Biosensors and Bioelectronics 54 (2014) 462–467

Contents lists available at ScienceDirect

Biosensors and Bioelectronics

journal homepage: www.elsevier.com/locate/bios

All electronic approach for high-throughput cell trapping and lysis with electrical impedance monitoring

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ARTICLE INFO

Article history:
Received 19 August 2013
Received in revised form
27 October 2013
Accepted 8 November 2013
Available online 18 November 2013

Keywords:
Dielectrophoresis
Cell trapping
Cell lysis
Microfluidics
High-throughput

ABSTRACT

We present a portable lab-on-chip device for high-throughput trapping and lysis of single cells with in-situ impedance monitoring in an all-electronic approach. The lab-on-chip device consists of microwell arrays between transparent conducting electrodes within a microfluidic channel to deliver and extract cells using alternating current (AC) dielectrophoresis. Cells are lysed with high efficiency using direct current (DC) electric fields between the electrodes. Results are presented for trapping and lysis of human red blood cells. Impedance spectroscopy is used to estimate the percentage of filled wells with cells and to monitor lysis. The results show impedance between electrodes decreases with increase in the percentage of filled wells with cells and drops to a minimum after lysis. Impedance monitoring provides a reasonably accurate measurement of cell trapping and lysis. Utilizing an all-electronic approach eliminates the need for bulky optical components and cameras for monitoring.

1. Introduction

Single cell analysis plays an important role in biological studies such as in the field of genomics, proteomics and metabolic engineering (Fritzsch et al., 2012; Marcy et al., 2007). Compared to the conventional approach of studying the culture of cells which measures average cell response, single cell studies allow one to catalog individual cell behavior and capture cellular heterogeneity. Techniques for isolating single cells in miniaturized platforms and studying them in a high-throughput manner are becoming essential in biological studies. There are various techniques for cell trapping such as using optical fields (Zhang and Liu, 2008), hydrodynamic forces (Valero et al., 2005), magnetic fields (Matthew et al., 2010), ultrasonic standing waves (Evander et al., 2007) and dielectrophoresis (DEP) (Kim et al., 2011). Among these methods, DEP-based cell trapping provides a low cost and efficient route to build such platforms for routine use in biology and medicine (Bocchi et al., 2009). This is because DEP is a fully electronic approach that does not require bulky and expensive optical components such as laser/light sources, objectives or lenses. DEP has the potential to provide high-throughput parallel control of many individual cells. Furthermore, it is possible to trap different types of cells selectively and control them in both space and time. DEP has been used for various biological applications such as cell sorting (Cheng et al., 2009; Sano et al., 2011; Khoshmanesh et al., 2010) study of cell behavior and properties (J.E. Gordon et al., 2007; Morgan et al., 2007; Sun et al., 2007; Guido et al., 2012) and cell manipulation (Cha et al., 2011). In many biological investigations, after the cells have been captured through trapping, it is necessary to extract proteins or DNA from them for further downstream sensing and analysis. To perform such tasks, cell membrane must be ruptured to release cells organelles and other contents in a process that is termed lysis. Some popular approaches for cell lysis are through the use of chemical, mechanical and thermal means (Piersimoni et al., 2009; Baek et al., 2010; Di Carlo et al., 2003). Although these methods are simple, they are neither energy efficient nor do they have high yield. Moreover, they may not be appropriate for targeting specific cell types because they do not possess sufficient selectivity. Combining methods for selective trapping of specific cell types for lysis provide a robust platform for high quality cellular material extraction. Electrical approaches for cell lysis provides a highly controllable method, which can be combined with dielectrophoresis to provide an integrated low cost platform which is consistent with both high-throughput cell

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http://dx.doi.org/10.1016/j.bios.2013.11.031

