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Characterization of several cancer cell lines at microwave frequencies

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ABSTRACT

This paper presents the complex permittivity measurement of Cervical (HeLa), Prostate (PC3), Breast (MDA231), Uveal melanoma (92.1 and OCM) cancer cell lines and white blood cells WBC-Jurkat Clone E6 at microwave frequencies. The measurement uses resonant cavity perturbation technique. The results, for the cell lines under consideration, show that the relative dielectric constant of a single cell is between 42 and 68 and the relative dielectric loss is between 12 and 22. The information of high frequency dielectric properties of different types of cell lines enables the detection and signature identification of cells in a microfluidic device at microwave frequencies.

1. Introduction

The dielectric properties of biological material (tissues and cells) provide important information in the applied research and for the development of new diagnosis and therapeutic medical devices [1–4]. Extensive experimental research is performed to determine dielectric properties of different human tissues, body fluids, and cells within a spectrum covers large range of frequencies [5–13]. Dielectric parameters are mostly measured at low frequencies from 1 kHz to 100 MHz [14–16], and at high frequencies in the Ultra high frequency (UHF) to Ku-band (12–18 GHz) [17–20].

In the last two decades, the dielectric properties of several biomaterials were studied at low frequencies in the range of 100 Hz to 10 MHz using impedance-based techniques. The complex permittivity (CP) of particles, in a specific media solution, was measured mainly through dielectric spectroscopy techniques [12,21–24]. Various impedance models with different respective hypotheses were used to determine the CP of particles. The results obtained, either in frequency or time domains, were presented in the form of CP frequency response [25]. The same parameters were also used to estimate the Clausius-Mossotti factor, the crossover frequency, and the relaxation time constants [26–29]. Analytical models were derived to validate the frequency and time domain results [30,31]. Furthermore, numerous microwave measurements on materials were conducted, based on different microwave measurement techniques in frequency and time domains, using coaxial probing, transmission line, free space and resonant cavity measurements [32–34]. This article is the first to report the complex permittivity of several cell lines at high frequency in range of 2–4.5 GHz. The measurement of complex permittivity of cells is detailed in this article and is developed particularly for characterization, detection and signature identification of cancer cells in microfluidic systems.

The complex permittivity includes two parts, dielectric constant and dielectric loss. The dielectric constant describes the interaction of the material with the electric field and the dielectric lost describes the loss of energy of the material due to the effect of the electric field. These parameters are essential in detection and characterization of cancer cells in microfluidic devices [35]. In fact, when the complex permittivity of cancer cell is very close to the one of the culture media solution, the identification would be very difficult due to the overshadowing effect of the two dielectric properties. Therefore, knowing the complex permittivity of different cancer cells could define the use of suitable biological media during detection and measurement of a specific type of cancer. The measurement of complex permittivity of single cell with precision is not yet possible. We estimated the dielectric properties of single cell from the same bulk of cells with predetermined volume and

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counts. The complex permittivity of specific number of cells (bulk) is measured at high frequencies using the rectangular cavity perturbation method. Once the complex permittivity is measured (cancer cells and media suspension solution), the single cell complex permittivity is deduced using Hanai formula [36].

2. Theory

As the dielectric characterization of cells at high frequencies includes very small volumes, the cavity perturbation method seems to be an appropriate and accurate measurement technique. In the open literature, rectangular cavity perturbation has been extensively used for measurements of the CP of biological samples. The technique has shown a difference in the dielectric properties of tissues from healthy individuals versus cancerous patients [16,37]. The relative or normalized complex permittivity can be written as:

$$\varepsilon^* = \varepsilon' - j\varepsilon'' \tag{1}$$

where ε' and ε'' are the real part and the imaginary part of the CP, respectively and $j = \sqrt{-1}$.

Microwave energy applied on certain material, in general, is not only absorbed at its surface but penetrates its entire volume [38]. The incident microwave energy can be transmitted, reflected and diffracted [39]. Therefore, microwave dielectric measurement is the response of all these energy transformation mechanisms.

Resonant cavity perturbation is an accurate and non-destructive measurement method [33,40]. The rectangular or circular cavity perturbation methods require small sample volume that is much smaller than the physical dimension of the cavity. This is because the effect of introducing a sample into a cavity is treated by the first order perturbation theory for resonant frequency and quality factor calculations. The CP of cells at high frequencies is computed and deduced by measuring the resonant center frequency and the quality factor for the cavity with and without the cells. The measurement is first performed with an empty glass capillary tube (low loss) inserted at the position of the maximum electric field and then with the same glass tube filled by cells. The volumes of the sample and the cavity are used in the calculation of CP of cells.

