CODE-MULTIPLEXED SENSOR NETWORKS FOR MICROFLUIDIC IMPEDANCE SPECTROSCOPY

Ningquan Wang, Ruxiu Liu, and A. Fatih Sarioglu
Georgia Institute of Technology, Atlanta, USA

ABSTRACT

In this paper, we integrate microfluidic impedance spectroscopy with the Microfluidic CODES sensor technology, which allows distributed Coulter sensing of particles across a microfluidic device. This combination allows simultaneous measurement of particle size and location together with dielectric properties from computational analysis of an electrical waveform. As an added benefit to impedance spectroscopy capabilities, the multi-frequency operation of code-multiplexed electrical sensors aids the decoding process to resolve interfering sensor signals due to coincident cells. We present our preliminary results on this platform from processing of cultured human cancer cells.

KEYWORDS: Lab on a chip, Microfluidic CODES, Microfluidics, Impedance spectroscopy, Independent component analysis, Multifrequency

INTRODUCTION

Microfluidic impedance spectroscopy is an invaluable technique for label-free characterization of biological particles. The technique relies on the differences between complex impedances to discriminate different particles and typically employs a multi-frequency excitation to measure the particle frequency response [1]. In this paper, we present a combination of multi-frequency impedance spectroscopy with the Microfluidic CODES technique, a code-multiplexed sensor network technology for distributed electrical sensing on a microfluidic device [2]. The combined technique not only provides information on the complex impedance of particles, which could further be used for particle classification through machine learning [3], but aids the decoding of interfering code-multiplexed sensor signals due to coincident particles using an algorithm based on independent component analysis (ICA).

THEORY

The ICA is a mathematical method for separating a multivariate signal into additive components. In ICA, we assume that the multivariate signal is a linear combination of components that are statistically independent. As shown in Figure 1, when two signals are linear combinations of two source signals, s_1 and s_2, with different coefficients, ICA can extract the two independent sources without prior knowledge on source signals. In multi-frequency implementation of the Microfluidic CODES, when sensor signals interfere due to coincident particles, the resulting signal at each drive frequency is a multivariate signal. Each of these multivariate signals can also be considered as independent linear combinations of code signals with different coefficients as no two cells have identical dielectric properties. Therefore, interference signal analyzed at different frequencies provide the ICA additional information to recover the identities of interfering sensors.

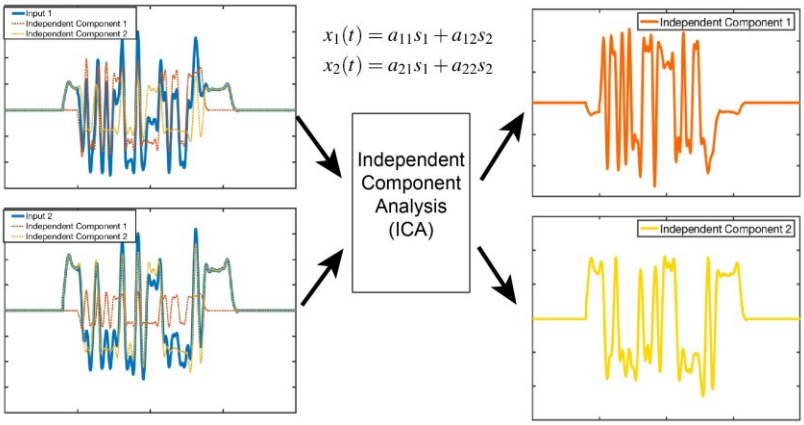

Figure 1. Principle of independent component analysis (ICA).

EXPERIMENTAL

To test our approach, we fabricated a 10-sensor Microfluidic CODES device. The device was composed of two layers, a top polydimethylsiloxane (PDMS) microfluidic layer that was fabricated using soft lithography, and a bottom glass substrate with coplanar coding electrodes (Figure 2). For the glass substrate, a 500 nm-thick Cr/Au film stack was patterned using lift-off to create three electrodes, namely a common electrode, a positive electrode, and a negative electrode. The common electrode was then driven with a multi-frequency excitation signal, and the impedance changes are measured by measuring differential current from the other two electrodes. In this setup, the electrode pattern for each sensor determined the distinct sensor code that was produced when a particle was detected.

