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MEMS-BASED CHARACTERIZATION OF BREAST CANCER CELLS AND COLON CANCER CELLS

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Abstract

The study of electrical characteristics of cells based on their biophysical properties, and their relevance with their status, has been a very useful non-invasive tool for disease diagnosis and treatment. A MEMS device is modelled and simulated for characterizing the electrical behavior of a type of breast cancer cells and colon cancer cells. The sample of highly invasive breast cancer cells (Hs 578T) was compared with the HT-29 colon cancer cells in the frequency range of 1 to 13 GHz. It is found that the rate of change of capacitance of the given colon cancer cells is less than that of the given highly metastatic breast cancer cells. This shows the difference in electrical characteristics of cells with different cell types and could be a basis for discriminating cell types and related metastasis.

Keywords: MEMS, capacitance, breast cancer cells, colon cancer cells.

I. Introduction

The biophysical characteristics of cells have played a major role in the diagnosis of various diseases including cancer [XVI]. Cancer is a deadly disease and is mainly due to genetic abnormalities originating in a cell or group of cells. Such cells lack the normal signaling track and hence do not respond partially or fully to the normal signaling. They start multiplying uncontrollably and form bulk cancerous tissues. They can be categorized as breast cancer, lung cancer, skin cancer, and so on, based on the cells in which they originate. Metastasis, which results in the spread of cancer to various parts of the body, introduces a new dimension to different types of cancer (lung cancer, breast cancer, ovarian cancer, prostate cancer, melanoma, etc) needing different treatments. Early diagnosis of cancer helps in effective treatment and reduced the mortality rate. In normal cells, the inner cellular area has more concentration of potassium, and the outer cellular area has more sodium concentration [VIII, IX]. As the cell membrane is selectively permeable to sodium and potassium ions, a different concentration of these ions and other charged mineral ions will build up on either side of the membrane. The different concentrations of these will cause the outer surface to have a relatively higher positive charge than the inner membrane surface and create an electrical potential difference across the membrane [I]. Cancer cells have altered membrane composition and membrane permeability, which results in the movement of potassium, magnesium, and calcium out of the cell and the accumulation of sodium and

water into the cell [XXIII, V]. As a result of these mineral movements, membrane composition changes, leading to energy abnormalities and membrane charge distribution abnormalities, and there occurs a decline in the normal electronegative membrane potential [V, VI, VII, X]. The depolarization (fall in membrane potential) of the cancer cell membrane due to the accumulation of excess negative surface charges may precede and create the reduction in intracellular potassium and the rise in intracellular sodium ions [XI]. Membrane degeneration occurs in the initial phase of carcinogenesis first in the external cell membrane and then in the inner mitochondrial membrane and these degenerative changes in the surface membrane causes these membranes to become more permeable to water-soluble substances so that potassium, magnesium, and calcium migrate from the cells and sodium and water accumulate in the cell interior. The degenerative changes in the inner membrane of the mitochondria cause loss of storage of critical mitochondrial enzymes, due to which, mitochondria cancer cells degenerate [XV]. Two of the most outstanding electrical features of cancer cells are that they constantly maintain their membrane potential at a low value and their intracellular concentration of sodium is of high magnitude [V-VII]. This sustained elevation of intracellular sodium may act as a mitotic trigger causing cells to go into cell division (mitosis) [V].

Microfabricated biosensors utilizing electrical, mechanical, piezoelectric, and acoustic signal transduction mechanisms have been developed over the years. 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, sensing system, etc. in one chip. . There are many structures and shapes for the realization of MEMS devices as per the requirement. The one chosen for the present work is interdigitated electrodes (comb structure) type. In interdigitated electrodes, the impedance/resistance across the electrodes shall be infinite without any material/ sample in between the electrodes. But if any material is deposited on or in between it, a change in impedance could be monitored.

Biological tissues are heterogeneous and show frequency-dependent variation in permittivity [IV]. There are three dispersion mechanisms α, β, and γ as the frequency response of cell suspensions which is shown in *Figure 1*.

The basic criterion for the bio-impedance-based study is the change in dielectric behavior of the cells/tissues and hence, the impedance in response to the a.c. electric field.

