International Journal of Electrical and Computer Engineering (IJECE)
Vol. 7, No. 3, June 2017, pp. 1513~1521
ISSN: 2088-8708, DOI: 10.11591/ijece.v7i3.pp1513-1521

A Novel Integrated Dual Microneedle-Microfluidic Impedance Flow Cytometry for Cells Detection in Suspensions

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Article Info

Article history:

Received Feb 18, 2017
Revised Apr 20, 2017
Accepted May 10, 2017

Keyword:

Cell concentration detection
Impedance flow cytometry
Tungsten needle

ABSTRACT

In this study, a new, simple and cost-effective impedance detection of yeast cell concentration by using a novel integrated dual microneedle-microfluidic impedance flow cytometry was introduced. The reported method for impedance flow cytometry detection utilizes embedded electrode and probe in the microfluidic device to perform measurement of electrical impedance when a presence of cells at sensing area. Nonetheless, this method requires costly and complicatedly fabrication process of electrode. Furthermore, to reuse the fabricated electrode, it also requires intensive and tedious cleaning process. Due to that, a dual microneedle integrated at the half height of the microchannel for cell detection as well as for electrical measurement was demonstrated. A commercial available Tungsten needle was utilized as a dual microneedle. The microneedle was easy to be removed from the disposable PDMS microchannel and can be reused with the simple cleaning process, such as washed by using ultrasonic cleaning. Although this device was low cost, it preserves the core functionality of the sensor, which is capable of detecting the passing cells at sensing area. Therefore, this device is suitable for low cost medical and food safety screening and testing process in developing countries.

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1. INTRODUCTION

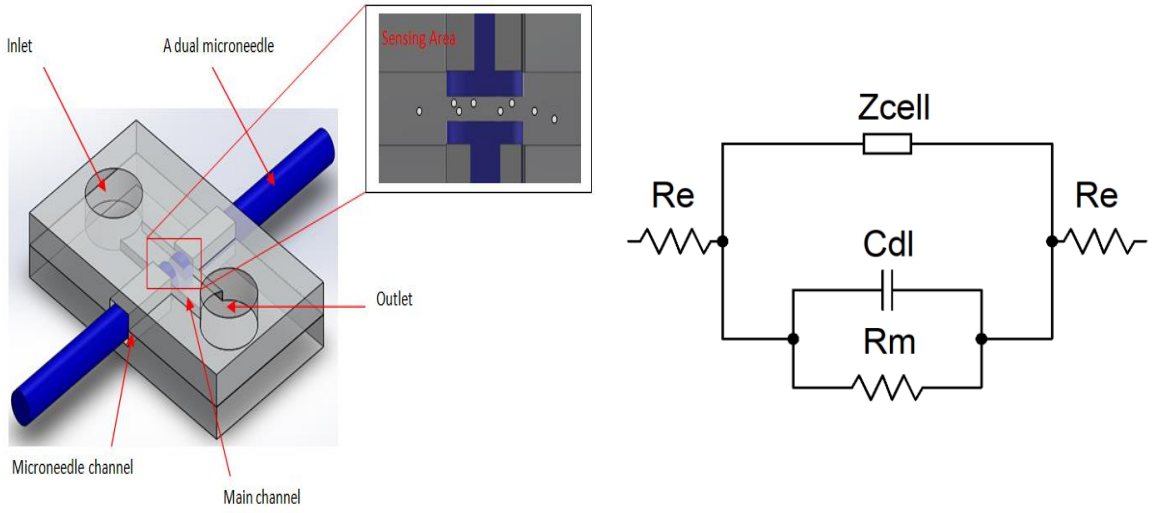
The detection and quantification of cells in complex samples remain a challenge and an important issue for applications such as medical diagnosis and food safety. For application of medical diagnosis, detection of cancer cells and pathogenic bacteria cells in blood is utilized as a diagnosing infectious disease. It is reported that detection of circulating tumor cells (CTCs) in the blood has shown to be clinically important for early stage metastasis or recurrence of cancer. The presence of rare CTCs in blood is ranging from only 1 to 100 CTCs/ml blood [1]. Plasmodium falciparum malaria, which kills mainly children in developing countries infected the blood sample of patients at concentration of ~ 1/50ul of blood [2]. For application of food safety, contamination of drinking water or waste water with microorganism, such as E. Coli and Salmonella has been a serious issue for several developing countries [3]. As those bacteria can multiply rapidly, it would be necessary to detect them quickly, easily and inexpensively. In order to meet the requirements for applications discussed, the platforms need to be rapid, sensitive and cost-efficient.