We prepared a suspension of MDA-MB-231 human breast cancer cells in phosphate buffer saline (PBS) to test the device. The cell suspension was driven through the device using a syringe pump. At the same time, we used a lock-in amplifier (HF2LI with multi-frequency option) to excite the common electrode with a multi-frequency signal that contained 4 tones (222 kHz, 460 kHz, 759 kHz, and 1 MHz) of equal amplitude. The output was recorded and demodulated with 4 independent oscillators to extract the signal in each frequency.

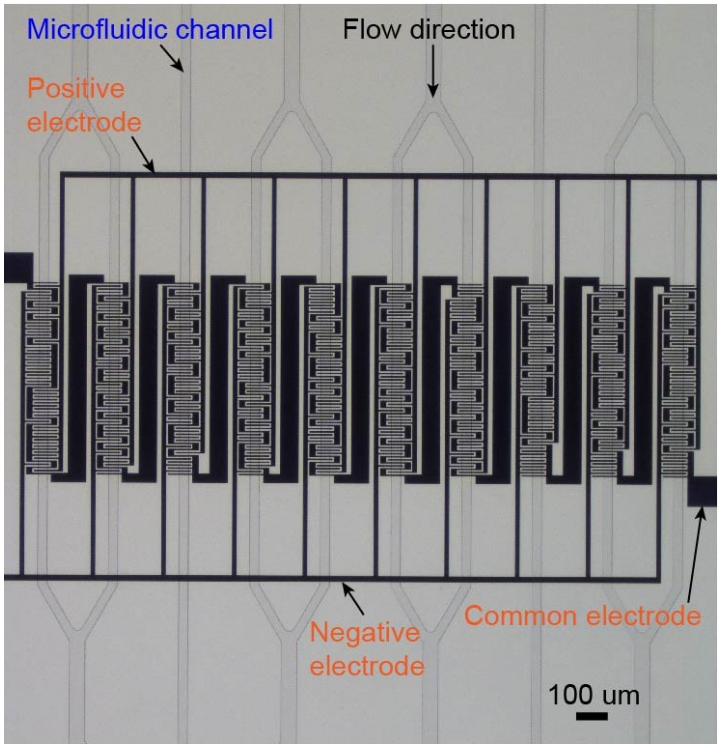

Figure 2. An image of the fabricated microfluidic device with surface electrodes on a glass substrate and PDMS microfluidic channels. The device has 10 code-multiplexed Coulter sensors, each of which generates a distinct sensor signal when a particle is detected.

RESULTS AND DISCUSSION

Figure 3a shows the sensor signal for a single MDA-MB-231 cell recorded at 4 different frequencies. By measuring the signal amplitudes at different frequencies from 131 cells, we were able to generate an average frequency response for the MDA-MB-231 cell population under test (Figure 3b).

The multi-frequency excitation of code-multiplexed electrodes was also utilized to decode interfering sensor signals due to two coincident cells (Figure 4a). The interfering signals were analyzed using the ICA and separated into two subwaveforms, each corresponding to code waveforms from individual sensors (Figure 4b). The identity of these two ICA-generated subwaveforms were computationally determined by cross-correlating these signals with a template library of expected waveforms from sensors in the network (Figure 4c).

CONCLUSION

We introduced a microfluidic characterization platform that enables multi-frequency impedance spectroscopy of suspended particles by a network of code-multiplexed Coulter counters. This technology not only offers established utility of impedance spectroscopy for cell characterization, but also simplifies the decoding of interfering sensor signals though independent component analysis.

