CDF Analysis of Particle Magnetophoresis in Multiphase Continuous-Flow Bioseparators

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ABSTRACT

The use of magnetic particles has recently expanded for a process known as detoxification in which different toxins are captured from the bloodstream of septic patients. Due to the laminar flow developed in microfluidic devices, the particle separation after the toxin capture can be carried out in a continuous mode using multiphase microfluidic channels. In this work, the design for a two-phase continuous-flow microseparator and an optimization study for the separation of magnetic beads from blood are presented. The numerical method includes a combination of magnetic and fluidic computational models that were solved using the VOF method with the commercial flow solver ***FLOW-3D***, whereas an external Fortran subroutine was employed for the calculation of the magnetic fields and forces. For optimization purposes, a dimensionless number J is introduced. The results show that complete and safe separation is achieved only for a certain value of J (≈0.3). To the best of our knowledge, this is the first computational study of the interaction between two different fluids flowing simultaneously in the device that takes into account two-way coupled particle-fluid interactions in the flow field and the particle motion effects as they cross the interface between the fluids under various magnetic field intensities.

Keywords: magnetic bead separation, two-phase liquid-liquid microfluidic systems, fluid-particle coupling, bioseparation, blood detoxification

1 INTRODUCTION

In recent years, there has been a proliferation of applications of superparamagnetic beads in a diverse range of fields. Nonetheless, the majority of their applications have been in the field of biomedicine where they mostly act as magnetic carriers for the capture of different molecules (i.e. bioanalysis, medical diagnosis or therapy) [1]. Indeed, some of the most recent works have addressed the use of magnetic beads for the extracorporeal removal of toxic substances (biotoxins, microorganisms, toxic chemicals or drugs) from blood [2]. In fact, for a number of clinical conditions such as intoxication, bacteraemia or autoimmune diseases, the removal of the disease-causing agents from blood can be considered as the most direct conceivable treatment [2]. Blood detoxification using magnetic beads is an extracorporeal process wherein the patient's blood is infused with magnetic materials. The ultimate goal of this process is the selective removal of toxins while maintaining healthy functionality of blood constituents. Some magnetic materials have shown to have high affinity to different toxins and have enabled high removal capacities and very fast kinetics (less than 1 minute)[3] in various studies. Once the adsorption of the toxins onto the beads surface is completed, the magnetic separation stage takes place and the toxins are removed along with the material, leading to a toxin-free blood solution that returns to the circulatory system of the patient.

Numerous microfluidic magnetic separator designs have been proposed in the last years for carrying out the recovery of magnetic beads from different biological fluids, including blood [4]. These are usually batch separators where the particles are trapped on the separator walls due to a magnet located next to the channel. However, in several recent studies continuous separators have been introduced, where the particles are deflected from the blood stream and collected into a flowing buffer solution by a magnetic gradient applied perpendicular to the flow direction [5]. The use of continuous microfluidic systems poses several advantages compared to batch magnetic separators (i.e. the flow is not restricted, blood cell entrapment is avoided, increased separation efficacy and throughput, etc.) [6].

The application of continuous magnetic separators in this process must meet two fundamental requirements: i) the complete recovery of the magnetic beads from the blood solution and, ii) the elimination or minimization of intermixing between the blood and buffer streams inside the device. While the requirement i) has been the subject of study in previous works [7], the requirement ii) has received minimal attention and no numerical analyses of the process have been reported so far. Furthermore, relatively few experimental results addressing this issue are available [3,5]. Hence, magnetic bioseparator design parameters such as the flow conditions of both phases and the flow perturbation due to particle-fluid interactions, which might affect the composition of the two streams or their separation at the outlets, are issues that remain unresolved and have never been described before, to the best of our knowledge. Advancing this novel technology to the next stage requires