The classical method for cell detection in suspension is through the use of flow cytometry, which is rapid and highly accurate measurement technique. These technique was first reported by Coulter [4] in order

to analyze microscale particle with high sensitivity. For instance, colloids as small as 87 nm was able to be detected by a microchip Coulter counter on a quartz substrate [5]. However, flow cytometry is high cost manufacturing and involves labelling the cells with fluorescent antibodies [6]. Recently, the impedance flow cytometry (IFC) has gained attention for the significant promising techniques to replace and overcome the limitations associated with flow cytometry. The IFC is preferable because of fast, real-time, and non-invasive methods for biological detection. This technique is capable to be utilized as cell counting [7], cancer cell detection [8] and bacteria detection [9].

Some groups have demonstrated detection and counting of cells by using a microfluidic integrated with electrode for various electrical measurement method in an application of food safety [10] and real-time monitoring bio-threat [11]. This measurement technique is based on the alteration of impedance across a measurement electrodes due to the deceasing of ionic current passing between electrodes when a presence of the cells. The IFC is capable to distinguish and count lymphocytes, monocytes and neutrophils in human whole blood [7]. The concentration of spermatozoa in semen also causes a change in impedance when passing the electrodes [12]. Other studies reported that IFC can detect the presence of cells based on probing the impedance inside the cell at frequency greater than 1 MHz [13]. Fabricated nanoneedles probe inside microfluidic was utilized for measuring the presence of cells at sensor surface and making it sensitive to the dielectric properties of solution [14]. However, this device requires patterning of electrode or probe on the substrate resulting in higher cost of the fabrication process. Another limitation also needs to consider is time-consuming cleaning process of the device. Several groups have sought to lower the cost of microfabrication of electrodes by using printed circuit board (PCB) as a measurement electrode. They demonstrated contactless conductivity detection in a capillary electrophoresis manners [15] and cell manipulation using dielectophoresis [16]. Recently, the contactless impedance cytometry was developed to reduce the fabrication cost of impedance cytomerty device [17],[18]. The electrode was fabricated on the PCB substrate (reusable component) and the thin bare dielectric substrate bonded to a PDMS microchannel (disposable component) was placed onto PCB substrate. The sensitivity of this device is the limitation since the electric field was buried in dielectric substrate and not reaches the electrolyte. Several designs and method have been used in IFC in order to detect and analyzed a cell has been reported [19],[20].

In this paper, a novel integrated dual microoneedle-microfluidic system for yeast cell concentration detection in suspension was proposed. The development device focus on reducing the fabrication cost while preserving the main functionality of cell detection sensor. This device utilized the Tungsten needle as measurement electrode which can be reused and easily to be cleaned. The dual microneedle was placed at half height disposable microchannel to detect and enabling impedance measurement of passing cells through the applied electric field. Figure 1(a) illustrated the schematic diagram of microfluidic chip has two microneedle integrated at both sides of the microchannel. The main microchannel length, width and thickness are 500 µm, 25 µm and 25 µm respectively. The device is suitable for early cancer cell detection and water contamination application in developing countries since it significantly reduces the fabrication cost.



