Biochemical Engineering Journal 51 (2010) 110–116

Contents lists available at ScienceDirect

Biochemical Engineering Journal

journal homepage: www.elsevier.com/locate/bej

Three-dimensional CFD modelling of a continuous immunomagnetophoretic cell capture in BioMEMs

Swati Mohanty[a,*], Tobias Baier[b], Friedhelm Schönfeld[c]

[a] Institute of Minerals & Materials Technology (C.S.I.R.), Bhubaneswar 751013, India
[b] Technische Universität Darmstadt, Center of Smart Interfaces, Nanofluidics and Microfluidics, Petersenstr. 32, 64287 Darmstadt, Germany
[c] Fachhochschule Wiesbaden, Am Brückweg 26, 65428 Rüsselsheim, Germany

ARTICLE INFO

Article history:
Received 3 January 2010
Received in revised form 24 May 2010
Accepted 6 June 2010

Keywords:
BioMEMs
Cell capture
CFD
Magnetophoresis
Magnetic beads
Continuous sorting

ABSTRACT

Separation of rare cells from blood stream using paramagnetic/superparamagnetic beads in microfluidic device has gained importance in recent years for early diagnosis of several critical diseases. However, the performance of immunomagnetophoretic cell sorters (ICS) crucially depends on their design and operational conditions. Here, we present a three-dimensional CFD model based on the Navier–Stokes equations governing the fluid dynamics and continuum descriptions for the cell, bead and cell–bead complexes for a continuous ICS. The spatial-temporal evolution of the concentration fields are governed by convection–diffusion equations for non-magnetic cells and Nernst–Planck type equations for beads and cell–bead(s) complexes. The attachment rates between cells, cell–bead(s) complexes and beads are deduced from the collision probabilities which are derived by means of classical scattering theory. The CFD model is used to investigate the performance of a generic continuous cell separation system. Since the cells are larger in diameter, more than one bead can get attached to the cells. Multiple beads binding to the cell has been considered in this study, which has not been reported in literature till date. Exemplarily, we investigate the performance of Y-shaped geometry used for contacting of cells and beads.

1. Introduction

Immunomagnetic separation of rare cells has gained importance in bio-medical applications, primarily for early diagnosis of various types of serious diseases, for isolation of cells for genetic and immunological studies as well as for regenerative medicine. The process involves mixing nano or micro-sized ferromagnetic, paramagnetic or superparamagnetic beads coated with antibodies having affinity for a specific type of antigens on the surface of the cell, with a fluid sample containing the cells. Finally a magnetic field is applied to separate the beads and cell–bead(s) complexes. As the volume of sample to be handled is typically very small, designing and fabrication of such microdevices is difficult and continuous efforts are being made to improve upon these to make them suitable for use in lab-on-chip. A number of state-of-art reviews have been published [1–3], which discuss the application of magnetic force for manipulation of cells and magnetic beads in a microfluidic device. Several designs of micro immunomagnetic cell sorters (ICS) have been reported and research is on to improve upon these for use in a continuous process. Continuous process has distinct advantage over the batch process as it can be integrated into a lab-on-chip system more easily, has high throughput and can be better controlled.

Inokuchi et al. [4] propose a design for an on-chip separation of stem cells from peripheral blood. The mixing is first carried out in a laminated chaotic micro-mixer where the magnetic beads get attached to the target cells and then the cell–bead mixture and a buffer fluid are fed into a separator through 2 different inlets. The target cells captured by the magnetic beads migrate to the top buffer layer due to the applied magnetic field generated by the magnetic coil. Choi et al. [5] propose a glass microchip with micro-channels and semi-encapsulated spiral electromagnet for efficient separation of target cells. Pekas et al. [6] designed a hybrid micromagnetic–microfluidic structure that exerts both repulsive and attractive forces at microscale for better diversion of the target particles. Xia et al. [7] have designed a micro device in which a high gradient magnetic field concentrator is integrated into the microfluidic channel. Target particles are efficiently pulled from one fluid lamella to the other, flowing parallel to each other. The targeted particles are continuously drawn out as a separate stream preventing accumulation in the micro device and allowing continuous operation. A continuous cell sorter designed by Inglis et al. [8] consists of a magnetic strip integrated to the micro-channel so that the captured cells flow in the direction of the magnetic strip rather than the direction of the main fluid flow. Rong et al. [9] have designed micromachined magnetic tips for microfluidic device for separation of biological cells using magnetic beads.

* Corresponding author. Tel.: +91 674 2581635x235; fax: +91 674 2581637.
E-mail address: swati.mohanty@gmail.com (S. Mohanty).