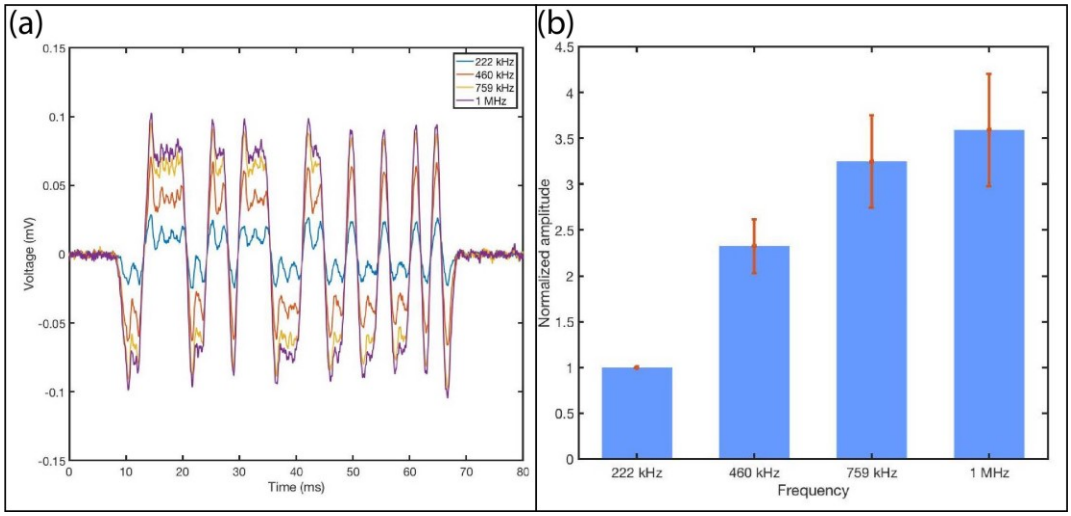

Figure 3. (a) Signal generated by a sensor encoded with "00111100110111000110010010010 10" when an MDA-MB-231 cell is detected. Because of the multi-frequency excitation, sensor signal could be simultaneously acquired at 4 different frequencies. (b) Frequency response measured from a population of 131 MDA-MB-231 cells. For each cell, the peak signal amplitude at each frequency was normalized to the peak signal amplitude recorded at 222 kHz.

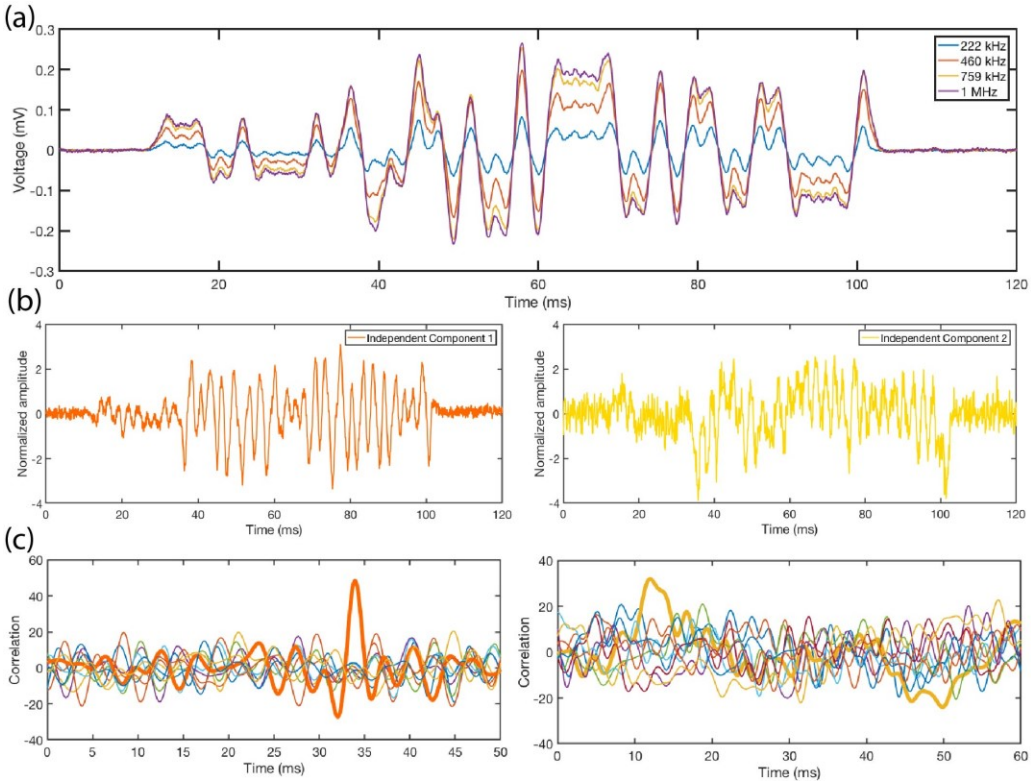

Figure 4. (a) An interference signal due to two coincident cells. (b) Two subwaveforms extracted by ICA. (c) Identification of interfering sensors through cross-correlation with a templated library.

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CONTACT

* A. F. Sarioglu; phone: +1-404-894-5032; sarioglu@gatech.edu