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Numerical optimization and inverse study of a microfluidic device for blood plasma separation

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ABSTRACT

In this paper, a passive microfluidic device for continuous real time blood plasma separation has been studied and optimized. A numerical model is used to solve both the fluid flow and the particles confined within it. Red blood cells are considered as particles with diameter of 7 µm. A parametric study is performed in order to characterize the effect of different parameters on separation and purity efficiency. In this study, four different variables were introduced to design the microfluidic device for blood plasma separation including: the angle between the daughter channels and the main channel, the widths, the diffuse angle and the number of daughter channels. Results show that the separation and purity efficiency have an opposite trend. Since finding the optimal design, where both separation and purity efficiency are desirable, was the goal of this research, an optimization is performed by means of Pattern Search algorithm including all the variables. By means of optimization, it is shown that the performance of device can be improved considerably. Optimal design with separation efficiency of 83% and purity efficiency of 85% is achieved. Moreover, an inverse study has been done to calculate the design variables based on the desired separation and purity efficiency. According to related research, separation and purity efficiency were set to (40%, 53%) and (25%, 100%). Design variables were obtained with less than 1% and 4% error, respectively.

1. Introduction

Blood is the main biological fluid that is composed of cells and a free cell medium called plasma. Approximately 45 volumetric percent of blood includes the cells and the remaining 55% includes plasma. Blood plasma is the medium that carries the cells through vessels. It is an aqueous solution and a rich source of proteins that can be used as biomarkers for various types of clinical assays and laboratory research [1]. Conventional methods used in laboratories for plasma separation are filtration and centrifugal techniques. The main drawback of these conventional methods is that they are usually labor intensive which prevents them to be used in point of care diagnostic systems. In contrast, microfluidic devices have some advantages like portability, low volume consumption, point of care usages and lower prices. Based on the mentioned advantages, the increasing interest in microfluidic devices for biological applications is justified [2].

Active and passive methods are used for blood plasma separation within microfluidic devices. Active methods are those that utilize an external force field in order to separate the cells from plasma. External force fields used in active methods are typically categorized into acoustic and electric forces [1,3]. In standing wave, particles suspended in a medium experience a radiation force that pushes them towards special regions of the microchannel [4]. Particles migrate towards distinct regions of the microchannels depending on their different density and compressibility properties [5]. Nilsson et al. [6] used this method for separating plasma from non-diluted blood with throughput of 600 µl min^{-1} and with purity close to 99%. Doria et al. [7] presented a novel acoustic plasma separation that utilizes air–liquid cavity acoustic transducers (ALCATs). They have reported a throughput of 0.63 µl min^{-1} of whole undiluted blood with purity efficiency more than 90% and separation efficiency of 40%. Another active separation method is utilizing the dielectrophoresis phenomenon as the separator mechanism. Dielectrophoresis force is applied to dielectric particles suspended in a medium when exposed to a non-uniform electric field. Strength and direction of this force depend on the difference between electrical properties of the medium and the suspended particles, frequency of the electric field, and the size and shape of particles [8,9]. Nakashima et al. [10] utilized both capillary effect and dielectrophoresis in order to trap red blood cells. They have reported separation of plasma from 5 µl, 1:9 diluted blood

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samples with purity efficiency of 98% but with a low separation efficiency of 6%.

Deterministic lateral displacement (DLD), inertial and viscous hydrodynamic lift forces are the most promising mechanisms used in passive devices. DLD method consists of a microchannel with obstacles embedded in the way of the fluid flow that are shifted laterally compared to the corresponding obstacle. Particles bigger than a size threshold collide to these obstacles and migrate laterally while the smaller ones are confined to the flow streamlines. This novel idea was first introduced and tested by Huang et al. [11]. Davis et al. [12] used this method for separating blood cells from the whole non-diluted blood, thus leaving cell free plasma with purity near to 100% and volumetric rate up to 1 μl min^{-1}. Despite its advantage of being selective, this method has some drawbacks including high cast fabrication, the possibility of clogging and having low throughput [13].

Hydrodynamic inertial lift force is a phenomenon in which the particles migrate laterally in laminar confined flows. This phenomenon was first observed by Segré and Silberberg in 1960s, and not surprisingly known as Segré–Silberberg effect [14]. In laminar flows, when the Reynolds number is more than unity, tiny particles tend to migrate laterally to an equilibrium position [13,15]. Papautsky et al. and Di Carlo et al. were among the first research groups to utilize curvilinear microchannels and inertial lift forces for the separation purposes. However, these inertial devices are mostly focused on cell separation from the whole blood [16,17].

