A Review on Impedance Spectroscopy Based Microfluidic Technology

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***Abstract*— One of the most difficulties researchers facing in the field of microfluidic technology is labeling when characterizing the dielectric properties. Impedance based microfluidics can overcome this problem by characterizing the dielectric properties of cells, medium, and particles without labeling. Cell sorting or separating can also be done by this technology which took the highly complex image or video processing in other ways. Now, impedance spectroscopy and impedance flow cytometry are being combinedly used to measure the single-cell properties. This article presents the present condition of impedance spectroscopy in the field of microfluidic technology along with a short history.**

Keywords*— *Impedance Spectroscopy, microfluidics, dielectric property, cell sorting; permittivity

I. INTRODUCTION

Biological cell offers good heterogeneity which enables to study all the cell by analyzing a single cell [1]. The biophysical properties of a single cell can give necessary information about nuclear size, membrane morphology, ion channel status, and cytoplasm. For example, the cytoplasmic resistance or conductance change or membrane permittivity can be used to determine whether the red blood cell is infected by plasmodium or not [2]. Like this, the electrical properties have been used for characterizing biophysical states and distinguishing cells for many applications such as cell sorting and quantifications [3,4], cell counting [5], disease diagnosis [6], drug screening [7], etc.

Several methods have been developed to measure cell electrical property [1]. Among them, impedance spectroscopy is very sensitive and nondestructive. The most traditional methods used for cell sorting or separation are the off-chip method which suffers from time-consuming and sample loss/ quantification error problems [4]. On-chip quantification is much better than off-chip quantification as is it has fewer sample handling steps and fewer errors. In that case, using a high-speed camera and image processing can be a solution but the problem is that a high-resolution camera is needed for moving particle/cell quantification that costs more [4]. Photomultiplier tubes (PMTs) or photodiodes (PDs) could be good solutions for cell quantification but they face the problem of a short footprint on the device and also detection and high-speed imaging are difficult. A fluorescence-based system is another good solution for it but it also offers a big problem which is labeling. Also, it can affect the separated cell properties.

Impedance spectroscopy is a method used in microfluidic technology for cell sorting or separating which is label independent and practically used for many applications. This label-free technology offers many advantages like simplicity in design, higher speed in measurement, easy to fabricate [8]. Impedance spectroscopy-based microfluidics is being used in high throughput cell counting and quantifying applications and as it needs only a pair of electrodes for integrating with the microfluidic channel so multiple channel output can be detected and counted using multiple pairs of electrodes. Though these impedance-based spectroscopy methods offer a great advantage compared to other methods but still the commercially available devices cost more (usually more than 20K USD) and also 4-channel is the maximum available device still now [4]. To mitigate this problem, Sobahi et al. have proposed a multi-outlet non-parallel single pair of electrodes for high throughput, low-cost applications [4].

II. METHODOLOGY

The authos has focued on the present development of the impedance based microfluidic technology. For picturing the present conditions, the author has explained the basaic of impedence spectrospy measuremt methods and also the equilavent circuit of cell. data extraction procedure has also been explaind for better understsanding.

III. IMPEDANCE SPECTROSCOPY

Dielectric impedance spectroscopy is a method that measures the electric field change due to the targeted particles (with the medium) when the electric field passes from one electrode to another electrode keeping the targeted particles in the middle of two electrodes. Fig.1 represents a general structure of impedance spectroscopy. The electric field distribution can be possible using parallel or planner electrodes. The produced electric field strength depends on the applied voltage on the stimulating electrode but the response of the detecting electrode depends on the applied voltage on the stimulating electrode and the medium between the two electrodes. The medium generally consists of a liquid to carry the targeted particles. As the liquid is present in between the two electrodes, its dielectric property has to be calculated at the time of determining electric field change due to targeted particles.

Another big issue of impedance spectroscopy is permittivity which is the reduction or absorption of the electric field by the materials [9]. As the dielectric spectroscopy is related to the phase difference, it is measured with spectrum frequency. The dielectric spectroscope method is used for any materials; solid, liquid, or gases [10]. In the biological analysis, this method is greatly used for cell or DNA analysis because its permittivity is different from the liquid media.