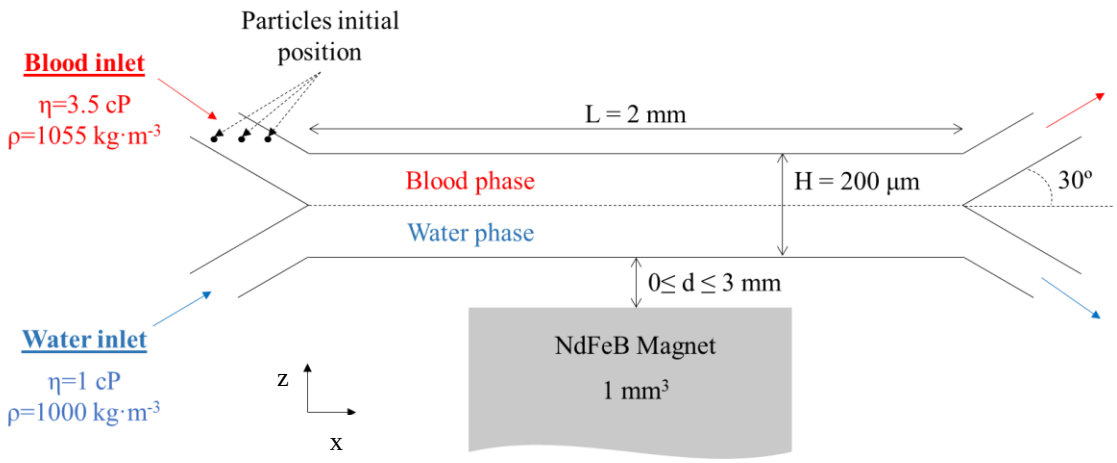

Figure 1. Schematic view of the design of the two-phase microfluidic separator employed in the analysis.

the reliable removal of the magnetic beads by appropriately studied magnetic fields and the independent flow of both solutions without any intermixing inside the device. In this work, we introduce a combination of magnetic and fluidic computational models that describe the bead trajectory inside a symmetric microchannel under the influence of an external permanent magnet along with the potential mixing or modification between fluid streams. This approach is well-suited for parametric analysis and optimization, thereby facilitating the development of novel microfluidic systems not only for blood detoxification processes but also for many other biomedical applications that involve two or more confined liquid phases.

2 THEORY

The model for predicting the magnetophoretic particle transport inside the separator shown in **Figure 1** involves a CFD-based Eulerian-Lagrangian approach. The Lagrangian framework is used to model the bead dynamics, whereas the fluid transport, which is predicted by solving the Navier-Stokes equations, is calculated with an Eulerian approach. According to the Lagrangian approach, particles are modelled as discrete units and the trajectory of each one is estimated by applying the classical Newtonian dynamics:

$$m_p \frac{d\mathbf{v_p}}{dt} = \sum \mathbf{F_{ext}} \qquad (1)$$

where m_p and $\mathbf{v_p}$ are the mass and velocity of the particle and $\mathbf{F_{ext}}$ represents all external force vectors exerted on the particle. Although different force contributions act on the particles during separation, only the dominant magnetic ($\mathbf{F_{mag}}$) and fluidic ($\mathbf{F_{drag}}$) forces were considered in this work. Expressions for the magnetic and drag forces acting on a particle can be found in our published work [6]. A cubic-shaped rare-earth NdFeB magnet was chosen as the magnetic source, with dimensions of 1 mm^3, and the analytical model developed by Furlani [8] was adopted for the calculation of the field distribution. The fluid velocity field was estimated by the modified Navier-Stokes and continuity equations that account for the interactions between fluid and particles. For optimization purposes, a dimensionless number (J) that takes into account all the key fluidic and magnetic variables and parameters that affect the force balance was developed. More specifically, the J number describes the relation between magnetic (particle volume V_p and magnetization $f(H_a)$, magnetic field strength $\mathbf{H}_a$ and gradient inside the channel $\nabla\mathbf{H}_a$) and fluidic (particle size r_p, viscosity of the fluids η and inlet mean velocities v_{mean}) variables that impact the process. Thus, the J number scales both the magnetic (in z direction) and drag (in x direction) force on a particle located in the middle of our channel just above the magnet (this location was chosen because of the average values of the magnetic force acting at that point). The J number can be written as follows:

$$J = \frac{\overline{F_{mag,z}}}{\overline{F_{drag,x}}} = \frac{\mu_0 V_p f(H_a)\left(H_{a,z\left(\frac{L}{2},\frac{H}{2}\right)} \cdot \nabla\right) H_{a,z}}{6\pi r_p (\eta v_{mean})_{blood}} \qquad (2)$$

where

$$f(H_a) = \begin{cases} \dfrac{3(\chi_p - \chi_f)}{(\chi_p - \chi_f) + 3}, & H_a < \left(\dfrac{(\chi_p - \chi_f) + 3}{3(\chi_p - \chi_f)}\right) M_{s,p} \\ \dfrac{M_{s,p}}{|H_a|}, & H_a \geq \left(\dfrac{(\chi_p - \chi_f) + 3}{3(\chi_p - \chi_f)}\right) M_{s,p} \end{cases} \qquad (3)$$

where μ_0 is the permeability of the free space, χ_p and χ_f are the susceptibilities of the particle and the fluid and $M_{s,p}$ represents the saturation magnetization of the particles.

