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MEMS Based Diagnosis of Breast Cancer

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Abstract*: *Based on the fact that the chemical, geometrical and other biophysical characteristics effect the electrical response of cells and tissues, a sensor is proposed which could be utilized for diagnosis and treatment of breast cancer as an economic and easy to use sensor. Endeavor has been made to model an in vitro sensor for early diagnosis of breast cancer considering sample data of normal breast cells (MCF-10A), less invasive cancer breast cells (MCF-7 & T47D) and highly invasive cancer breast cells (MDA-MB-231 & HS-578T). The simulation is done in COMSOL Multiphysics environment to find the impedance and capacitance of the cells with and without culture medium so as to characterize the types of cells. It is found that the impedance decreases sharply from 0.2 to 1 GHz and the normal breast cells could be distinguished from their cancer counter parts by comparing their electrical impedance and capacitance within the given frequency range. Apart from distinguishing normal breast cells from their cancer counterparts, the types of breast cancer cell types could also be determined by the differences in their frequency responses.

Keywords: Breast cells, capacitance, COMSOL, impedance, MEMS.

I. INTRODUCTION

Breast cancer is the second largest cancer known till date. Its early diagnosis is related to fast recovery and high survival rate. The chemical, geometrical and other biophysical characteristics of cells and tissues effect their electrical response. As the size of biological cells and tissues are in micrometers, MEMS are most suitable for biological applications. MEMS, the acronym of "Micro Electro Mechanical Systems", are generally considered as micro systems consisting of micro mechanical sensors, actuators and microelectronic circuits integrated in a single chip. The fabrication process of MEMS is majorly adopted from the fabrication process of ICs [1]. The application of BIOMEMS is rapidly increasing due to its microstructure and capability of handling micro integrated multiple units like sample collection, sample preparation, microfluidic components and sensing system, etc. in one chip [1]. The time consumption and complexity of traditional system has been rectified by BIOMEMS. There are many structures and shapes for realization of MEMS device as per the requirement. The one chosen for the work is interdigitated electrodes (comb structure). In interdigitated electrodes, the impedance/ resistance across the electrodes shall be infinity without any material/ sample in between the electrodes.

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But if any material is deposited on it, a change in impedance and capacitance could be monitored. Till date, bio impedance measurement has been used for a number of application in the field of cellular technology.

Bio impedance measurement is a promising, label-free means of monitoring biological cells and their responses to physical, chemical and biological stimuli.

Breast cancer is the second most common type of cancer among women in the world and tends to become the first with the present statistics [2]. Although significant progress has been made in diagnosis and treatment of this disease, there is a need for robust, user friendly technologies that can be used for the identification and discrimination of critical subtypes of breast cancer in patients.

Impedance spectroscopy has been an extremely useful tool in rapid and non-invasive method of diagnosis of physical materials and their physical as well as chemical changes [3]. The increased water content of the cancer cells and tissues enable the use of high frequency in distinguishing normal cells and tissues from their cancer counterparts [4]. The changes in the cellular electrical response is being utilized in the present work for discriminating normal breast cells from less invasive as well as highly invasive breast cancer cell types.

Biological tissues are heterogeneous and show frequency dependent variation in permittivity [3]. The basic criterion for bio-impedance based study is the change in dielectric behavior of the cells/tissues and hence the impedance in response to the ac electric field. Impedance, which is given as the ratio of electric potential to current, is expressed in ohms and can represent the magnitude as well as the phase difference between the electrical potential and current. Alternating voltage is expressed in classic form of sinusoidal waveform as:

$$V = V_m \sin \omega t$$

and the resulting current flowing through the circuit is given as:

$$I = Vm/Z$$

where I, V and Z are phasor quantities, which means that they are represented in both magnitude and direction. This implies that there is phase difference between these quantities. The term 'Z' is called impedance. The ratio of component of current which is in phase with voltage gives the real component of impedance and that which is in phase displaced, gives the imaginary component of impedance. It is, thus, a complex number and represented as:

$$Z = Re(Z) + j\, Im(Z)$$

where 'j' is unit imaginary number.

The real component of impedance is resistance and resistance is independent of the frequency but imaginary part is mainly due to capacitance, which is frequency dependent [4, 5]. The ions in cells are basically the conduction channels.