(a) (b)

Figure 1. (a) 3D schematic diagram of the device structure and top view of sensing area
(b) An equivalent circuit model of sensing area of microfluidic chip

2. PRINCIPAL

The basic principle of detection suspended biological cell in the media is based on Ohm's law. An AC current with a frequency sweep was applied across passing cells to determine the changing impedance value of media. An equivalent circuit model to understand the interface of dual microneedles with the suspension media was developed, as represented in Figure 1(b). The sensing area of mirofluidic chip can be modelled electrically as cell impedance Z_{cell} in parallel with the impedance contributed by all materials between the two electrodes, which are consist solution resistor R_m in parallel with a capacitance of double layer C_{dl}. The both impedance in series with a pair of electrode resistance R_e. The Z_{cell} represents a cytoplasm resistor (R_c) in series with a membrane capacitor (C_c) [21]. The overall impedance of the measurement system Z_T is given by [22]

$$Z_T=2R_e+ 1/((1/R_m) +j\omega C_{dl}+ 1/(R_c-j\omega C_c)) \quad (1)$$

where ω is an angular frequency of the electrical signal. As a result, the Z_T is changing according to the concentration of suspension medium flow at sensing area, because of the number of cells present in the medium. Our main measurement focus is impedance at the interface of the electrode (microneedle) and electrolyte (solution medium).

3. EXPERIMENTAL

3.1. Cell Culture

In the present study, Sacharomyces ceresiae cells were used as a model for proof of concepts. Sacharomyces ceresiae were cultivated in a petri dish containing 10ml of YPD broth (Yeast extract Peptone Dextrose). The YPD broth contained 1% yeast extract, 2% peptone and 2% glucose. The YPD dishes were incubated at 37°C for 24 hours. The cells were washed several times by centrifugation, then they were suspended in sterilized DI water at various dilutions (1:10) concentration. The cells were incubated on agar plates at 37°C for 24 h for determining the number of cells. The diameter size of yeast cells varies from 4 µm to 7 µm. The number of cells was 1.3 x 10^8 colony forming units per milliliter (cfu/ml). The conductivity of DI water is 1.4 mS/m.

3.2. Fabrication of Device

The microfluidic device was fabricated by a photolithography technique. First, the masks were designed by layout editor software. Two masks (top and bottom) were written by a laser lithography system (µPG501, Heidelberg Instruments, Germany) on the chromium (Cr) masks. Firstly, the top layer mold was fabricated by two-step photolithography using SU-8 2025 negative photoresist (MicroChem, USA). The first layer has a thickness of 25µm and was spin coated onto a silicon substrate. After pre-baking, the first layer photoresist was exposed to top layer Cr mask by using a mask aligner (Suss MicroTech MA-6) and post-baking with development. Then, the second layer with 60µm thickness was spin coated on the first photoresist layer and pre-baking. The bottom layer Cr mask was aligned with the substrate of the first photoresist layer and exposed by UV light. The photoresist substrate was post-bake and developed to obtain a top mold master. Following the SU-8 microchannel photolithography step for the top mold master, the bottom mold master with 60µm thickness was fabricated. PDMS was prepared by thoroughly mixing PDMS pre-polymers (SYLGARD184A) with curing agents (SYLGARD 184B) in a ratio of 10:1 by weigh and poured on an SU-8 mold master (top and bottom mold master). PDMS microchannel was obtained after an overnight cured at room temperature. The top side PDMS and bottom side PDMS were cleaned with Isopropyl alcohol (IPA) and treated by oxygen plasma (Plasma Etch PE-25) for 30 seconds to increase bonding strength. The alignment of both side PDMS channels was completed in less than two minutes to prevent loss of oxygen plasma effectiveness. Finally, the right and left sides of the microchannel chip were cut and leaving a square (60µm x 120µm) hole for inserting a dual microneedle. A commercial available Tungsten needle (Signatone) coated by parylene was utilized as a measuring electrode (dual microneedle). The tip diameter, shank diameter and length of tungsten needle are 20µm, 250 µm and 31.7 mm respectively