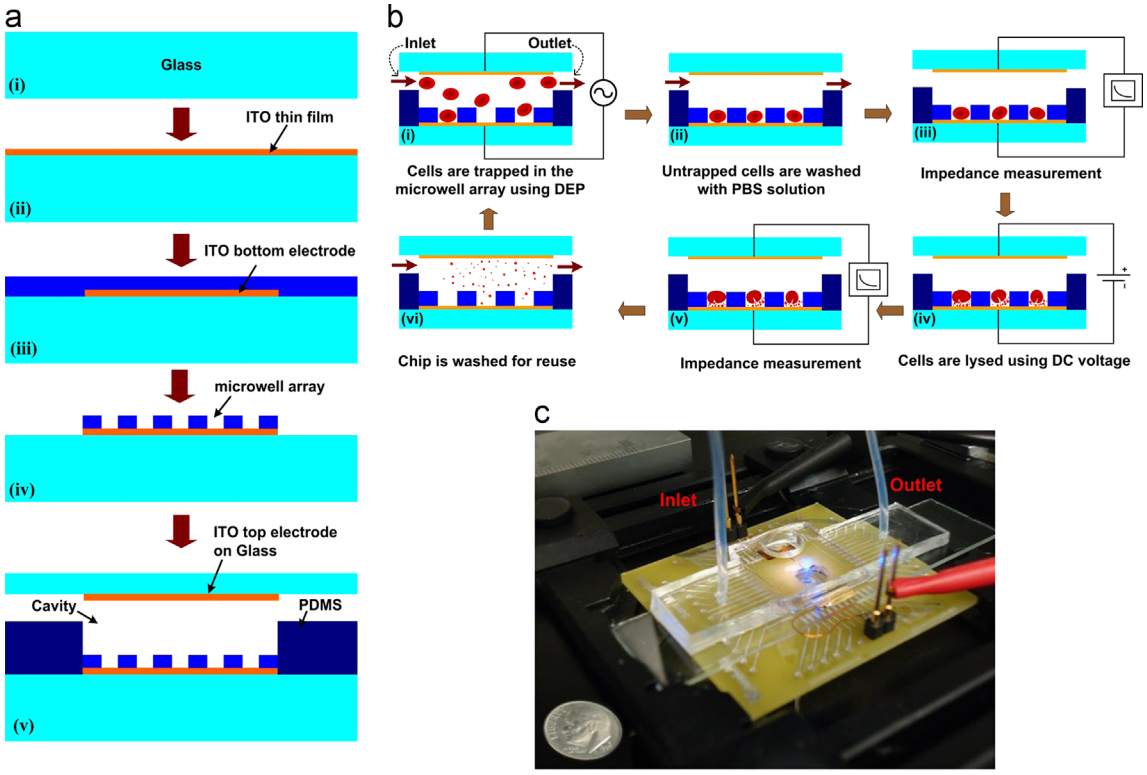

Fig. 1. (a) The fabrication process for the microfluidic HT cell trapping/lysis chip. (i) Start with a 3 in. glass substrate, (ii) coat with a thin film of ITO, (iii) create the bottom electrodes by patterning ITO film using photolithography and coat with SU8 (iv) fabricate SU8 based microwell array on top of the bottom electrode using photolithography, (v) create a PDMS microfluidic cavity with inlet and outlet channels; bound the top and bottom electrodes onto the PDMS microfluidic channels. (b) Experimental steps for cell trapping, lysis and impedance measurements. (c) Photo of the chip consisting of the microwell array, inlet, outlet and electronic connections; device placed next to a dime (10 cent) US coin.

trapping and lysis. There has been some work on combined trapping and lysis using electronic approaches (Kim et al., 2011; Jen et al., 2012; Sedgwick et al., 2008). However these platforms are still bulky and not amenable for lab-on-chip realization due to the need for optical or fluorescent microscopes for monitoring and characterizing DEP and lysis processes. For example, in a previous report (Kim et al., 2011), DEP is utilized with planar electrodes to trap single cells inside microwells with electrophoresis, and subsequently lyse them. Planar electrodes necessitate a physical approach for confinement to achieve effective lysing of cells. The whole process is monitored optically that still requires bulky optical instrumentation for characterization. Moreover none of the electronic method for combined trapping and lysis provides any precise control over the number of cells trapped in the microwells.

We have developed a high-throughput, non-optical approach for single cell trapping and lysis using electric fields, and in-situ monitoring based on impedance spectroscopy. The proposed platform consists of a single chip with 6400 microwells, sandwiched between two transparent electrodes with built-in microfluidic channels for cell delivery and extraction (Fig. 1(a)). An AC electric field is applied between the top and bottom electrodes to create a dielectrophoretic force for cell trapping. Then DC electric field is applied to lyse the cells. In this design, Indium Tin Oxide (ITO) has been used as the transparent conducting electrodes. Even though transparent electrodes were not necessary, their use will enable various optical imaging modalities (e.g. fluorescence). Impedance is measured both before and after trapping, and before and after lysis to measure the efficiency of cell trapping and lysis. This lab-on-chip platform allows for full electronic monitoring of cell trapping and lysis with an additional ability to perform optical monitoring.

2. Theory

The movement of a polarized dielectric particle as the result of a non-uniform electric field is known as dielectrophoresis (DEP) (Pohl, 1951). The DEP force, F_{DEP}, for a spherical particle with radius a, in the known electric field, E, can be calculated using the following relation (Kim et al., 2011).

$$F_{DEP} = 2\pi\varepsilon_e a^3 \mathrm{Re}[k(2\pi f)]\nabla E^2 \quad (1)$$

where ε_e is the permittivity of the external medium, f is the frequency and $k(2\pi f)$ is known as the Clausius–Mossotti and for the lossy dielectric is defined as

$$k(2\pi f) = \frac{\varepsilon^*_{cell} - \varepsilon^*_e}{\varepsilon^*_{cell} + 2\varepsilon^*_e} \quad (2)$$

the ε^*_e is the complex electrical permittivity of external medium and ε^*_{cell} is the electrical permittivity of the spherical particle and is defined as

$$\varepsilon^*_{cell} = \varepsilon_{cell} - j\frac{\sigma_{cell}}{2\pi f} \quad (3)$$

where σ_{cell} is the particle's conductivity. When the real part of Clausius–Mossotti factor is greater than zero, particles will move towards local maxima of the electric field, the process is known as positive dielectrophoresis. But when the real part of Clausius–Mossotti factor is smaller than zero, particles move towards minima of the electric field, and this process is known as the negative dielectrophoresis. Due to frequency dependent dielectric parameters, the Clausius–Mossotti factor, k, can be varied by changing the frequency of the applied field and by adjusting the