INERTIAL MICROFLUIDICS: HIGH-THROUGHPUT FOCUSING AND SEPARATION OF CELLS AND PARTICLES

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ABSTRACT

Here we describe a continuous particle focusing and separation system taking advantage of microscale physics but with throughput comparable to macroscale systems. The device simply consists of a single asymmetrically curved channel with tuned dimensions and flow conditions. Unlike mechanical filters, deformable and rigid particles are shown to focus and separate with equal efficiency. Additionally, unlike centrifugation the physical mechanism appears independent of particle buoyancy, decoupling separations based on size from density. The described system, able to process large volumes (~ 1 mL/min, 1% w/v particles) in a small footprint (2.5 cm^2) is expected to be useful for a range of applications in which particles of mixed densities must be separated by size, particles are deformable or rigid, and/or large samples must be processed quickly, such as clinical blood cell sorting.

KEYWORDS: cell separation, inertial migration, filtration, cell focusing

INTRODUCTION

Microfluidic devices for continuous separation of particulates and cells have recently received attention in the community for uses largely in biomedical diagnostic systems [1]. The majority of these techniques, however, have not been implemented in commercial products, presumably because of complexity or low sample throughput. Addressing these issues, the main advantages of inertial focusing are the rapid continuous processing of samples (orders of magnitude more than most microfluidic systems) and the absence of small filters, mechanical, or electrical parts, making it ideal for reduced-complexity integrated systems that can be easily injection molded.

THEORY

Cell focusing and separation is dependent on two hydrodynamic forces intrinsic to the flow that increase with increasing fluid velocity. The interaction of inertial lift and Dean drag forces to create focused streams of particles in straight and curved channels has been described very recently by us [2-3]. The superposition of these forces allows the creation of equilibrium positions for particles in the flowing stream with locations that are size dependent. The ratio of lift to Dean drag, which can be shown to scale as ($R_f \sim ra^3/h^4$) should remain ~ 1 for successful focusing. Where the average radius of curvature of the channel, r, the channel dimension, h, and the particle diameter, a, are important factors.

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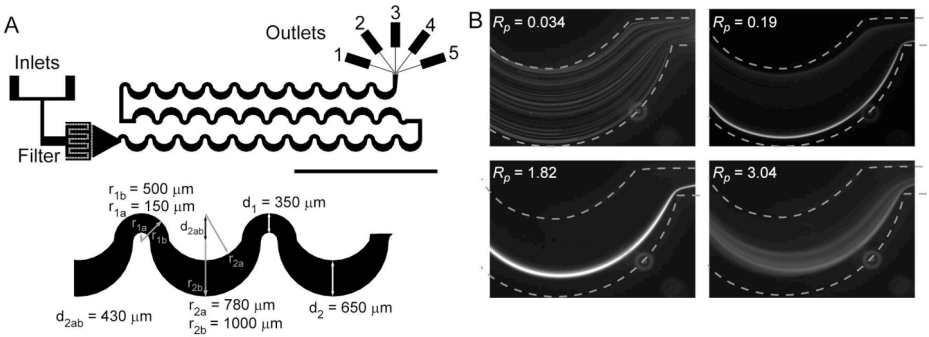

Figure 1: Device design and flow. (A) The device consists of inlets, a coarse filter, 62 asymmetric separation turns, and 5 outlets to collect the filtrate (scale bar is 1 cm. (B) Streak images of 10 μm beads are shown for four increasing particle Reynolds numbers (R_p) or flow rates. At the lowest flow rate no focusing of polystyrene beads is observed. As flow rates are increased focusing into two then a single stream is observed. At R_p = 3.04, the stream is seen to be defocused again. Dotted lines outline the channel walls.

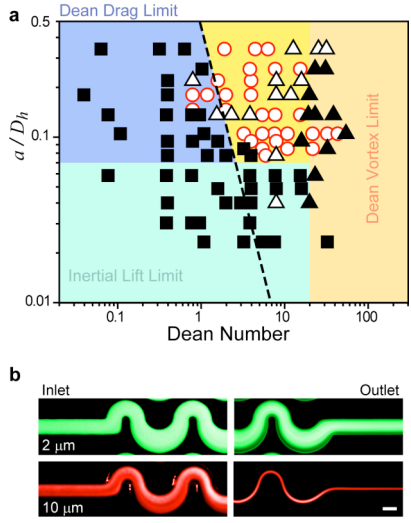

Figure 2: Size dependence of particle focusing. (A) No focusing or focusing to four streams - filled squares, focusing to two - open triangles, focusing to a single stream - open circles, complex behavior - filled triangles. The dotted line is constant F_D of 0.5 nN. (B) Differential focusing of 10 and 2 μm mixed particles (scale 50 μm).

EXPERIMENTAL

Devices were fabricated using standard soft lithography techniques. Experiments to determine the distribution of particle positions within the channels were performed using time-lapse fluorescence microscopy and high-speed microscopy. Solutions were injected by syringe pump. Separation experiments were conducted with EDTA treated whole blood diluted to 1-2% w/v or fractions of polystyrene particles 0.5%-2%.

RESULTS AND DISCUSSION

Here we demonstrate continuous focusing of particles and cells in the system (Fig. 1), tunable separation of particles based on size (Fig. 2, with a resolution approaching 1.5 μm for 10 μm particles), and 100X enrichment of platelets from red and white blood cells in diluted whole blood at bulk throughputs of 1 mL/min (Fig. 3). Additionally, we measured < 80 nm accuracy in focusing position, allowing particle positioning comparable to hydrodynamic focusing using solely a single inlet channel. This feature also yields easily implemented parallelization.

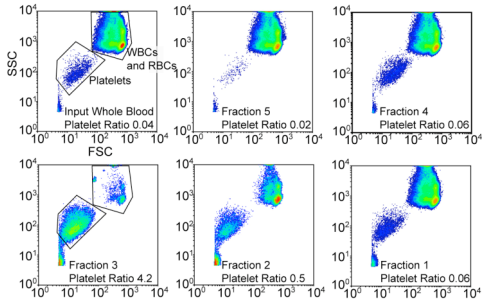

Figure 3: Separation of platelets from blood. Flow cytometry data for initial blood and various fractions collected from the system are shown. Plots show side scatter and forward scatter which allow discrimination between smaller platelets (2-4 μm) and larger RBCs and WBCs. The initial fraction of platelets to cells in blood was 0.04. Fraction 3 had the highest ratio of depletion of cellular components, increasing the fraction of platelets 100 fold. Fraction 5 contained a depleted level of platelets. Fractions correspond to outlets in Figure 1.

Recently, we have also shown that inertial focusing and separation scales up to the 100 μm scale, and down to 2 μm, with the promise of focusing submicrometer bioparticles such as viruses in the near future.

CONCLUSIONS

The work highlights the non-intuitive results that particles and cells self-focus in a flow, and explores the many possible applications. This very fascinating behavior was not historically recognized, most likely because of the notion that microfluidic systems do not operate at intermediate Reynolds numbers (Re ~ 100). This should be of immediate interest to the community because of the ease of implementation with existing microfluidic components and robust operating nature.

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