Particles with sizes of 5 μm, density of 2,000 kg·m^{-3} and saturation magnetization of 100,000 A·m^{-1} were modeled. Blood was assumed to follow a Newtonian rheology, and its viscosity was quantified by an analytical empirically based expression [7] obtaining a value of 0.0035 Pa·s. The buffer solution used as the collecting phase is water with viscosity of 0.001 Pa·s. For every simulation, different values of the J

number were obtained by varying the distance between the lower wall of the channel and the top of the magnet "d", while keeping the same inlet velocities of the fluids (0.035 $m \cdot s^{-1}$ and 0.01 $m \cdot s^{-1}$ for the buffer and blood phases, respectively). The simulations were performed on a 48-core workstation with 128 GB of RAM. The running time for each simulation was approximately 300 hours.

3 RESULTS AND DISCUSSION

3.1 Particle Separation

In this section, the particle trajectories under variable magnetic forces and constant drag forces are studied. In **Figure 2**, the trajectories of the particles under different J values are presented. When the value of this dimensionless number is approximately above 0.2 (i.e. when the $F_{mag,z}$ is 0.2 times the average value of the $F_{drag,x}$), all the particles are separated independently of their original position at the inlet. However, for J numbers between 0.06 and 0.14, the separation is incomplete since the particles that enter close to the upper wall of the straight channel leave the device within the blood solution through the upper outlet. For lower values, none of them are separated due to the low magnetic forces, as seen in **Fig. 2** for J numbers lower than 0.06. Hence, medium to high magnetic forces are necessary for achieving the complete particle separation. However, under high magnetic fields and forces, particles could be extremely accelerated towards the high magnetic gradient region, which may be undesirable due to the perturbation of the flow patterns. This issue is analyzed in the next section.

3.2 Perturbation of the flow field

The fluid perturbation due to particle motion and the consequences of this effect on the phase separation inside the device are illustrated in **Figure 3**. As seen in **Fig. 3** a), the velocity field is greatly affected when the particles are separated under high field conditions (J≈4). In this case, the particles greatly accelerate and reach very high velocities (higher than the fluids) as they travel to the high gradient region, thus dramatically changing the velocity patterns at the interface. The effects of this perturbation in the phase separation are represented in **Fig. 3** c), where the volumetric fraction of the blood phase when the particles are crossing the interface is shown for this magnetic condition. As seen in this figure, the interface between fluids is highly altered. On the other hand, the velocity flow field under lower magnetic fields (J=0.36) is shown in **Fig. 3** b). Under smaller magnetic fields, the particles barely alter the flow velocity vectors due to their slow deflection to the water phase. As seen in the figure, the fluid velocity vectors are parallel to the x-axis when the particles are located near the interface, and the interface at that time, which is represented in **Fig. 3** d), is not as affected as much as in the previous case.

Although lower magnetic fields ($0.01 \leq J \leq 0.14$) result in a negligible fluid perturbation (not shown), these conditions may not be conducive to successful particle removal as it was previously shown in **Fig. 2**. Therefore, medium magnetic forces compared to the average drag force (i.e. J numbers around 0.3) are required for the complete particle separation while maintaining the biofluid integrity at the outlet and the interface stability.