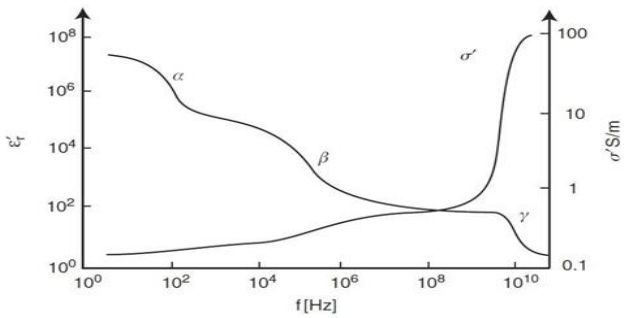

Fig. 1 α, β and γ dispersions of cells [XXI, XIII, XIV]

Impedance, which is given as the ratio of electric potential to electric current is expressed in ohms and can represent the magnitude as well as the phase difference between the electrical potential and current. An alternating voltage is expressed in the classic form of the sinusoidal waveform as:

$$V = V_m sin\omega t \tag{1}$$

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

$$I = V_m/Z \tag{2}$$

where I, V, and Z are phasor quantities, which means that they are represented in both magnitude and direction. This implies that there is a phase difference between these quantities. The term 'Z' is called impedance. The ratio of the 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:

$$Z = Re(Z) \pm j\, Im(Z) \tag{3}$$

where 'j' is a unit imaginary number

The ions in cells are basically the conduction channels. Different cells have different ionic content and mobility [XXII, II]. 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 an increase in frequency the permittivity decreases while the conductivity increases [XII, XV]. The permittivity is 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 [XII]. The change in this behavior of cells and tissues is not instantaneous and exhibits a 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 [XVIII]. 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:

$$\varepsilon = \varepsilon' - j\, \varepsilon'' \tag{4}$$

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=√-1

$$\varepsilon'' = \sigma/\omega_0 \tag{5}$$

where 'σ' is the electrical conductivity, 'ω' is the angular velocity=2*π*f with 'f' as frequency, and ω_0 is the free space permittivity [XVIII].

The vast difference in the dielectric properties of biological cells and tissues, in the range of frequency from 1Hz to 100GHz, makes them an important basis of differentiating the cell status with electrical stimuli [XXIV]. The frequency response of permittivity of dielectric materials with polarization is shown in *Figure 2*.

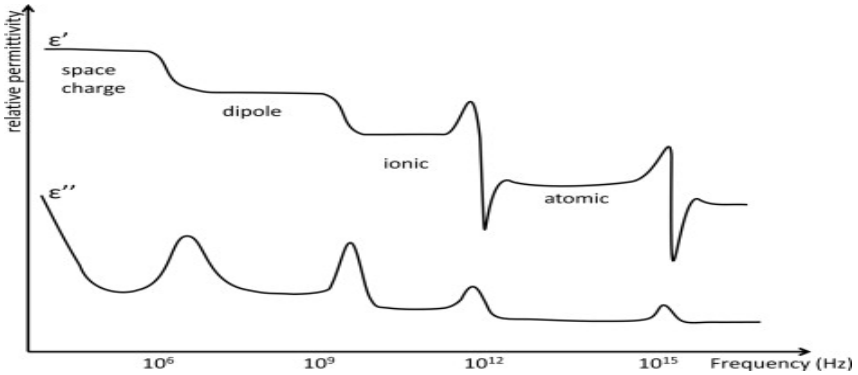

Fig 2. Frequency response of permittivity of materials [22]

When the frequency is between 100MHz to some GHz, γ-dispersion occurs due to the internal structure of the cells which is the nuclear envelope, the membrane of organelles, and water concentration in each cell [XIV, XXIV, XIX, XX]. As most soft tissues have water as the main component, γ-dispersion is very important in the study of the dielectric properties of biological tissues.

Since biological cells have both hydrophobic and hydrophilic parts, they exhibit dielectric properties which have relevance to the electrical field and applied frequency. Depending on the cell status, they respond correspondingly to the range of input frequency and exhibit α, β, and γ dispersion with the change in permittivity for different ranges of frequencies.

II. Methodology

The MEMS planar interdigitated electrode sensor is modeled 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 [XVII]. The study of discretization of Electric potential is Quadratic (Lagrange). The sensor is surrounded by air and is modeled on a glass substrate. There are six numbers of gold electrodes. The electrode's effective length is 130μm. The thickness of the material used (cell solution) above the sensor surface is less than twice the effective length. The 3-dimensional view of the device is shown in *Figure 3*.

