ULTRASONIC MANIPULATION IN A MICROFLUIDIC CHIP FOR INDIVIDUAL HANDLING OF PARTICLES AND CELLS

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Abstract

We have developed a microfluidic platform for individual particle handling by the use of ultrasonic standing waves. Elementary manipulation functions, useful in cell-based biotechnology applications, are demonstrated. Oblique coupling of ultrasound allows for any kind of high-NA optical microscopy, which is important for individual characterization of cells.

1. Introduction

Ultrasonic standing wave (USW) manipulation is a suitable technique for high-throughput, continuous separation, concentration or alignment of particles or cells in microfluidic systems. In flow-through systems, suspended particles or cells are focused into the pressure nodes of the standing wave, typically oriented parallel with the microchannel [1]. However, USW technology is primarily considered as a "coarse" and long-range tool for simultaneous manipulation of all particles inside the chip, in comparison to "sharp", short-range tools such as laser tweezers or dielectrophoresis [2]. Here, we investigate USW-generated elementary manipulation functions (EMFs) for handling of individual or low numbers of particles or cells inside a microfluidic chip. The demonstrated EMFs may be used in different kinds of cell-based biotechnology applications, where step-by-step handling and individual characterization of the cells are important.

2. Experimental arrangements

The chip, illustrated in Fig. 1, consists of a glass-silicon-glass structure, compatible with label-free, high-resolution transmission microscopy. The ultrasound is coupled into the fluid channel by an external transducer combined with a refractive element in an oblique arrangement

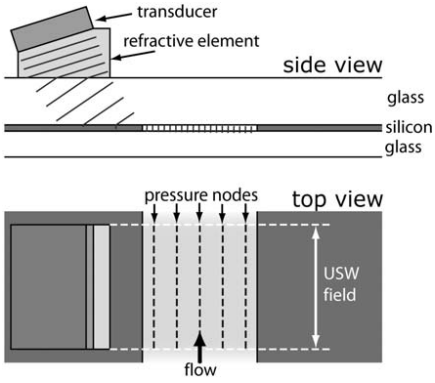

Figure 1. Schematic of chip and the USW transducer.

Figure 2. One-dimensional aggregation of 10 μm beads in four subsequent pressure nodes.

(cf. Fig 1), which allows both focusing and direction of the wave. The microchannel in the silicon layer has a cross section of 750 μm (width) × 40 μm (height). This elongated shape of the cross section is chosen for optimized microscopic view of all cells in the chip. Furthermore, since the channel height has the same scale as the cell size, the cells are rearranged into only one dimension in the pressure nodes (cf. Fig. 2).

3. Results and discussion

The most fundamental EMF is parallel alignment in multiple nodes (Fig. 3a). The number of nodes is chosen by the ultrasound frequency. The frequency may be tuned from the fundamental resonance at 2.12 MHz (equivalent to 2 nodes) to the fifth harmonic overtone at 13.4 MHz (equivalent to 13 nodes). Other EMFs are one-dimensional particle aggregation ('line-aggregation') (Fig. 2 and Fig. 3b) and fusion of line-aggregates by USW frequency shift (Fig. 3c). Line-aggregation can be used for distinction and numbering of individual particles (cf. Fig. 2) or cells (cf. Fig. 4), while fusion of line-aggregates may be used in cell-based assays. The method is also compatible with other manipulation tools, e.g., it is possible to combine the USW chip with dielectrophoretic manipulation for increased spatial precision [2].

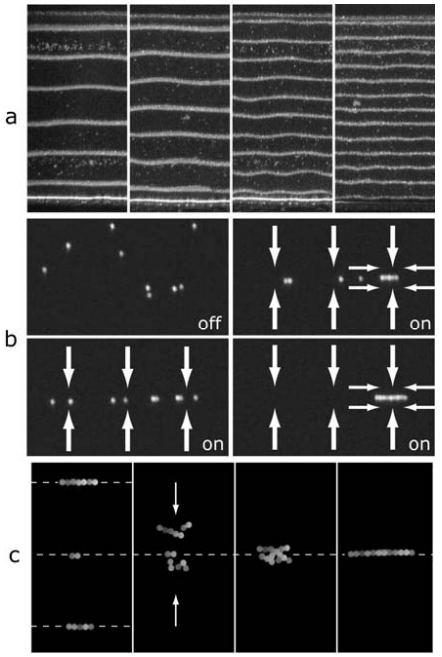

Figure 3. Parallel alignment in multiple nodes (a), one-dimensional aggregation (b), and fusion of one-dimensional aggregates (c).

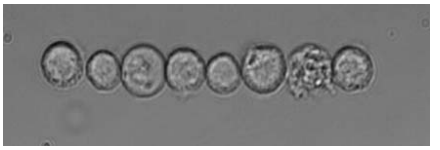

Figure 4. One-dimensional aggregation of U-937 cells.

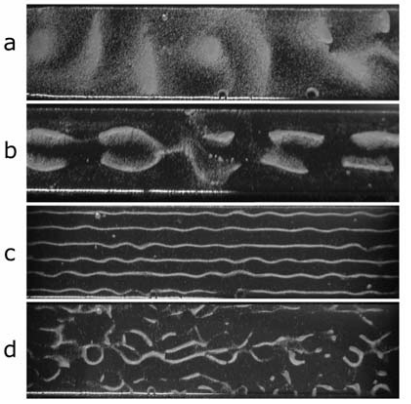

Figure 5. Complex patterns of the USW field by mode coupling and acoustic streaming at 1.48 MHz (a), 1.72 MHz (b), 6.20 MHz (c), and 6.61 MHz (d).

In miniaturized USW resonators, such as a microfluidic channel, the geometrical properties of the cavity are important for the shape of the nodes. This is illustrated in Fig. 5, where the transducer is driven at frequencies not matching the basic resonance condition (i.e., where the channel width corresponds to a multiple of half the acoustic wavelength). In such cases, complex mode coupling occurs, sometimes in combination with acoustic streaming.

4. Conclusions and outlook

The general goal of the work presented here is to design a flexible, multi-purpose and gentle cell handling system for surface-based and long-term biotechnology applications. An example of such an application is controlled cell differentiation ('cell programming') by surface-to-surface contact of a cell with a functionalized bead, or with another cell. Since the differentiation procedure is assumed to take long time (~days), USW manipulation is superior to alternative techniques from a viability point-of-view [3]. In this context, the experiment shown in Fig. 3c (fusion of one-dimensional aggregates) can be considered as a proof-of-principle experiment of a gentle cell handling device for 'cell programming'. Furthermore, our flat channel design is perfectly suitable for high-throughput and multiplexed USW cell handling, but still in the individual (one-by-one) format. This makes it possible to study not only the average properties, but to perform high-speed characterization of each single cell. In addition, our oblique USW coupling technique allows for either fluorescence-based or label-free (non-contaminating) optical characterization.

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Keywords: Ultrasonic manipulation, cell handling, cell aggregation

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