weaken the resultant HGMF, they facilitate significantly higher RBC separation. Nevertheless, periodic arrays are more appropriate for relatively deep microchannels since, unlike continuous microstructures, their separation effectiveness is independent of depth. The results are relevant to the design of microfluidic devices that leverage HGMFs to fractionate blood by separating RBCs and WBCs.

1. Introduction

Medical diagnostics to detect, control, manage and prevent disease use blood fractionation [1,2]. Conventional methods of fractionation are slow and laborious, involving multistep batch processes that include several manual handling and centrifugation stages. These stages slow down fractionation and introduce multiple sources of error [3]. Magnetic cell labeling is a workaround that binds magnetic beads to targeted cells [4–6]. Upon application of a magnetic field, cells that are bound to the beads separate from the remainder of the medium through magnetophoresis and propagate towards regions that experience the highest magnetic field strength (such as a magnetic surface) [7,8]. However, magnetic beads are relatively expensive and, when the cell-bead conjugates are washed, the magnetic pull that the beads exert on cell membranes can damage the cells.

Continuous label-free methods leverage the intrinsic properties of cells that allow cell separation from a host medium [2]. We investigate label-free separation due to differences in the magnetic susceptibilities of different cell types. Diamagnetic materials are repelled by a magnet. The presence of free electrons in a material leads instead to paramagnetic, ferromagnetic, ferrimagnetic and antiferromagnetic behaviors. The iron ions in hemoglobin molecules are responsible for oxygen transport through the body. Each hemoglobin molecule contains four heme groups, each with a single Fe^{+2} ion that can bind to an oxygen molecule. In its deoxygenated state, an RBC contains no oxygen so that its Fe^{+2} ions contain free electrons. The spins of the free electrons induce the paramagnetic behavior for RBCs. In contrast, the iron ions contained in oxygenated RBCs lack free electrons due to oxygen binding, inducing diamagnetic behavior. The iron ions in RBCs can be oxidized to form methemoglobin, Fe^{+3}, which is unable to bind to oxygen and is thus also responsible for paramagnetic RBC behavior. Hemoglobin can be intentionally oxidized to methemoglobin, ensuring that RBCs remain deoxygenated, producing a larger magnetic susceptibility contrast between RBCs and white blood cells (WBCs), leading to more effective separation. Since WBCs contain

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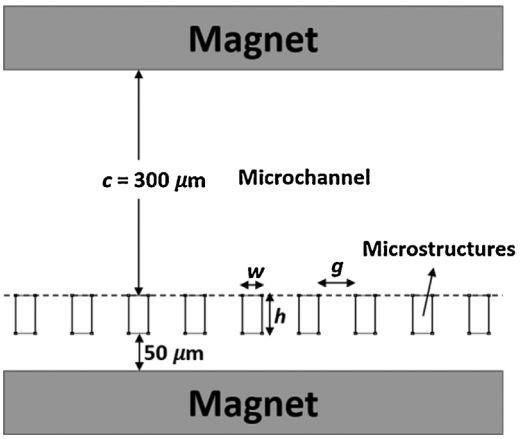

Fig. 1. Microstructure array of width w, height h and separation gap g placed within a microchannel and within a double magnet configuration. The array pitch p = w + g, the channel height c = 300 μm, and the array and bottom magnet are separated by 50 μm. Magnetic properties are obtained from the FEMM material library (Finite Element Magnetic Method Version 4.2 November 15, 2013).

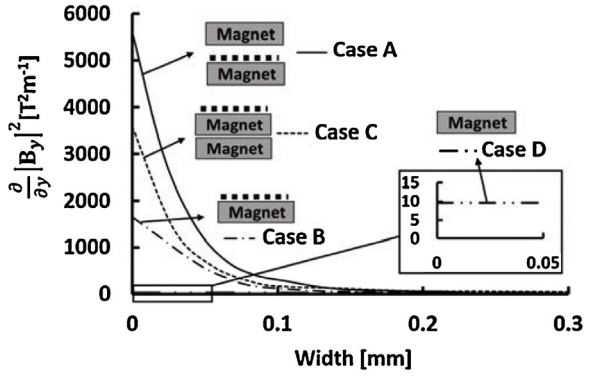

Fig. 2. Variation of the magnetic field gradient $\partial|\boldsymbol{B_y}|^2/\partial y$ across a channel containing a single 50 × 80 μm nickel microstructure for the double and single magnet configurations. The largest gradient occurs for Case A, which is a double magnet configuration. The lowest gradient for a microstructure occurs for Case B that involves a single magnet. Case C provides intermediate results, which is also a single magnet configuration but where the volume of the bar magnet is now two times that of Case B and equal to the combined volume of the two magnets placed on either side of the microchannel for Case A. Case D contains no microstructures and yields the lowest overall $\partial|\boldsymbol{B_y}|^2/\partial y$.

no iron ions or free electrons, they are diamagnetic. The magnetic susceptibility of hemoglobin has been extensively investigated in its oxygenated and deoxygenated states [9–14]. The resulting difference in the susceptibilities of the RBCs and WBCs can be leveraged to fractionate blood.

