A MICROCHIP FOR CONTINUOUS-FLOW MAGNETIC-ACTIVATED INCUBATION AND SEPARATION OF MICROPARTICLES

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ABSTRACT

This paper presents a novel microfluidic chip that exploits magnetic manipulation for integrated incubation and separation of microparticles in continuous flow. The chip integrates an active-mixing enhanced incubator and a magnetic fractionation-based separator. In the incubator, surface-functionalized magnetic beads capture target particles through specific binding, which is enhanced by magnetic active mixing. Subsequently in the separator, the captured target particles are separated and retrieved in the same magnetic field. In contrast to current devices that are limited by manual off-chip incubation or complicated fabrication processes, our device offers automated and continuous operation with a simple structure design.

KEYWORDS: Magnetic separation, On-chip incubation, Continuous flow

INTRODUCTION

Continuous magnetic-activated separation is an attractive scheme for sorting of microscale particles such as cells. Current continuous-flow magnetic separation devices suffer from limitations such as long off-chip incubation prior to separation and complicated on-chip magnets fabrication (e.g., [1-2]). To address these limitations, we present a novel continuous-flow microchip that integrates magnetically based active mixing/incubation and separation. The chip achieves active mixing/incubation and separation by exploiting the interplay between magnetic pulling and laminar flow that jointly manipulate magnetic beads movement. Experimental results have demonstrated excellent separation efficiency (>90%) and flexibility of the device.

DESIGN AND PRINCIPLE

The device consists of a serially connected incubator and separator placed next to a permanent magnet (Fig. 1). The incubator comprises two inlets, “sample inlet” and “bead inlet”, for the introduction of particle sample and magnetic beads, respectively. The inlets are merged and followed by a serpentine microchannel, “incubation channel”. During operation, target/non-target particle mixture and magnetic beads are introduced at respective incubator inlets. Magnetic beads, initially on the channel’s far side from the magnet, are attracted by the magnet and cross streamlines. After passing each turn, beads follow streamline emerging on the far side, but are pulled back towards magnet as they flow downstream. This repeated stream-crossing by magnetic beads allow them to actively mix with and capture target particles, which shortens incubation time. Upon exiting the incubator, the bead-bound target particles enter the separator from the separator entrance. An additional inlet, “buffer inlet”, introduces a buffer stream and merges with the separator entrance into

a wide straight channel. As the bead-bound target particles flow down the channel, they are deflected towards the magnet and washed while crossing the buffer stream, and are finally separated from the non-target particles which remain in their stream.

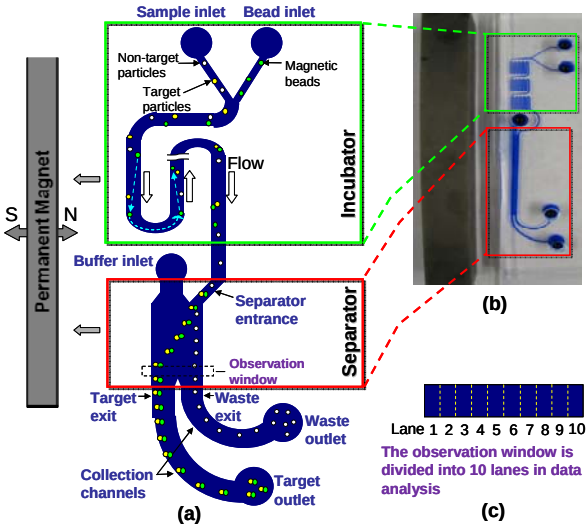

Figure 1. Integrated incubation and separation microchip. (a) Device design schematic and operating principle. (b) Image of a fabricated chip. (c) Lane division at the observation window to facilitate charaterization.

EXPERIMENTAL RESULTS AND DISCUSSION

The device was fabricated using standard soft lithography. Microfluidic experiments were carried out under a fluorescence microscope. First, to characterize the incubator for effective mixing, we introduced fluorescent solution and magnetic beads at two respective inlets. For experimental control, water was used in replace of magnetic beads. Fluorescence intensity profiles were acquired at different locations along the incubator, and compared to the control experiments (Fig. 2). In comparison, active mixing reduces the intensity gradient faster and changes the shape of intensity profiles, highlighting the effectiveness of mixing.