The impedance between the electrodes without a medium is infinite. 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 concentrations and statuses along with biomolecules coming in the vicinity of the electrodes. The property of the medium is related to the electric displacement 'D' and the electric field 'E'. The flux density or electric displacement 'D' is expressed in terms of electric field 'E' and dielectric loss parameters as:

$$D = \varepsilon_0(\varepsilon' - j\varepsilon')E \quad (6)$$

where ε' represents the energy stored by dipole polarization due to the applied field, ε" represents the dielectric loss when the dipoles do not align instantly with the changing field and ε_0 represents the permittivity of the free space. The values of ε' and ε" parameters are taken for the materials (sample of highly invasive breast cancer cells Hs 578T and HT-29 colon cancer cells).

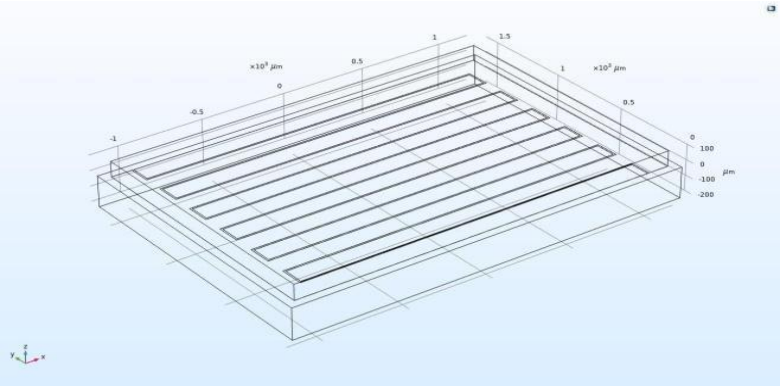

Fig 3. IDE 3-D structure with dimensions

The capacitance values are extracted from the model considering the simple alternating sinusoidal voltage-current relation based on the dielectric characteristics of the given cells with and without medium at a frequency range of 1 GHz to 13GHz.

III. Results

The potential distribution across the electrode is observed to be continuous and periodic throughout the frequency range with and without the sample. The images at two different frequencies of 7 and 10 GHz are shown in Figures 4.1 & 4.2 respectively. The potential distribution has been observed for the whole range of frequency under consideration.