Different cells have different ionic content and mobility [6]. Thus cells can be characterized by conductivity and permittivity where ionic mobility is expressed as the conductivity and dielectric properties are expressed as the permittivity. Permittivity describes the ability of a material to resist the flow of current through it. Hence, the impedance could be related to the conductance and the permittivity of the cells. The conductivity and permittivity are both dependent on frequency and with increase in frequency the permittivity decrease [7, 8]. The permittivity is basically related to the extent to which the bound charges of the cells and tissues are displaced or polarized under the influence of an electric field [7]. The change in this behavior of cells and tissues is not instantaneous and exhibit complex dielectric form. The exposure of biological cells and tissues to high frequency input causes energy storage due to dipole polarization and energy dissipation when the dipoles do not align instantly with the varying field [4]. This behavior of biological cells is utilized in dielectric spectroscopy. The relative permittivity is, therefore, a function of frequency and is expressed in complex form as:

$$\epsilon = \epsilon' - j\,\epsilon''$$

where ϵ' is the real part representing the energy storage and ϵ'' is the imaginary part representing loss with j being a complex number and $j = \sqrt{-1}$

There are mainly three dispersion mechanisms α, β, γ based on the frequency response of cell suspensions on the application of electrical field as described by Schwan. The α-dispersion is significant over the frequency range of 10 Hz–10 kHz. This influences the ions or extracellular factors outside cells because of the increased reactance offered by the cellular membrane capacitance. The α-dispersion is characterized by the very large permittivity values produced by diffusion processes at the site of the cellular membrane at very low frequencies. From 0.1MHz to 10 MHz, the current is able to pass through the cell membrane and cytoplasm because the cell membrane acts as a capacitor and capacitive reactance decreases with increase in frequency, which causes the β-dispersion to occur. β-dispersion is affected by the changes of the cell membrane. The β-dispersion is mainly due to the polarization and charging of cell membranes, which separates the conducting extracellular medium and the cytoplasm. The membrane structure blocks ion movement under an external electric field, preventing the flow of ions between the intra and extracellular media. When the frequency is between 100MHz to some GHz, γ-dispersion occurs due to the internal structure of the cells that is the nuclear envelope, membrane of organelles and water concentration in each cell. As most of the soft tissues have water as the main component, γ-dispersion is very important in the study of dielectric properties of the biological tissues. The bioelectrical characteristics has been utilized in designing a MEMS based sensor for diagnosis of cancer in breast cells.

II. METHODOLOGY

The MEMS planar interdigitated electrode sensor is modelled and simulated in COMSOL Multiphysics software tool version 5.4 with Finite Element Method (FEM) for electric field and current density distribution. FEM is capable of handling the complexities of biological cells with higher accuracy [9]. The study discretization of Electric potential is Quadratic (Lagrange). The sensor is surrounded by air and is modelled on a glass substrate. There are six number of gold electrodes each having width of 120 µm and the gap between two electrodes being 10 µm. The thickness of the glass substrate is 200 µm and that of the electrodes is 0.5 µm. The electrode effective length is 130µm. The thickness of the material used (cell solution) above the sensor surface is 100µm, which is less than twice of the effective length. The structure of the sensor modelled in COMSOL is shown in Figure 1.

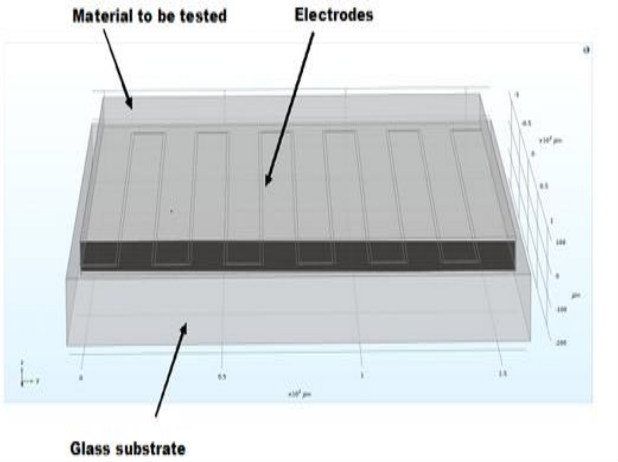

Fig. 1. IDE 3-D structure with dimensions

The impedance between the electrodes without medium is infinity. As soon as the solution is placed on the sensor the impedance could be traced. This impedance is owing to the electrochemical properties of the solution with different cell concentration and status along with biomolecules coming in vicinity of the electrodes. The property of the medium is related to the electric displacement 'D' and the electric field 'E'. Since the high frequency input is applied, it has been made considering the dielectric loss components.

