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A High Throughput Lab-On-A-Chip System for Label Free Quantification of Breast Cancer Cells under Continuous Flow

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Abstract

This paper presents an LOC system combining microfluidic DEP channel with a CMOS image sensor for label and lens free detection and real-time counting of MCF-7 cells under continuous flow. Trapped and then released MCF-7 cells are accurately detected and counted under flow with a CMOS image sensor integrated underneath the DEP channel, for the first time in the literature. CMOS image sensor can capture 391 frames per second (fps) that allows detection of the released cells flowing through the channel with a flow rate up to 130µl/min (0.468 m/s). Therefore, the proposed system is able to detect the cells under high flow where conventional techniques for cell quantification such as fluorescent tagging become unusable. Detected cells are automatically counted with a computer program and the counting accuracy of the whole system is 95%.

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Keywords: CMOS image sensor, lab-on-a-chip, dielectrophoresis, cancer cell, detection, microfluidic

1. Introduction

DEP has been intensively employed in cell manipulation by allowing separation and trapping of the cells based on

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their distinguishing electrical properties such as cytoplasmic conductivity [1]. CMOS image sensors can be used alone for cell quantification. However, several surface modifications should be applied for cell capturing, which is not easy to implement [2]. Additionally, fully integrated CMOS image sensor with a microfluidic channel is expensive and labor intensive process [3, 4]. In a previous work, in-house fabricated DEP device and CMOS imager chip are integrated without implementing any complex processes [5]. However, the integrated system is not able to individually distinguish the trapped cells, and hence has accuracy limitations in cell counting. Besides, since the imaged cells are trapped, and hence stationary, only limited number of cells could be imaged at a time, resulting in low throughput. The proposed system integrates a CMOS image sensor with a DEP device allowing automatic quantification of MCF-7 cells with a counting accuracy of 95% in a high throughput manner.

2. System Design

The proposed system includes of two separately microfabricated devices: a microfluidic DEP device and a CMOS image sensor (Fig. 1). The DEP device consists of 27 3D-electrodes, with 40µm width and 15µm gaps in between, placed on the sidewalls of 300µmx20µm parylene microchannel, and parylene posts for hydrodynamic focusing of cells to DEP traps. The CMOS image sensor has 32x32 pixel array with the pixel dimension of 15µmx15µm [2]. DEP device is attached on the CMOS image sensor such that the trapped and then released cells can be accurately imaged with a flow rate up to 130µl/min (Fig. 1). A custom designed imaging program with adjustable frame rates automatically processes the raw CMOS images and counts the flowing cells. This enables quantification of 1 ml of cell solution with >95% accuracy, in less than eight minutes.

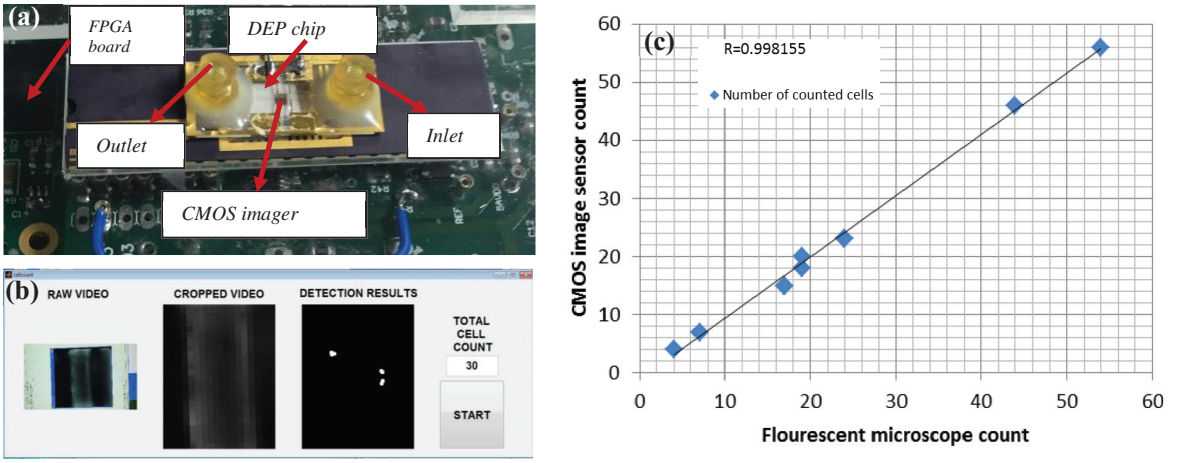

Fig. 1. (a) *Proposed system that combines a microfluidic DEP channel with CMOS image sensor*; (b) *screenshot of the MATLAB program that detects and automatically counts released cells;* (c) *graph that presents number of detected cells with CMOS imager versus microscope count for verification.*

3. Experimental Results & Conclusion

Firstly, cells were were trapped with a microfluidic DEP device under 10µl/min flow rate at $9V_{pp}$, 47.97 MHz. Then, the channel is washed with medium until no cells except the trapped ones remained in the channel. Finally, trapped cells were released by washing the channel at 20µl/min flow rate and cutting the applied voltage off. The released cells are imaged with CMOS sensor and raw sensor images are processed with a program implemented in MATLAB that applies several image processing operations such as erosion, dilation and binarization. Eight different experimental data verifies that the proposed system can detect and count the trapped MCF-7 cells with an accuracy of 95% (Fig. 1). Additionally, throughput of the system can be increased up to $2.5x10^5$ cells per minute by adjusting the flow rate and cell concentration of the solution under test.

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