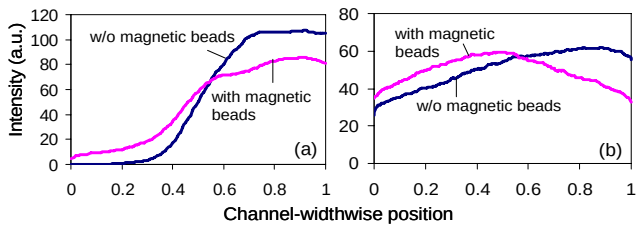

Figure 2. Fluorescent intensity distribution across the incubator channel: intensity distribution at (a) 2nd turn, (b) 30th turn.

We then examined the magnetic pulling capacity in the separator. Bare magnetic beads and water were introduced into the bead (or sample) and buffer inlets, respectively, and cross-channel bead distribution was observed at the separator exit (Fig. 3). An observation window at the separator exit was selected, where the channel width was divided into 10 lanes and the percentage of beads falling into each lane was obtained to quantify the bead distributions. Most beads (96.2%) were clustered to the left half of the channel under magnetic field, demonstrating adequate magnetic pulling. Without the magnetic field, 96.7% of the beads remained in the right half.

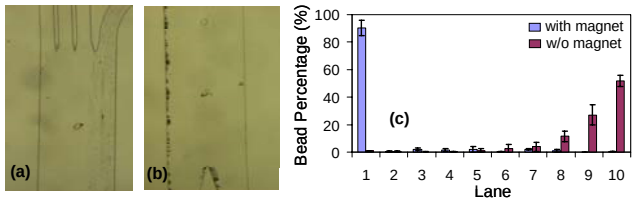

Figure 3. Separator fractionation capacity: images at (a) the inlet (b) and exit of the separator. (c) Distribution of magnetic beads at the separator exit.

Finally, the performance of the integrated device, coupling incubator and separator, was determined. Target and non-target particles (with concentration ratios 1:1 and 1:10) were introduced from one inlet of the incubation channels, and magnetic beads from the other, while water from the buffer inlet of the separation channel. Particle distribution was observed (Fig. 4). It was observed that separation efficiencies for target and non-target particles were 92.7% and 99.9% for the 1:1 case, and 91.1% and 99.3% for the 1:10 case. These results confirm the effectiveness of this device regardless of particle distribution.

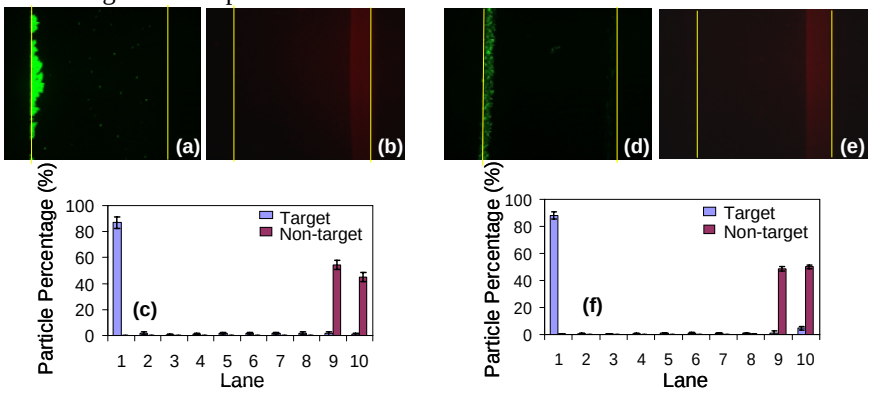

Figure 4. Distribution of target and non-target particle across the channel width at the exit of the separator. The target vs. non-target particles ratio is 1:1 in (a)-(c) and 1:10 in (d)-(f). (a) and (d) Fluorescent images of target particles. (b) and (e): Fluorescent image of non-target particles. (c) and (f): Distribution of target and non-target particles across the channel width.

CONCLUSIONS

A novel integrated microchip for specific capture and separation of target microparticles using magnetic manipulation in continuous flow has been presented. The seamless coupling of incubation and separation results in reduced incubation times and ease of process automation, which holds the potential for automated cell sorting where high separation accuracy and throughput are desired.

REFERENCES

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