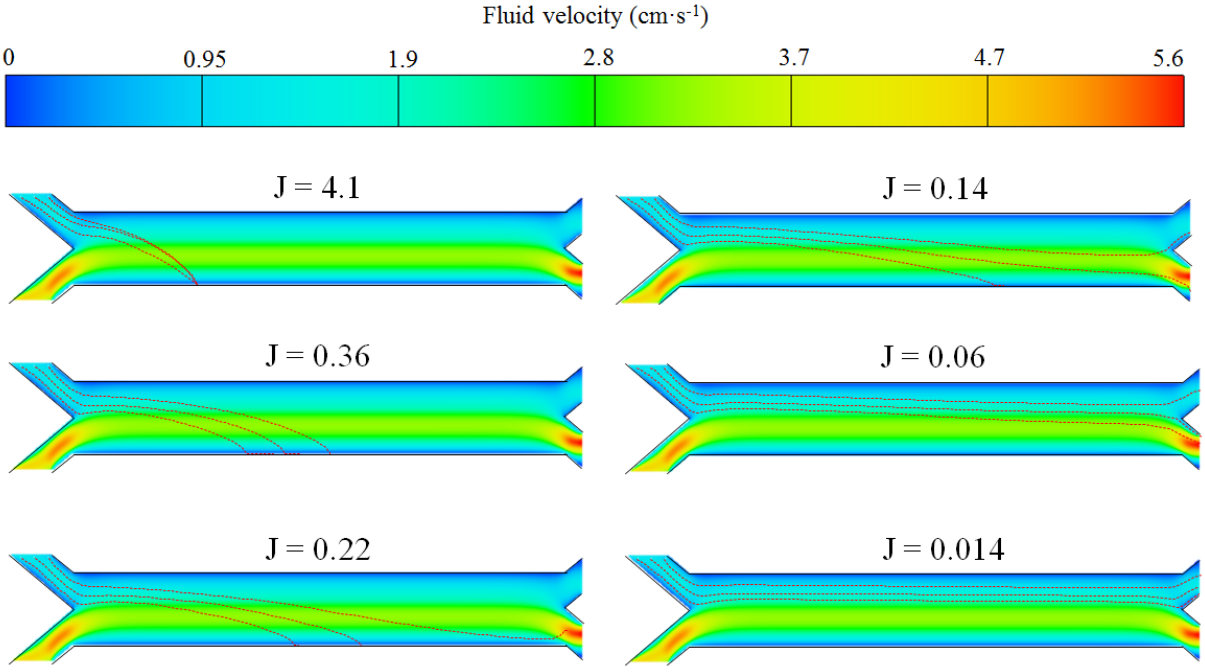

Figure 2. Particle trajectories (red lines) under different magnetic conditions (J values). The contour plot represents the initial fluid velocity value.

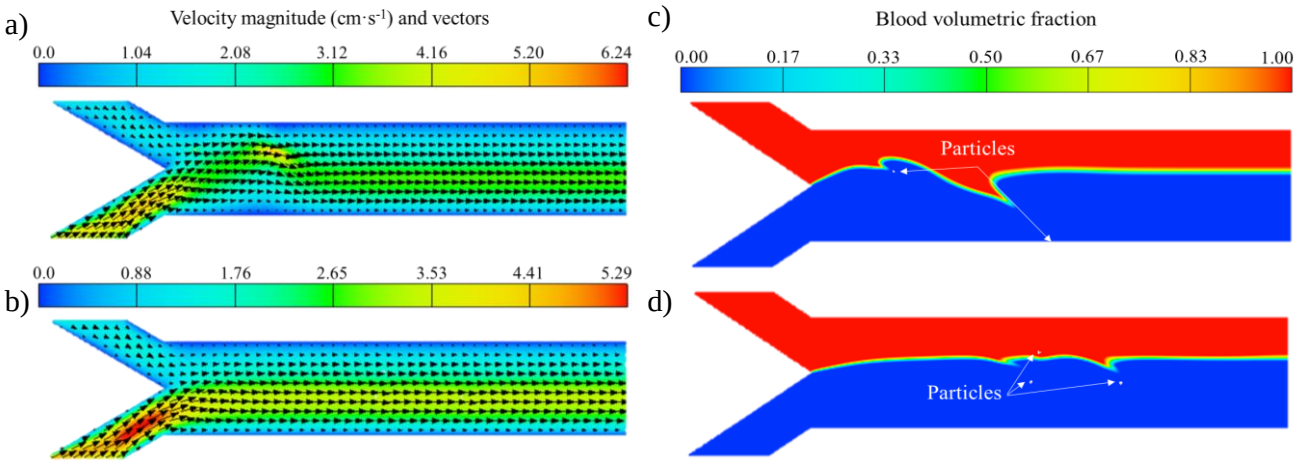

Figure 3. Velocity vectors at the time when the particles are crossing the interface between phases for a) J=4.1 and b) J=0.36; Blood volumetric fraction at that time for c) J=4.1 and d) J=0.36.

4 CONCLUSIONS

We have introduced a novel computational model for predicting and optimizing the process of magnetic bead separation from blood in a multiphase continuous-flow microdevice. This model takes into account the dominant forces acting on the particles and can be used to study critical details of the separation process, including the trajectories of individual particles, the time required for the separation and the perturbation of the blood/buffer co-flows (i.e. instability of the blood/buffer interface). Our results demonstrated that medium magnetic forces compared to the average drag force appear to be ideal for this kind of processes, because the complete bead separation can be achieved while maintaining the biofluid integrity and interface stability. The experimental validation of the theoretical model will be the focus of our future work.

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