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Magnetic separation of particles and cells in ferrofluid flow through a straight microchannel using two offset magnets

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ABSTRACT

The separation of particles and cells is critical in many chemical and biological applications. This work presents a simple idea for utilizing a pair of permanent magnets to continuously separate diamagnetic particles and cells in ferrofluid flow through a straight microchannel. The first magnet is placed close to the microchannel for focusing the particle mixture to a single stream without the use of a sheath flow. The second magnet, which is offset from the first magnet and placed farther from the channel, is to displace the aligned particles to dissimilar flow paths for a continuous sorting. This idea is first demonstrated through the separation of 3 μm- and 10 μm-diameter polystyrene particles, where the effects of flow speed and magnet distance are both examined. The experimental data are found to fit well with the predictions of an analytical model. Furthermore, a continuous separation of live yeast cells from 10 μm polystyrene particles is implemented in the same device.

1. Introduction

Separating particles and cells is often necessary in a variety of chemical and biological applications. Starting from a sample mixture, particles of distinguishable properties (e.g., size, density, charge and shape) may be continuously separated and sorted by means of an externally provided or internally induced force field. Among these are electric [1,2], magnetic [3,4], acoustic [5,6], optical [7,8], and hydrodynamic [9,10] methods, all of which have been and will continue being the research foci in microfluidic devices for diverse lab-on-a-chip applications [11–15]. However, many of these continuous methods catered towards particle separation have a burdened secondary effect of requiring expensive equipment and/or complicated device fabrication etc. In contrast, with utilizing permanent magnets that naturally produce their own magnetic field, magnetic separation techniques exhibit a number of advantageous features such as low cost (cheap magnets off-the-shelf) and unwanted fluid heating issues [16–20].

Magnetic field-induced particle and cell separation has been implemented in primarily two modes [21,22]. The first mode works primarily for the separation of magnetic particles (or magnetically tagged bioparticles) from diamagnetic (or non-magnetic as often called) particles, where the former are first retained by a magnet and later released by removing the magnetic field after diamagnetic particles have all flown through the retention chamber [23,24]. One such example is magnetic-activated cell sorting (MACS) [25], which obviously takes place in a batch process. Other notable batchwise magnetic separations were reported by Yellen et al. [26] and Kose et al. [27] through the use of travelling-wave magnetic field. In the former study, superparamagnetic particles can be size-selectively locked onto patterned micro-magnets by varying the driving frequency of an external rotating magnetic field [26]. A similar idea was later employed by Kose et al. [27] to selectively trap and sort diamagnetic particles and cells in ferrofluid based on size, shape and elasticity using on-chip current carrying electrodes-generated travelling-wave magnetic field gradients.

In the second mode of magnetic separations, the particle mixture suspension is confined by a co-flowing buffer solution, upon which a transverse magnetic force deflects particles to distinct flow paths in the buffer solution. Such a continuous-flow method has been demonstrated to separate magnetic (or tagged) particles from diamagnetic particles by using either an external magnet (permanent or electric current-induced) itself [28–30] or external-magnet excited microfabricated soft magnets [31–33]. It can also work for the continuous separation of magnetic particles by size and/or magnetization, which, termed free-flow magnetophoresis [34], has been demonstrated by Pamme and her colleagues [35,36] and later applied to separate magnetically-labeled cells [37,38]. Moreover, the same approach has recently been applied to separate diamagnetic particles in magnetic solutions including paramagnetic solutions by Pamme's group [39,40] and ferrofluids by Mao's group [41,42]. The main drawback of this continuous magnetic separation technique lies in the use of a sheath

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fluid, which complicates the flow control and meanwhile dilutes the sorted particles.

To date, there has been little work reported on continuous-flow sheath-free magnetic separation of particles. Our group has recently demonstrated the use of a U-shaped microchannel to sort particles with a single permanent magnet [43]. This approach exploits the induced negative or positive magnetophoretic deflection to focus diamagnetic or magnetic particles to a single stream in the first branch of the U-channel without a sheath flow and then separate them continuously in the second branch. In this work, we present another simple method for diamagnetic particle and cell separation in ferrofluid flow through a straight microchannel. The use of two offset magnets enables particle focusing and separation in a single fluid flow while providing the flexibility to vary the magnet position for accommodating particles of various sizes. This technique is demonstrated through the sorting of polystyrene particles and yeast cells. An analytical model is also developed to simulate the magnetic control of particle transport and separation in ferrofluid microflows.

2. Experiment

The standard soft lithography method was used to fabricate the straight microchannel with polydimethylsiloxane (PDMS). Detailed procedures for channel fabrication can be referred to Zeng et al. [44]. The rectangular cross-sectioned microchannel has a length of 2.5 cm, width of 200 μm, and depth of 25 μm. There are four rectangular blocks designed at each of the two reservoir-microchannel junctions, which serve to filter out particle aggregates and PDMS debris at the inlet and provide distinct flow passages for sorted particles and cells at the outlet. Two equal and opposing Neodymium–Iron–Boron (NdFeB) permanent magnets (B221, 1/8 in. × 1/8 in. × 1/16 in., K&J Magnetics Inc.) were imbedded in the PDMS slab with their magnetization directions perpendicular towards the microchannel. As shown in Fig. 1, the device has its first magnet placed 500 μm (edge to edge) away from the microchannel. The second magnet, which is 1 mm offset from the first one along the flow direction, stays further away from the microchannel with a distance being variable in experiments.