3.3. Experiment Setup

The microchannel chip system was placed under a microscope (Olympus Inverted Microscopes IX71) to monitor the sensing area. A dual microneedle held by the micromanipulator (EB-700, Everbeing) was inserted into microchannel chip through the square hole at right and left side of the chip. The gap between microneedles was fixed at 15 µm for this experiment. The schematic of the experimental setup is shown in Figure 2. The impedance analyzer (Hioki IM3570) was connected with a dual microneedle as an input and was displayed on the computer. The sample of yeast concentration was introduced using 3 ml

syringes controlled by syringe pumps (KDS LEGATO 111, KD Scientific, and USA). Two tygon flexible tubes, connected to the syringes and waste bottle were inserted into the PDMS layer at the inlets for the introduction of liquids and outlet for waste liquids.

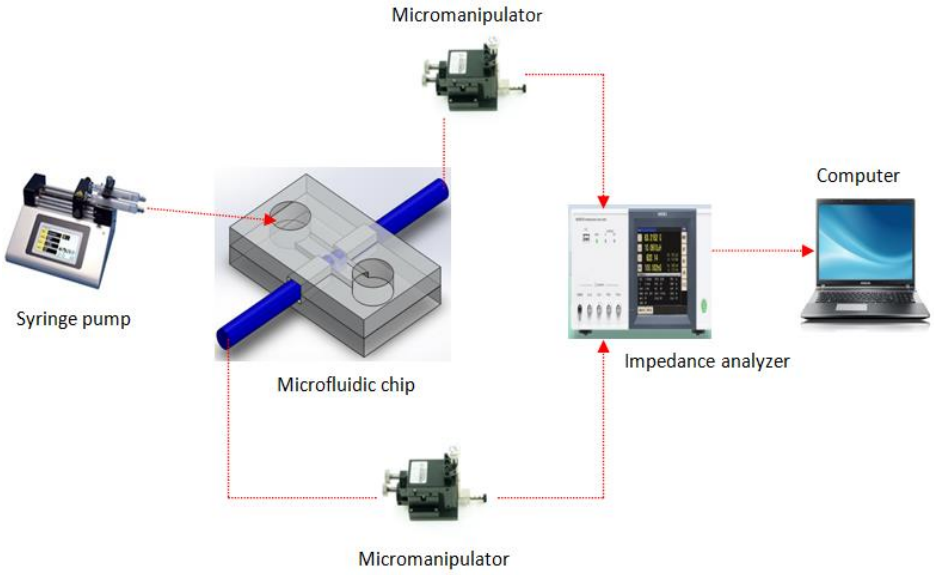


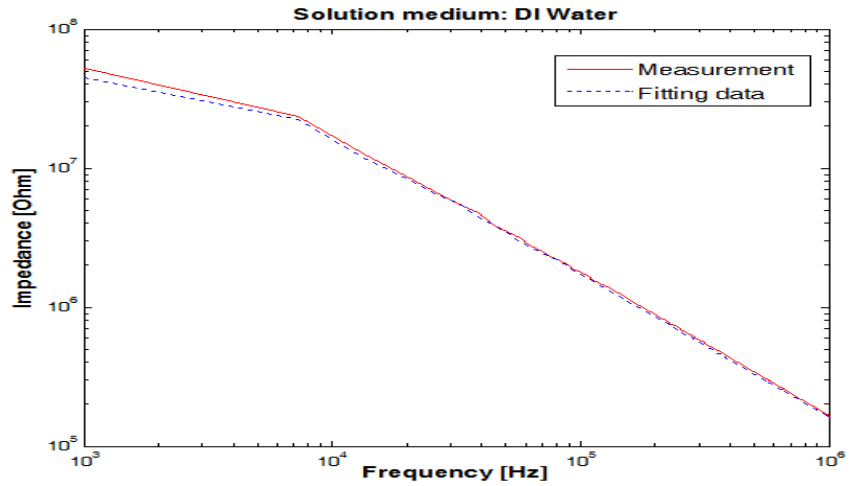
Figure 2. A schematic diagram of the experimental set-up