The flux density or electric displacement 'D' is expressed in terms of electric field 'E' and dielectric loss parameters as

$$D = \epsilon_0(\epsilon' - j\epsilon'')E$$

Where ε' represents the energy stored by dipole polarization due to applied field, ε'' represents the dielectric loss when the dipoles do not align instantly with the changing field and ε0 represents the permittivity of the free space. The values of ε' and ε'' parameters are taken for the material (breast cells), both normal and cancer cells [4]. The impedance and capacitance values are extracted from the model considering the simple alternating sinusoidal voltage current relation. The present study focusses on study of two different electrical parameters of the IDE, impedance and capacitance, based on the dielectric characteristics of the given cells with and without medium at a frequency range of 0.2 GHz to 14 GHz.

III. RESULT AND DISCUSSION

The frequency was varied from 0.2 to 14 GHz and the potential distribution across the electrode was observed to be continuous and periodic throughout the frequency range with and without the sample.

The image at two different frequencies of 7 and 10 GHz are shown in figure 2 (a) & (b) respectively. The potential distribution has been observed for the whole range of frequency under consideration.

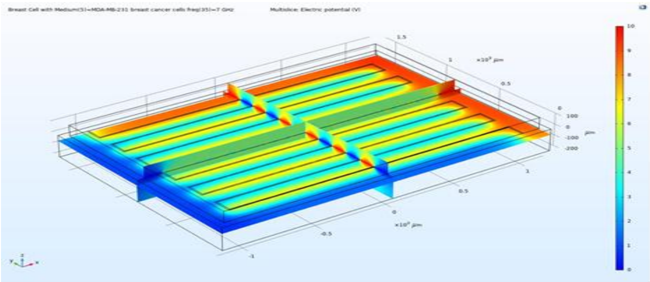

Fig. 2. (a) Potential Distribution across the sensor electrodes at 7 GHz

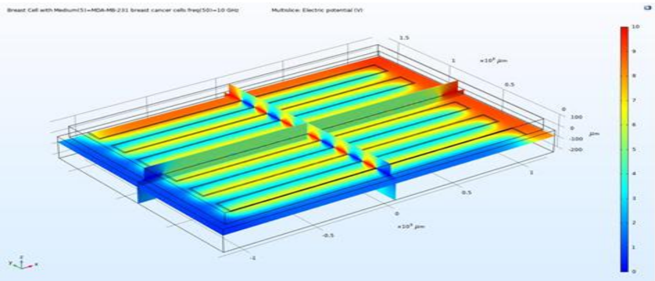

Fig. 2. (b) Potential Distribution across the sensor electrodes at 10 GHz

The impedance characteristics of breast cell samples was studied with the same structure of sensor and the result obtained is shown in figure 3. The impedance (in Ω) characteristics reveal that the impedance of normal cells and cancer cells drops sharply from 0.2 GHz to 1GHz. This signifies that the cellular membrane potential barrier offers almost negligible opposition to the flow of current in γ-dispersion range of frequency. Hence the intracellular information could be extracted in the given range and the intracellular electric properties are predominant at this range. This also signifies the importance of impedance measurement and diagnosis of cell status for the given sensor. The dielectric behavior of the intracellular material was observed by deriving the capacitance of the specified breast cells with and without culture medium. The dielectric behavior of water (being the major component of biological tissues) contributes mainly to the changes in electrochemical behavior and hence the capacitance of cells at this frequency spectrum. The capacitance (in pF) derived from the simulation is given in figure 4. The capacitance frequency response reveals an explicit difference in the capacitance of normal cells with their cancer counterparts.