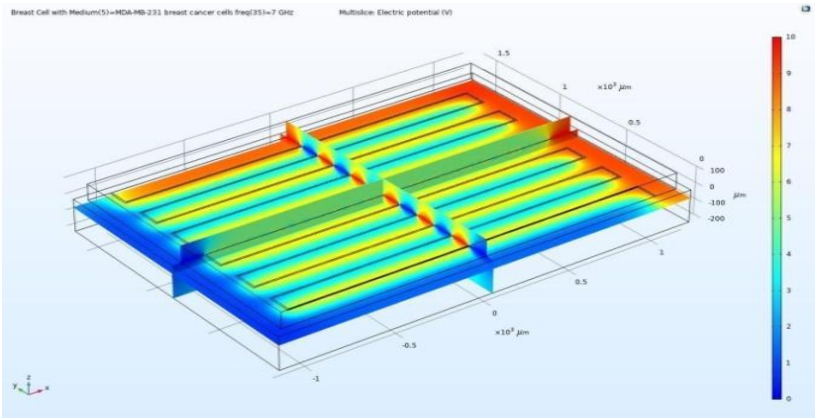

Fig 4.1. Potential Distribution across the sensor electrodes at 7GHz

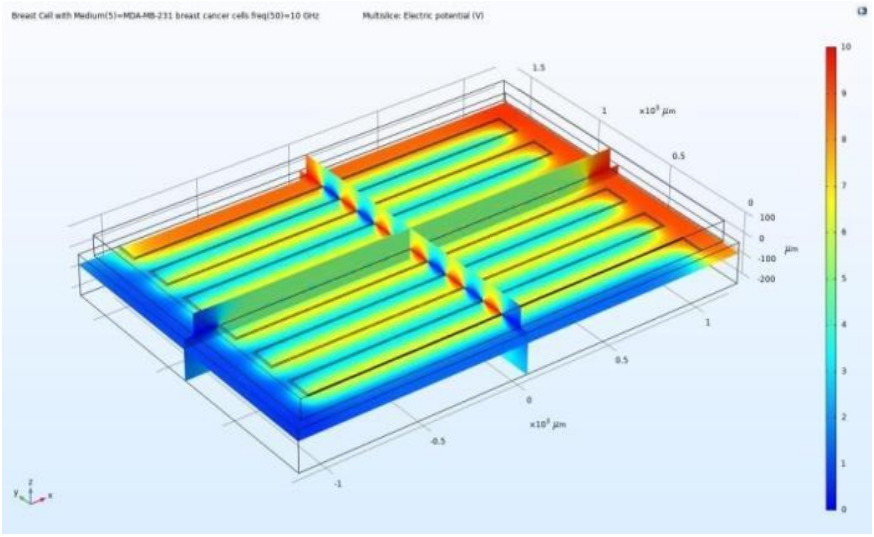

Fig 4.2. Potential Distribution across the sensor electrodes at 10GHz

The capacitance of the specified cell samples is derived from the modeled device and simulated to get the capacitance characteristics of both samples. The capacitance (in pF) derived from the simulation for both the samples with and without medium are compared and given in Figure 5.1 and Figure 5.2 respectively.

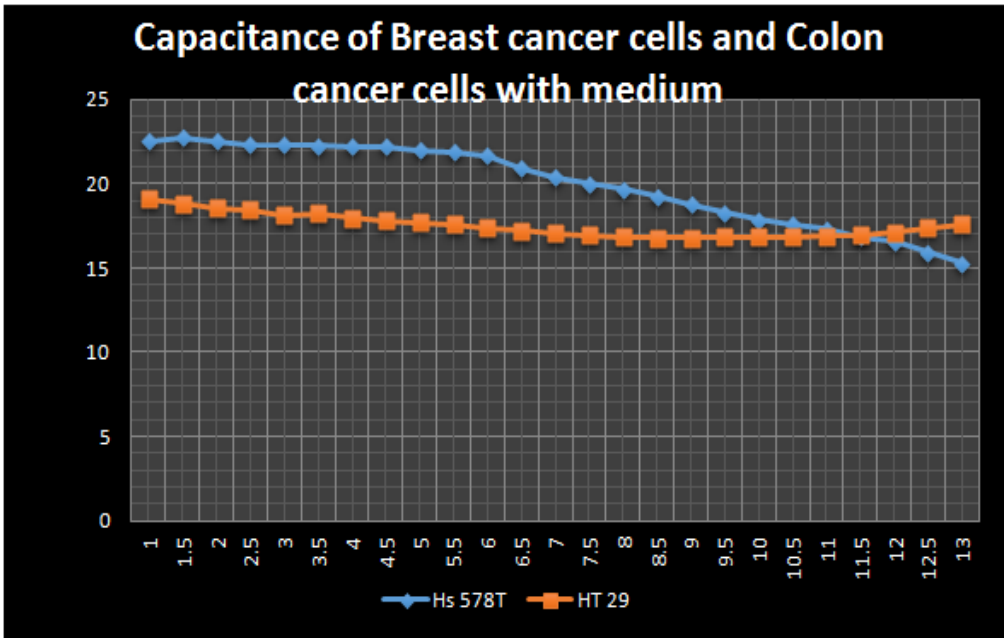

Fig 5.1. Comparison of Capacitance of Breast cancer cells Hs 578T and colon cancer cells HT 29 with medium