3.4. Electrical Measurement Procedure

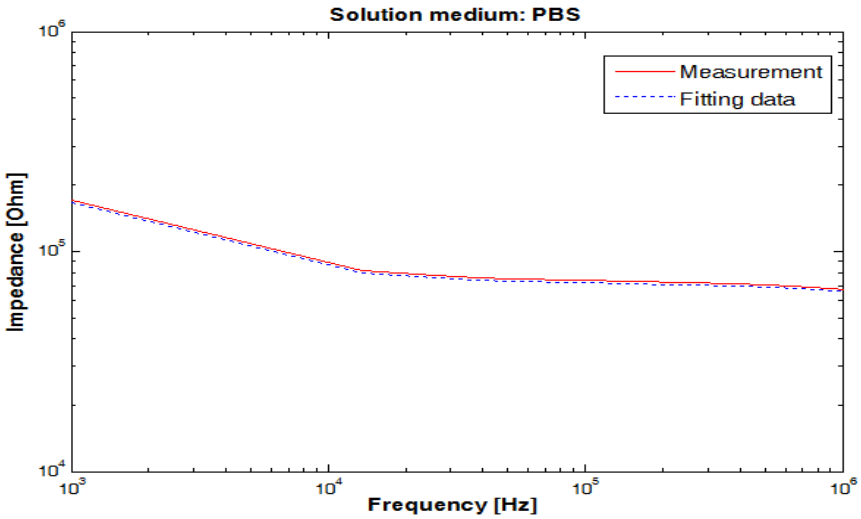
Initially 1 ml of each five different concentrations of sample from 10^4 to 10^8 cfu/ml was prepared for the measurement. Each sample was loaded into a syringe and five measurement cycles were conducted to measure all samples. The sample was driven through the microchannel using a syringe pump with the flow rate of syringe pump was kept constant (6 µl/min). The dual microneedle connected with impedance analyzer was used to measure the impedance change during the passage yeast cells at sensing area. Impedance spectra (impedance and phase vs. frequency) were measured using an AC signal frequency range from 1 kHz to 1 MHz with an applied voltage of 1 Volt. The data were recorded with the impedance analyzer (Hioki IM3570) GUI and post-processed in MATLAB (MathWorks Inc,USA). In order to perform the measurement, the impedance analyzer was self-calibrated by using short and open standard calibration. All experiments were conducted at room temperature. Impedance at three frequencies (1 kHz, 40 kHz and 200 kHz) was measured to observe the changing of impedance for each sample. To validate the equivalent circuit model impedance of medium between microneedle was measured. Two separate solutions with different conductivities were used. The solutions were sterilized DI water and PBS (photosphate-buffered saline) with conductivities 1.4 mS/m and 16 S/m respectively.

4. RESULTS

As a proof of concepts, the capability of this sensor in the present of a different number of yeast cells in the suspension medium was studied. Figure 3 presents the measured impedance spectra of the system for two of microchannel filled with sterilized DI water and PBS. The agreement between the measured and fitting spectra result indicated that our developed circuit model for this system is feasible to determine the impedance characteristics of solution medium. The results show the sensor can differentiate between solution medium due to the change in relative dielectric permittivity of the solution. A rising of the conductivity of solution was affected on the capacitance measurement, as the result in an increase in capacitance and thus a decrease in impedance measured [23]. To illustrate the detection capability of the device, yeast cell with different concentration was utilized. Yeast cells concentration ranging from 10^4 to 10^8 cfu/ml were infused inside microchannel with fixed flow rate 6 µl/min. As can be seen in Figure 4, the yeast cells were flowing passes through a dual microneedle which have fixed gap (15 µm). A sweep frequency (1 kHz to 1 MHz) AC signal (1 Volt) was applied to the one side of the microneedle and the current entering at another side of microneedle was measured to calculate the impedance of concentration of yeast cells in DI water.