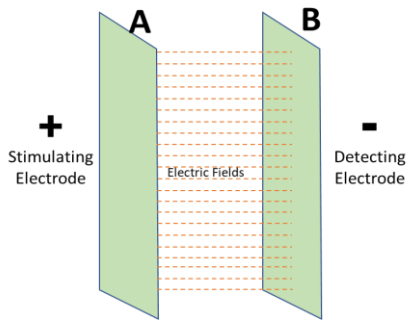
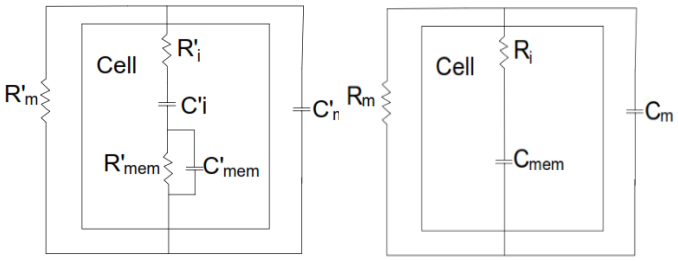


Figure 1. Illustration of electric filed of a typical impedance spectrum

IV. Equivalent Circuit Diagram

For analyzing a cell using impedance spectroscopy, there must be an equivalent circuit diagram of the cell. Fosteret et al have proposed an equivalent circuit diagram of a single cell shown in fig.2 [11]. The cell cytoplasm is equivalent to a resistor that is connected to a capacitor that is equivalent to the cell membrane. In this model, the medium's capacitance (C'm) and resistance (R'm) are also considered. The resistance of the cell membrane is much higher than the reactance so it has been ignored in simplified figure 2b. Likewise, the cytoplasmic capacitance has been ignored by in fig 2b. This simplified model of a single cell has provided good agreement with the experimental results [12]. In some cases, the simplified model does not give good results especially when electroporation or cell lysis occurs or when the cell resistance or cytoplasmic capacitance varies widely [12].



(a) (b)

Figure 2. Equilavent circuit diagram of cell: (a) shows the complete equivalent circuit diagram of a single cell. The resistor R'_i and capacitor C'_i represent the value of cytoplasm in series combination with cell membrane's resistance R'_{mem} and capacitance C'_{mem}. In (b), the circuit has been simplified by using cytoplasmic resistance R_i and cell membrane capacitance C_{mem}.

V. Flowing Cell Impedance Analysis

Impedance based microfluidic technology was a great achievement of the scientists. In 1999, Ayliffe et al. have demonstrated the first single-cell impedance measurement [12]. The microchannel was fabricated from epoxy-based photoresists and electrodes, gold was used. This device was able to determine the impedance change for a specific frequency spectrum and Fuller et al. have demonstrated a device for multiple frequencies [13]. In 2001, Gawad et al. have reported the most significant single-cell impedance microfluidic technology which was capable of clear differentiating ghost cells, beads, and erythrocytes [14].

It is necessary to make the microelectrodes as the same size (10-30 µm) as a cell to determine the impedance signals. Generally, two pieces of information from the impedance signal is taken for the cell characterization or sorting or quantification; one is the signal height which says the amplitude of the signal, and the other one is the width of the signal that determines how much time is required for flowing through the electrode pair.

VI. Data Extraction Procedure

Before practically implement the microfluidic device, generally the researchers use COMSOL Multiphysics software for designing the device and data analysis. MATLAB is used for mathematical analysis and designing and extracting data from COMSOL Multiphysics.

Generally, electrodes are placed on a glass substrate and poly dimethyl siloxane (PDMS) is used for the microfluidic channels. Gold is preferred for the material used as electrodes which are prepared by the lithographic process. The electrodes can be used as simple as shown in fig. 1 or in many other ways [1, 4, 10, 12, 15-16]. After designing and implementing the devices, the inlet, outlet, and electrical ports are attached to them.

Syringe pumps are generally used for injecting the sample particle/cell through the inlet. The particles are flown through the channel using a liquid medium (glucose, sucrose, DI water, etc.). Generally, two paths are used for the sample flow where one is used to trapping the cell/particle for analysis and the other one is used for by-passing the materials when the first path is blocked. After passing through the paths, the sample goes out through the outlet [1, 15].

The impedance analyzer is used to measure the data extracted from the impedance electrodes. Some commercially available impedance analyzer is presented in Table I.

Table I: Commercially Available Impedance Analyzer

Method	Frequency Range	Impedance Range	Basic Accuracy
Direct I-V (Direct current-voltage) [17]	µHz to 50 MHz	10 µΩ to 100 TΩ	0.05%
ABB (Auto-balanced Bridge) [18]	20 Hz to 120 MHz	10 mΩ to 100 MΩ	0.05%
RF-IV (Radio Frequency Current-Voltage) [18]	1 MHz to 3 GHz	100 mΩ to 100 kΩ	1%

VII. CONCLUSION

The author has provided a comparison of impedance-based microfluidic technology with other methods. The basic principles and merits-demerits of impedance-based microfluidic technology have been focused on for better understanding. The simple design and label-free technology have made this method preferable to all the researchers. In this article, the author has given a short history of impedance spectroscopy and explained shortly the data extraction procedure.

VIII. REFERENCES

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