A commercially available water-based ferrofluid, EMG 408 (Ferrotec Corp.), was diluted with deionized water (Fisher Scientific) to 0.05 × its original concentration (1.2% magnetic nanoparticles in volume). To show evidence of size-based separation, 3 μm and 10 μm-diameter diamagnetic polystyrene particles (Thermo Fisher Scientific) were re-suspended in the diluted ferrofluid at a concentration of 5×10^6 and 4×10^5 particles/ml, respectively. Live yeast cells (*Saccharomyces cerevisiae*) were cultured overnight in Sabouraud's dextrose broth in a shaker incubator at 30 °C, and were re-suspended in sterile phosphate buffered saline (PBS) solution to a concentration of 6.85×10^8 cells/ml. Prior to use, yeast cells were washed with deionized water three times and re-suspended in 0.05 × EMG 408 ferrofluid along with 10 μm particles at similar concentrations mentioned above. The measured diameter of yeast cells is 5 μm in approximation. Tween 20 (Fisher Scientific) was added to both the particle and cell suspensions at 0.1% by volume to minimize their aggregations and adhesions to microchannel walls.

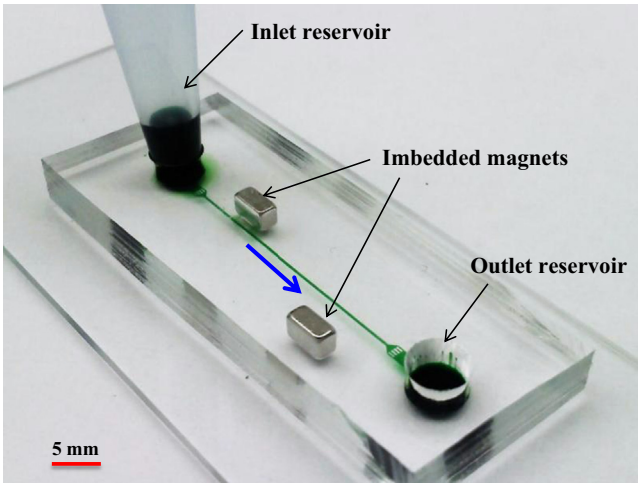

Fig. 1. Picture of the experimental microfluidic device with the straight microchannel and reservoirs filled with green food dye for clarity. The block arrow indicates the flow direction in the demonstrated diamagnetic particle and cell separation experiments. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The microchannel was rinsed thoroughly after its fabrication and prior to experiment. A standard 1-ml pipette tip was used to elevate the fluid height in the inlet reservoir in order to produce a pressure driven flow (see Fig. 1). Adjusting this fluid height provides an easy control of the flow speed. To reduce the effects of back-flow on particle/cell separation, the outlet reservoir was made large and manually kept free of fluid buildup during experiment using a pipette. As the diluted ferrofluid appears transparent in microchannels, the suspended particles and cells can be viewed without the need of fluorescent labeling. The particle and cell motion was visualized using an inverted microscope (Nikon Eclipse TE2000U, Nikon Instruments, Lewisville, TX) under a bright-field illumination. Digital videos (at a time rate of around 12 frames per second) and images were recorded through a CCD camera (Nikon DS-Qi1Mc) and post-processed using the Nikon imaging software (NIS-Elements AR 2.30).

3. Theory

3.1. Diamagnetic particle/cell separation mechanism

Diamagnetic particles and cells undergo negative magnetophoresis in a ferrofluid when subjected to a non-uniform magnetic field. This motion, $\mathbf{U}_m$, is directed towards the decreasing magnetic field and is expressed by [45,46]

$$\mathbf{U}_m = \frac{-\mu_0\phi a^2}{9\eta f_D}\frac{M_d L(\alpha)\nabla\mathbf{H}^2}{H} \tag{1}$$

$$L(\alpha) = \coth(\alpha) - \frac{1}{\alpha} \quad \text{and} \quad \alpha = \frac{\pi\mu_0 M_d H d^3}{6k_B T} \tag{2}$$

where μ_0 is the permeability of free space, ϕ is the volume fraction of magnetic nanoparticles in the ferrofluid with M_d being their saturation moment, a is the radius of diamagnetic particles or cells, η is the ferrofluid viscosity, f_D is the drag coefficient accounting for the wall retardation effects [47–49], $L(\alpha)$ represents Langevin function [50], $\mathbf{H}$ is the magnetic field with a magnitude of H, d is the average diameter of magnetic nanoparticles, k_B is the Boltzmann constant, and T is the ferrofluid temperature. Note that while the ferrofluid is diluted in the current work, its magnetization is still much larger than that of the diamagnetic particles and cells under uses. Therefore, the contribution of the latter to the magnetophoretic particle velocity, $\mathbf{U}_m$ in Eq. (1), has been neglected [45–49]. The dependence of $\mathbf{U}_m$ on the particle radius squared enables the separation of diamagnetic particles and cells by size.

Fig. 2 shows schematically the separation mechanism of diamagnetic particles and cells in ferrofluid flow through a straight microchannel. As seen from the magnetic field contour (represented by the background color, the darker the larger), the two offset magnets (see a picture of the device in Fig. 1) each creates its own magnetic field gradients within the ferrofluid. However, as the first magnet is placed closer to the microchannel, the induced magnetophoretic velocity, $\mathbf{U}_m$, (see the arrows in Fig. 2), is larger than that in the second magnet region. Thus, at an appropriate