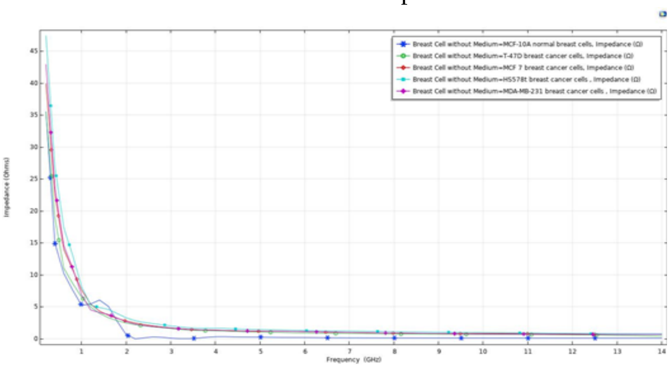

Fig. 3. Impedance characteristics of breast cells without medium

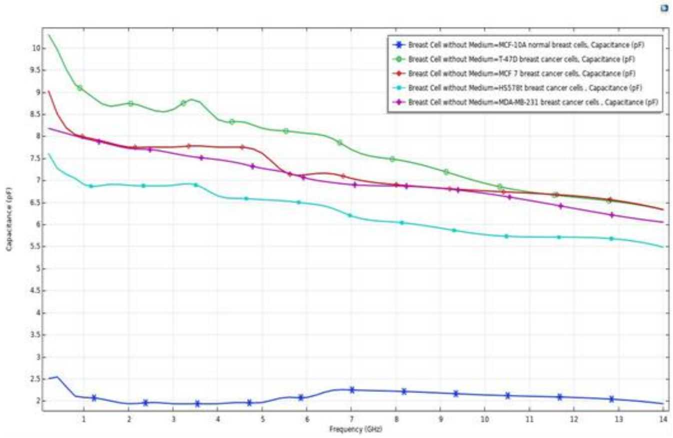

Fig. 4. Capacitance of breast cells without culture medium

The capacitance of normal cells exhibits considerable reduced values than the capacitance of cancer cells for the given range of frequency. As revealed from the capacitance frequency response in the given frequency spectrum, the gap between the capacitance characteristics of the normal and their cancer counterparts is highest between the frequency ranges of 1.3 to 4.7 GHz. Moreover, the different types of cancer cells exhibit different capacitance characteristics and could be distinguished from each other.

The impedance characteristics, with the simulation results from the sensor output obtained, shows that the impedance of normal breast cells are lower than their cancer counterparts. This output is validated by a number of other practical experiments done on the breast cells [10, 11, 12, 13] for frequency ranges in β-dispersion and lower range of γ dispersion with other methods. The impedance of the cells is also dependent on cell concentration [20]. This is related to the increased concentration of the cells in malignancy as compared to the normal cell concentration.

When treated with culture medium, the impedance of normal cells is higher than that of their cancer counterparts for lower frequency range (up to 6 GHz) and then decrease for the remaining range of frequency within the given frequency spectrum. Few previous practical studies based on both β- dispersion range and γ-dispersion range with other methods show similar characteristics [11, 14, 15, 16, 2, 17]. Though, the difference in the impedance characteristics show a little demarcation for the given breast cells. This is owing to the fact that the material has been modelled for dielectric parameters and this may be one of the reason why we have this ambiguity. In spite of all these, the difference in impedance characteristics between normal and cancerous cells could be seen from the results obtained by the proposed sensor and is still an important parameter for distinguishing the normal breast cells with their cancer counterparts.

As we are dealing with the higher frequency range, the capacitance characteristics obtained from the result show the intracellular capacitances of malignant cells which are much higher than that of the normal cells (figure 4). This is owing to the fact that the dielectric properties of cells play major role in the γ-dispersion range and both, the dielectric constant and dielectric loss of cancer breast cells are higher in cancer breast cells than the normal breast cells [4, 18, 19].

This may be due to the increased water content present in the cancer cells. This is because cells are mainly having water as their constituent and different extent of water content imply to different change in concentration of biomolecules. In γ-dispersion range, the dielectric strength of the cell membrane decreases and allows the electric waves to penetrate into the cell, thereby decreasing its capacitance with increase in frequency. This difference in intracellular capacitance of normal breast cells and the specified breast cancer cells is very prominent and could be employed for discriminating normal breast cells with the malignant ones under consideration. Hence, on the basis of capacitance characteristics, the proposed sensor could be employed for detection for breast normal cells from their cancer counterparts. It is noteworthy that the decrease in capacitance with increase in frequency is consistent in case of normal cells but showed marked differences for cancer cells. Moreover, the variation of capacitance characteristics for different types of cancer cells showed significant difference. The characteristics showed variation in capacitance response between 4 to 7GHz, after which there was a decline in their capacitance with increase in frequency. While this transition takes place for all the cancer cell types between these frequency ranges, the frequency at which this transition takes place is different for different cell types. As such, types of breast cancer could also be deduced from the cells with different transition characteristics.

IV. CONCLUSION

In this paper we had model an in vitro sensor for early diagnosis of breast cancer considering sample data of normal breast cells (MCF-10A), less invasive cancer breast cells (MCF-7 & T47D) and highly invasive cancer breast cells (MDA-MB-231 & HS-578T). The simulation has been done using COMSOL Multiphysics environment for the cells with and without culture medium. It is found that the impedance decreases sharply from 0.2 to 1 GHz and the normal breast cells could be distinguished from their cancer counter parts by comparing their electrical impedance and capacitance within the given frequency range.

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