1369-703X/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.bej.2010.06.002

Mathematical modelling helps in optimal design of any device without much experimentation, thus saving time, raw material and allowing simulating at conditions which may be quite dangerous to carry out experimentally. Several mathematical models for microseparators have been reported in literature. In general, all the models assume that there is no interaction between the particles and no body force on the fluid. Pekas et al. [6] have used the equation of motion, taking into consideration the magnetic and viscous drag forces, to predict the particle trajectory in a hybrid repulsion–attraction microseparator. Smistrup et al. [10] have simulated a microfluidic channel with planar spiral micro-electromagnets to predict the flow profile of the fluid using Navier–Stokes equation without the inertial terms and the particle trajectory using the Newton's equation of motion taking into consideration the viscous drag force and the force due to gravity. Kinetic modelling of interaction between cells and magnetic beads has been reported by Deponte et al. [11] with the assumption that only one bead gets attached to each cell. Kim et al. [12] have experimentally studied a continuous separation of T lymphocytes from biological suspensions and computed the binding probabilities. A sample stream containing target cells and a buffer stream containing magnetic beads flow side by side in a single channel. A first magnet pulls the magnetic beads into the sample stream and a second magnet further downstream pulls the beads–cell complexes back into the buffer stream such that the target cells are separated from the original sample stream. Mikkelsen and Bruus [13] have studied the motion of paramagnetic beads in a microfluidic device in the presence of a magnetic field using continuum approximation. Furlani et al. [14] have developed a model for a batch bioseparator similar to the design suggested by Choi et al. [5] to track the particle trajectory in the presence of a magnetic field. We [15] have developed a two-dimensional model for immunomagnetic cell capture in a flow-through microfluidic device, considering more than one bead binding to a cell. The two-way coupling between the magnetic beads and the fluid as well as the magnetic interaction has been studied by Mikkelsen et al. [16], considering two beads for flow through a microfluidic device. The magnetic interaction was insignificant compared to hydrodynamic interaction. Zolgharni et al. [17] have developed a two-dimensional steady state model to study the extent of mixing as well as the particle–particle collision that could predict the probability of a cell being tagged. Modak et al. [18] have developed an Eulerian–Lagrangian model for a straight and T-shaped microfluidic channel with line dipole for separation of biological cells. The model takes into consideration two-way coupling of the fluid–particle momentum interaction. They have reported that for large loadings of the particles the interaction was significant.

However, there is a lack of a suitable three-dimensional model for predicting the cell capture and the flow of different species in continuous micromagnetic sorters, particularly when possibly more than one bead gets attached to each cell. Necessity was felt to extend the model to three-dimension so as to study the distribution of the cell, bead and cell–bead complexes in the z-direction. In this paper we present a three-dimensional hydrodynamic and magnetophoretic model which explicitly accounts for binding kinetics for the formation of cell–bead(s) complexes and which can easily be integrated into a computational fluid dynamics (CFD) code. We apply the model for a specific application of continuous magnetic cell sorting considering a generic microfluidic geometry used for continuous cell sorting. The model allows predicting the concentration profiles of the unbound cells, beads and cell–bead(s) complexes. In this way, the model facilitates to design a device that can efficiently separate the target cells from complex mixtures. Moreover, the simulation methods could be used to deduce details of the binding kinetics from experimental data.

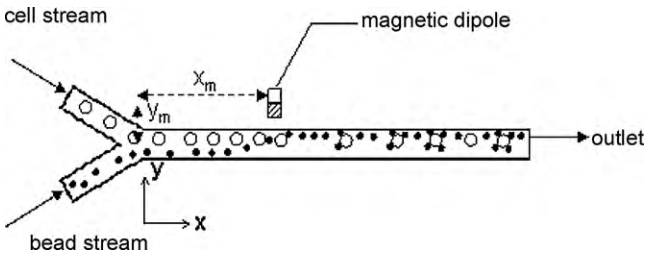

Fig. 1. Schematic diagram of the modeled microfluidic device for cell capture.

2. Materials and methods

In the present study we investigate immunomagnetic tagging of cells in a Y-channel which is probably one of the most often used microfluidic geometries. The Y-shaped micro-channel under study has a length of 1.12 cm, width (end-to-end of the arms) of 0.16 cm and a depth of 0.01 cm. Two streams containing beads and the target cells are fed into the reaction channel from 2 separate inlets as shown in Fig. 1. An external magnet, which is placed at a distance from the channel pulls the magnetic beads into the sample stream where cells and beads collide and immunological tagging of the target cells takes place. Due to the antibody–antigen reaction, the beads get attached to the cells. As the cells are typically much larger than the beads, more than one bead can bind to a single cell. However, the bead can bind to the cell only if it comes in contact with the free surface of the cell. The collisions can either be due to directional movement caused by external force fields like gravitational or magnetic fields or the collisions can occur through non-directional movement, viz. diffusion. More details about cell–bead binding are given in our earlier paper [15].

3. Mathematical model

A three-dimensional model was developed based on the following assumptions: the cells and the beads have been treated as continuum. The flow of both streams is laminar. The collision between a bead and a cell results in binding of the bead to the cell with a certain probability, which is assumed to be constant. The sedimentation of the cells and the beads is negligible. The external magnetic field is created by a magnetic dipole. The fluid is a Newtonian fluid and the properties are same as that of water. The fluid flow is not affected by the motion of the beads, cell-bead(s) complexes or cells, but the fluid has an influence on the motion of the cells, beads and cell–bead(s) complex, i.e., a one-way coupling has been considered. Note, basically all the assumptions are made in order to focus on the essential aspects of simulating immunomagnetic cell capture. The developed model can straightforwardly be expanded to account for more complex binding kinetics, sedimentation, arbitrary magnetic fields and two-way coupling between particle and fluid motion.

Because of the small time constant associated with movement of micro particles in water, acceleration phases can safely be neglected [19]. Thus, it is assumed that the cells have the same velocity as the fluids and beads as well as cell–bead(s) complex have a velocity equal to that of fluid plus an additional velocity contribution due to the magnetic force. The Navier–Stokes equations for incompressible fluid is used to model the fluid phase neglecting the body force. The unsteady state continuum model for the fluid phase can therefore be written as:

$$\frac{\partial \vec{u}}{\partial t} = -(\vec{u}\cdot\nabla)\vec{u} - \frac{1}{\rho}\nabla P + \upsilon\nabla^2\vec{u}. \quad (1)$$