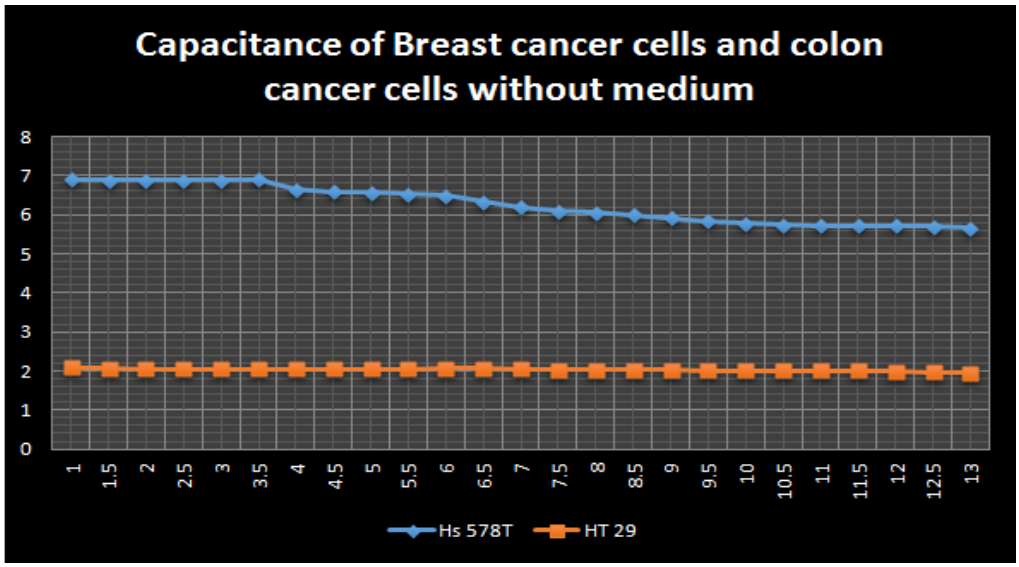

Fig 5.2. Comparison of Capacitance of Breast cancer cells Hs 578T and colon cancer cells HT 29 without medium

The capacitance values for both the cases, with and without medium, show that these values are higher for breast cancer cells (Hs 578T) than that for colon cancer cells (HT-29) under consideration.

IV. Discussion and Conclusion

The comparison of both types of cancer cells reveals the fact that different cell types have different electrical characteristics. The capacitance characteristics of breast cancer cells Hs578T and colon cancer cells HT-29, both with and without medium, were derived from the same sensor and the response obtained shows a significant difference in the capacitance characteristics of both the cancer cells with and without a medium. The capacitance characteristics of the cells show considerably reduced values for colon cancer cells than that of breast cancer cells for a wide range of frequencies. The variation of capacitance is also less in colon cancer cell lines than that of the breast cancer cell lines, both with and without a medium.

These characteristics reveal the explicit difference in the two cell types based on their respective electrical characteristics. The colon cancer cellular membranes are more resistant to changes with changes in frequency as compared to that of the breast cancer cells, showing the decreased impact of increased frequency on the given colon cancer cells. Also, there is a marked flex point in the capacitance characteristics of breast cancer cells, mainly after 6GHz, after which the rate of decrease in the capacitance value is high. In colon cancer cell response, the decrease in capacitance is a smooth curve which shows the sustainability of the membrane. The capacitance values for the cell types are much lower without medium, showing the influence of medium capacitance on the overall characteristics. But the respective difference in both the cell types is almost the same, revealing higher resistance of the specified colon cancer cell type than that of the given breast cancer cell type. The proposed sensor could be exploited for discriminating the cell types and could provide information on the level of sustainability of respective cell types based on their capacitance characteristics.

The present analysis suggests that each type of cancer cell line has different electrical characteristics and this property could be utilized for biomedical applications including cell type detection and identification. It also signifies different procedures for targeting these two different cell types based on their sustainability to resist external changes.

Conflict of Interest:

The authors declare that no conflict of interest to report the present study.

References

I. Aidley D. J., Stanfield P. R., "Ions on the move", in Ion Channels: Molecules in Action, Cambridge, UK, Cambridge University Press, 1996.

II. Allison Timothy M. and Landreh Michael, Ion mobility in Structural Biology, Comprehensive Analytical Chemistry, Vol.83, 2019, pp.161-195.

III. Asami K., "Dielectric spectra of biological cells and tissues simulated by three-dimensional finite difference method", ICEBI, IFMBE Proceedings book series, Springer, Vol.17, 2007, pp. 98-101.

IV. Bhura Dhiraj Kumar, "3D Interdigitated Electrode Array (IDEA) Biosensor For Detection Of Serum Biomarker, M.S. Thesis, Electrical and Computer Engineering, Portland State University, USA, 2011.

V. Cone Clarence D., "Unified Theory on the Basic Mechanism of Normal Mitotic Control and Oncogenesis" in Transmembrane Potentials and Characteristics of Immune and Tumor Cells, 1st edition, Boca Raton, Florida, CRC Press, Taylor & Francis Group, 1985.

VI. Cone C. D., "Variation of the transmembrane potential level as a basic mechanism of mitosis control", Oncology, International Journal of Cancer research and treatment, Vol. 24, Issue 6, 1970, pp. 438-470.