(a)



(b)

Figure. 3 Impedance spectra of sample solution (a) DI water (b) PBS

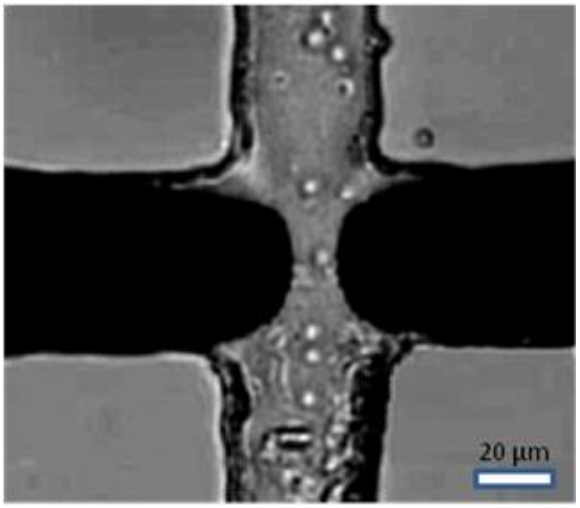


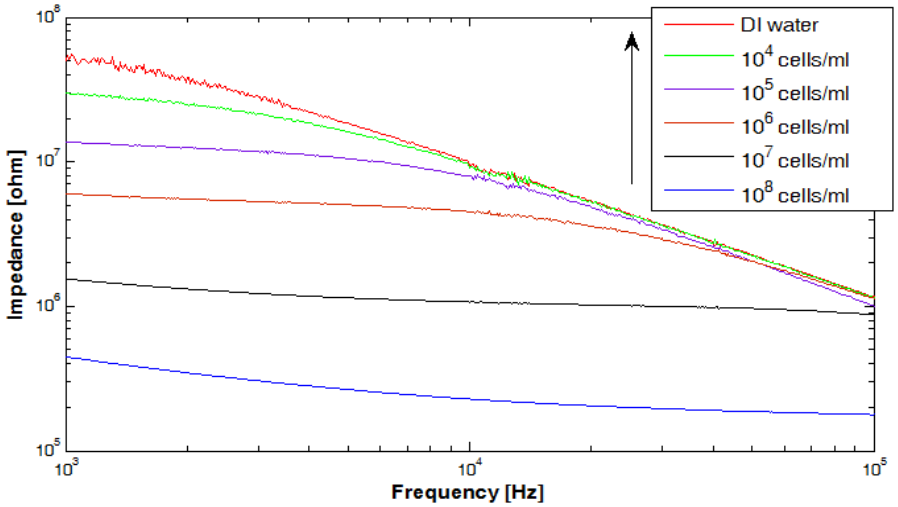
Figure. 4 Illustrated the sensing area of the device

Initially 10^8 cfu/ml were injected resulting in a drop in impedance by referring the impedance of DI water as a control. Afterward the microchannel chip was washed by flowing the DI water at maximum flow rate. The maximum flow rate of the liquid can flow inside microchannel without leaking is 50 µl/min. Figure 5(a) shows the impedance spectra of yeast cell in DI water with the different cell concentration in the range 10^4 to 10^8 cfu/ml, along with DI water as a reference. After washing the microchannel 10^7 cfu/ml was infused to the microchannel resulting in an increase in impedance. It can be seen the impedance spectra of yeast cell in DI water across the sensing area (dual microneedle) increase with decreasing the cell concentration of cells [14]. The experiment was repeated 3 times measurement and show the similar result. According to the observed result, it can be said that cell suspension with high concentrations is more conductive than those with lower concentrations. The conductivity of the solution varies proportionally to the number of cell concentration at fixed volume of solution [24].