The separation mechanism used in this study implements the hydrodynamic viscous lift forces and the bifurcation law. Hydrodynamic viscous lateral lift force is best described as a tendency of deformable red blood cells to migrate to the center of capillary vessels, thus leaving a cell free layer of plasma near to the microchannel wall. This phenomenon happens at Reynolds numbers of unity order where the viscous forces are dominant to inertial forces [1]. This phenomenon is known as Fåhræus effect or plasma skimming effect [18]. The other separation mechanism used in this study is the bifurcation law also known as Zweifach–Fung effect. Doyeux et al. [19] have done an exhaustive numerical and experimental research to elucidate the Zweifach–Fung effect. According to their research, the particles' tracks can be easily investigated near the bifurcation regions using particle trajectories, which are dependent to the repartitioning of the particles at the inlet. Moreover, they have shown that the enrichment of the particles in the main channel is not due to a specific attraction of particles towards the rate channel with high flow rate, but it is due to the cell free layer near the wall, where the plasma is extracted. Yang et al. [20] utilized plasma skimming and Zweifach–Fung effect to extract plasma from (1:10) diluted sheep blood and they reported 25% plasma yield with purity near to 100%. Sollier et al. [21] used the novel idea of geometric singularity in their design and showed a clear plasma formation region. They could separate plasma from 1:20 diluted blood with higher throughout of 100 μl min^{-1} but with lower separation efficiency of 17.8%.

In this study a numerical model is utilized to simulate diluted blood flow (1:100) in the plasma separation microfluidic device, also red blood cells have been modeled and tracked within the fluid flow. The majority of research in this field is done with experimental approaches that due to limits in fabrication cannot fully optimize the device [20–23]. For instance, Fekete et al. [22] experimentally investigated the effect of daughter channels with different bifurcation angles on separation and purity efficiency of the extracted plasma. They designed and fabricated a series of silicon-glass based microfluidic chips with bifurcation angles of (30, 45, 60 and 90°). In another research, Shamsi et al. [23] designed and fabricated a microfluidic chip by hot embossing of microchannels on a PMMA substrate and thermal bonding process. They investigated the effect of diffuser shaped daughter channels on separation and purity efficiency of the extracted plasma.

According to the shortcomings of the experimental studies, valid numerical approaches can help us design more efficient microfluidics. Numerical approaches reduce the number of necessary experiments and facilitate the experimental investigations. By means of CFD simulations, effects of four parameters including: the angle between the daughter channels and the main channel, the widths, the diffuse angle and the number of daughter channels have been investigated on separation and purity efficiency of the device. The main goal of this research is to utilize the numerical model in order to optimize the microfluidic device. Using the CFD simulations and Pattern Search optimization algorithm, the device has been optimized considering all the parameters mentioned before. The optimization procedure helps us increase the performance of the microfluidic device in terms of separation and purity efficiency, while it does not lead to more complex geometries. Moreover, in some cases specific separation and purity of extracted plasma is needed. For this purpose, a series of inverse studies were carried out which obtain design variables from desired separation and purity efficiency.

2. Governing equations and numerical method

2.1. CFD simulation and governing equations

In the presented study, a finite volume method was applied to solve the governing equations using a CFD package fluent (version 6.3).

It is assumed that the fluid is Newtonian, incompressible, with constant properties, and the flow is steady. The detailed flow field can be determined by solving the Navier–Stokes equations. Following those assumptions, the governing equations of continuity and momentum can be written as:

$$\nabla \cdot V = 0 \tag{1}$$

$$\rho \left(V \cdot \nabla\right) V = -\nabla P + \mu \nabla^2 V \tag{2}$$

where V is the velocity vector, ρ is the fluid density, μ is dynamic viscosity and P is the pressure.

Firstly, Navier–Stokes equations were solved using a second order upwind scheme along with the SIMPLE algorithm for pressure–velocity coupling [24].

Afterwards, previously solved fluid flow was used to obtain the particle trajectories. A Lagrangian approach, Discrete Phase Model, was implemented to track the particles.

Particle trajectories can be calculated by integrating the force balance acting on the particles which can be written as

$$\frac{d\vec{u}_i^p}{dt} = F_D \left(\vec{u}_i - \vec{u}_i^p\right) + \vec{F}_i \tag{3}$$

where, u_i^p is the particles velocity, F_i is the additional acceleration, and $F_D(u_i - u_i^p)$ is the drag force per unit mass. F_D is calculated by

$$F_D = \frac{18\mu}{\rho_p d_p^2} \frac{C_D Re}{24} \tag{4}$$

where, d_p is the particle diameter, ρ_p is the particle density and Re is the relative Reynolds number which is given by below equation:

$$Re = \frac{\rho d_p \left|\vec{u}_i - \vec{u}_i^p\right|}{\mu} \tag{5}$$

and C_D is the drag coefficient which is defined by below equation.

$$C_D = \frac{K_1}{Re} + \frac{K_2}{Re^2} + K_3. \tag{6}$$

In the above equation $K_1,\ K_2,\ K_3$ are empirical constants given by Morsi and Alexander [25].