The principle of rectangular cavity perturbation method is obtained from the cavity resonance. Different modes can exist in the cavity depending on its dimensions. Basic formulas for CP calculation through rectangular cavity perturbation method are given by [2]:

$$\varepsilon' = \frac{V_C(f_C - f_S)}{2V_S f_S} \tag{2}$$

$$\varepsilon'' = \frac{V_C}{4V_S}\left(\frac{1}{Q_S} - \frac{1}{Q_C}\right) \tag{3}$$

where V_C and V_S represent the volumes of the cavity and the sample respectively, f_C, Q_C, f_S and Q_S are the resonant frequencies and quality factors of the cavity without and with the sample, respectively. At microwave frequencies, conductive loss of a material is negligible compared to its dielectric loss. Therefore, the dielectric properties of the material at microwave frequency depend mainly on dielectric constant and dielectric loss. Several researchers developed different mathematical approximation relating the CP of a mixture (particle and media) to the particle and media individual CP. The Maxwell and Garnett mixing formula for spherical particles, much smaller than the wavelength of a uniform electric field, in an homogenous media, is given as [41]:

$$\varepsilon^*_{eff} = \varepsilon^*_m + 3v_f\varepsilon^*_m \frac{(\varepsilon^*_p - \varepsilon^*_m)}{(\varepsilon^*_p + 2\varepsilon^*_m) - v_f(\varepsilon^*_p - \varepsilon^*_m)} \tag{4}$$

where ε^*_{eff}, ε^*_p and ε^*_m are mixture, particle and media CPs respectively, v_f represents the volume fraction of the particles. This equation is a good approximation for low volume fraction (less than 0.1). Bruggeman [42] has introduced another formula for densely packed particles in media which has been improved by Hanai [36] and is given by:

$$\frac{(\varepsilon^*_p - \varepsilon^*_{eff})}{(\varepsilon^*_p - \varepsilon^*_m)} = (1 - v_f)\left(\frac{\varepsilon^*_{eff}}{\varepsilon^*_m}\right)^{1/3} \tag{5}$$

Therefore, the CP of a single cell/particle can be calculated by measuring the CP of the mixture (cells/particles and medium).

3. Materials and methods

Different cancer cell lines are obtained from Henry C. Witelson Eye Pathology Laboratory and MUHC Melanoma Laboratory, McGill University (Montreal). Cells were maintained in RPMI 1640 (5% FBS and 1% penicillin) at 37 °C temperature. Cancer cell lines and WBC-Jurkat Clone E6-1 cells were prepared for testing before starting the measurements. Cervical cancer HeLa cell line, Prostate cancer PC3 cell line, MDA 231 breast cancer cell line, Uveal melanoma cell lines 92.1 and OCM are removed from the flasks using the standard adherent cell detachment protocol. The detached cells are counted and verified under the microscope to evaluate the average size of the cells and their viability. Cells were suspended in a D-PBS solution and centrifuged for five minutes at 1000 rpm to form a cell pellet. Attention is given to remove all the media after centrifugation. The volume of the pellet is measured and density of the mixture is calculated. The bulk form of cancer cells is sucked into 10 μl micropipette using a syringe pump. The CP of single cancer cell is calculated using equation 5 after measuring the CP of the mixture (pellet). Similarly, the CP of non-adherent white blood cells (WBC) was performed.

To reduce the measurement error, the microwave frequency network analyzer was set on to heat up for a period of one hour before starting the measurement. Ports 1 and 2 of the network analyzer were connected to the cavity. The calibrated network analyzer is set on transmission measurement mode (S21) with an output power level less than 0 dBm avoiding heating effect of cells.

A special code written in LabView™ was used to perform real time, and continuous measurement of CP in the range 2–4.5 GHz. The complete measurement set-up with the inserted capillary tube at the center of the WR284 cavity is shown in Fig. 1.

The measurement procedure of CP was performed as follows:

- An empty capillary tube was inserted at the geometrical center of the cavity and unloaded measurements of resonant frequency and quality factor was obtained for all odd modes (maximum electric field exists at the center).
- Suspended cancer cells were filled in the 10 μl micropipette capillary tube then inserted at the same location for measurements.
- The sizes of analyzed cells are between 10 and 30 μm. The diameter of capillary tube is 0.5 mm and the effective length is the width of the rectangular cavity of 3.4 cm.
- The measurement of loaded resonant frequency and quality factor for all odd modes were performed. The diameter of the capillary tube being very small, it was assumed that no evaporation is taking place during measurement.
- The value of CP was calculated based on Eqs. (2) and (3) in the range 2–4.5 GHz.
- The tests were performed at room temperature of 23 °C. Coupled thermometers were used to observe any change in the temperature during the measurements. No change in the temperature was observed.