Microfluidics has advanced magnetic blood fractionation by making integrated miniaturized devices possible [15,16], such as those containing microstructures fabricated from ferromagnetic materials [17]. These materials are suitable for separating blood cells using both label and label free methods [3,17–26]. The magnetic force imposed on a cell depends on the gradient of the magnetic field, the cell's magnetic susceptibility and its volume. A microstructure that is integrated into a microchannel focuses the local magnetic lines of force imposed by an external magnet, thereby producing a high gradient magnetic field (HGMF). This reoriented field increases the magnetic force experienced by a cell and therefore the separation efficiency.

Analytical solutions are available for the magnetic force produced by inserting an array of rectangular microstructures into a microfluidic channel and also for the resultant force on the cells that are bound to paramagnetic beads [27,28]. Despite their promise, the geometries of the embedded microstructures, which range from periodic arrays to continuous ferromagnetic micro wires, have not yet been optimized. We examine rectangular magnetic microstructure arrays, which are often encountered in literature, to characterize how microstructure geometry variations influence the ensuing magnetic field in a microchannel and thus the blood fractionation efficiency.

2. Methodology

Two dimensional simulations are conducted using Finite Element Magnetic Method software (FEMM, version 4.2) to determine separation with an array of rectangular nickel microstructures of height *h*, width *w* and separation gap *g*, as shown in Fig. 1. The magnetic field is simulated for 12.9 × 5.8 mm NdFeB 52 magnets. These magnets sandwich the 300 μm high microchannel and the microstructure that adheres to one of the sides of the channel. The base of the microstructures lies at a 50 μm displacement from the magnet. All unfilled spaces assume the magnetic properties of air. Material properties are obtained from the FEMM software library. The influence of different array configurations on RBC trajectories in a plasma medium is simulated using MATLAB (R2014b, The MathWorks, Inc.) software along with the magnetic fields generated by the FEMM software.

3. Results and discussion

3.1. Effect of magnet configuration on the generated magnetic field

The magnetic force acting on a cell is [15,17,26],

$$\mathbf{F}_M = \left((\chi_{cell} - \chi_m) V_{cell}/2\mu_o\right) \nabla|\mathbf{B}|^2, \quad (1)$$

where χ_{cell} and χ_m denote the magnetic susceptibilities of the cell and fluid medium respectively, V_{cell} and μ_o the cell volume and permeability of the free space respectively, and $\nabla|\mathbf{B}|$ the magnetic field gradient. From Eq. (1), the magnetic force depends on the (1) difference in the magnetic susceptibilities of the cell and fluid medium, (2) cell volume, and (3) magnetic field gradient. From Eq. (1), we note that cell behavior changes with cellular content. When the susceptibility of a medium is selected such that, $\chi_{rbc} > \chi_m > \chi_{wbc}$, Eq. (1) reveals a positive force on an RBC, indicating paramagnetism, i.e., the cell is attracted towards the magnet. That magnet repels a diamagnetic WBC in the mixture, since $\chi_m > \chi_{wbc}$. The host medium plays an equally significant role. For instance, a paramagnetic medium can be prepared with $\chi_m > \chi_{rbc}$ and $\chi_m > \chi_{wbc}$. Here, Eq. (1) indicates magnetic repulsion for both RBCs and WBCs [29]. Hence, while an RBC is paramagnetic independent of the medium, it can behave as diamagnetic material in a manner similar to a WBC when an appropriate host medium is used. For the purpose of this study however, we assume that $(\chi_{cell} - \chi_m) V_{cell}/2\mu_o$ is constant and focus instead on the influence of the gradient in the cross-channel direction $\partial|\mathbf{B_y}|^2/\partial y$.

The literature commonly considers configurations where (1) a single bar magnet is placed in close proximity to the microchannel [19,26,30], and (2) two bar magnets are placed on either side of the microfluidic channel such that their opposite poles face each other [22,27,28]. First, we investigate the difference between use of these single and double magnet configurations for a single $w = 50$ μm and $h = 80$ μm nickel microstructure. Fig. 2 shows the variation of $\partial|\mathbf{B_y}|^2/\partial y$ for different configurations across the channel along the centerline of the structure moving away from its top surface.

Case (A) in Fig. 2 represents a double magnet configuration with single NdFeB 52 bar magnets placed on each side of the microchannel. Single magnet simulations are reported for Case (B) where a