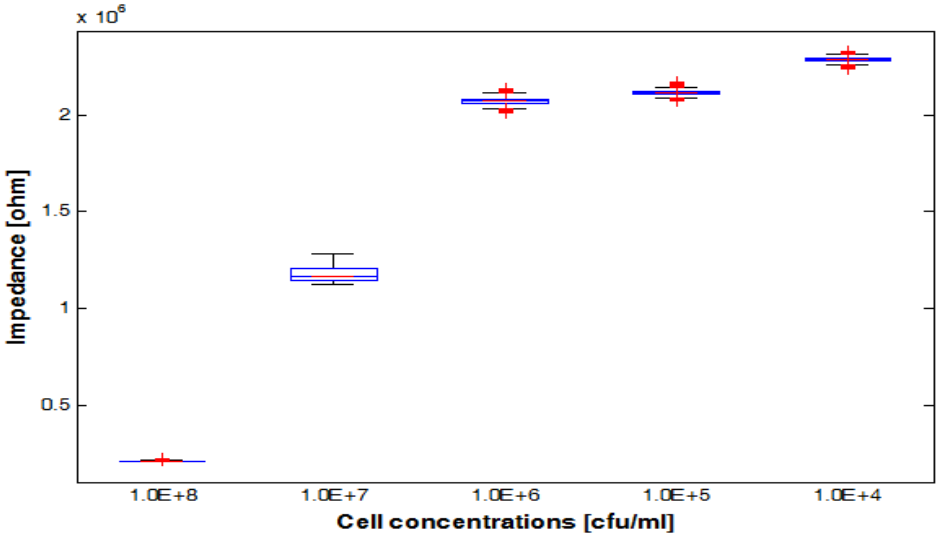
In some studies, the relative dielectric permittivity and charged polyelectrolytes inside the cell also may affect the impedance of solution [14]. The optimum region for sensing microneedle to differentiate the cell concentration in DI water occurs between 1 kHz to 50 kHz. In this experiment, the measurement at frequency lower than 1 kHz was not performed. In order to investigate the relationship between impedance value and cell concentration, we selected 40 kHz as the best representative frequency. Figure 5(b) illustrates the impedance responses of the sample containing different yeast cell concentrations at frequency measurement 40 kHz. The impedance of the solution was significantly increased from 210 kΩ to 1.21 MΩ, 2.09 MΩ when the yeast concentration decreasing from 10^8 cfu/ml to 10^7 cfu/ml, 10^6 cfu/ml. The changing of impedance value at yeast concentrations lower than 10^6 cfu/ml, showed a small difference between each other. However, we found the changing of the impedance value of yeast concentrations at frequency more than 60 kHz was unstable. The impedance of yeast concentrations of 10^6 cfu/ml was higher than 10^5 cfu/ml at high frequency (see Figure 5(a)). As the result, we conclude this device was capable of detecting the cell concentrations in solution medium at the frequency range between 1 kHz and 50 kHz. For the future work, we will focus on the geometry and size of microneedle as well as the gap between two needles in order to improve the performance of the device.

5. CONCLUSION

In summary, a very simple, label-free and low-cost microfluidic device for cell concentrations detection in the suspension medium has been demonstrated. This device contains a reusable dual microneedle which can be inserted into a disposable PDMS microchannel. We found the impedance value decrease with the increase of cell concentration in the solution medium. The capability of this device to differentiate the concentration of cell from 10^8 cfu/ml to 10^4 cfu/ml shows the core functionality of sensor even though the manufacturing cost was significantly lower. As a proof of concept, yeast cell was used in this study and we emphasize this sensing technique can be applied to variety of cell types with diameter size in a range from 5 µm to 25 µm. The device is suitable for early cancer cell detection and water contamination application in developing countries since it significantly reduces the fabrication cost.



(a)



(b)

Figure. 5 (a) Impedance spectra of yeast cells in water with cell concentrations in ranging from 10^4 to 10^8 cfu/ml, along with DI water as controls (b) Impedance responses to the sample with different concentrations of cells

ACKNOWLEDGEMENTS

The research was supported by the Ministry of Higher Education of Malaysia (grant Nos. 4L640 and 4F351), and Universiti Teknologi Malaysia (grant Nos. 03E11,03G47, 02G46, 03H82, and 03H80); we thank them for funding this project and for their endless support

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