VII. Cone C. D., "The role of surface electrical transmembrane potential in normal and malignant mitogenesis", Annals of New York Academy of Sciences, Vol. 238, pp. 420-435, 1974.

VIII. Cooper Geoffrey M., "Molecules and Membranes" & "The Plasma Membrane", in The Cell: A Molecular Approach, Eighth edition, Sinauer Associates, Sunderland, New York, Oxford University Press, 2019.

IX. Cope Freeman W., "A medical application of the Ling Association-Induction Hypothesis: The high potassium, low sodium diet of the Gerson cancer therapy", Physiological Chemistry and Physics, Vol.10, No.5, 1978, pg. 465-468.

X. Cope Freeman W., "A medical application of the Ling Association-Induction Hypothesis: The high potassium, low sodium diet of the Gerson cancer therapy", Physiological Chemistry and Physics, Vol.10, No.5, pp. 465-468, 1978.

XI. Cure J. C., "Cancer an electrical phenomenon", Resonant, Vol.1, No.1, 1991.

XII. Dean D.A., Ramanathanb T., Machadoa D., Sundararajana R., "Electrical impedance spectroscopy study of biological tissues", Journal of Electrostatics, Vol.66, 2008, pg 165-177.

XIII. Dorey A. Robert, "Microstructure- property relationships", in *Ceramic Thick films for MEMS and Microdevices*, First edition , Elsevier, USA, 2011.

XIV. Duan Wei, "Cell impedance of cancer cells: towards novel diagnostic and therapeutic selection methods", M. Phil thesis, School of life sciences, University of Sussex, England, January 2013.

XV. Grimnes Sverre and Martinsen Orjan, "Passive Tissue Electrical Properties", Bioimpedance and Bioelectricity Basics, 3rd edition, Academic Press, United States, 2014.

XVI. Guyton Arthur C. and Hall J.E., "Functional organization of Human Body and Control of the Internal Environment", in Textbook of Medical Physiology, Twelfth Edition, Saunders, Elsevier, USA, 2011.

XVII. Huclova Sonja, "Modeling of Cell Suspensions and Biological Tissue for Computational Electromagnetics", PhD Thesis in Chemistry, ETH Zurich, Switzerland, 2011.

XVIII. Mousa Hussein, Falah Awwad, Dwija Jithin, Husain El Hasasna, Khawlah Athamneh & Rabah Iratni, "Breast cancer cells exhibits specific dielectric signature in vitro using the open-ended coaxial probe technique from 200 MHz to 13.6 GHz", Scientific Reports, Nature, Vol.9, Issue 1, 4681, March 2019.

XIX. Muhammad Asraf Mansor , Masaru Takeuchi , Masahiro Nakajima , Yasuhisa Hasegawa and Mohd Ridzuan Ahmad, "Electrical Impedance Spectroscopy for Detection of Cells in Suspensions Using Microfluidic Device with Integrated Microneedles", Applied Sciences, Vol.7, issue 2, 170, February, 2017.

XX. Muhammad Asraf Mansor and Mohd Ridzuan Ahmad, "Single Cell Electrical Characterization Techniques", International Journal of Molecular Sciences, Vol.16, 2015, pg. 12686-12712.

XXI. Nasir Nida and Ahmad Mahmoud Al, "Cells Electrical Characterization: Dielectric properties, Mixture and Modeling Theories", Hindawi Journal of Engineering, Vol 2020, article id 9475490, 2020.

XXII. Qiao G, Duan W, Chatwin C, A Sinclair and W Wang, "Electrical Properties of Breast cancer cells from impedance measurement of cell suspensions, Journal of Physics, Vol 224(1), 012081, 2010.

XXIII. Revici Emanuel, "Biological Entities", in Research in Pathophysiology as Basis for Guided Chemotherapy, with Special Application to Cancer, Princeton, New Jersey, New York, USA, D. Van Nostrand Company, 1961

XXIV. Schwan H.P. and Takashima Shiro, "Dielectric Behavior of Biological cells and Tissues", Bulletin of the Institute for Chemical Research, Kyoto University, Vol.69, No.4, pg. 459-475, 1991.

XXV. Stern R. G., "Carcinogenesis and the plasma membrane", Medical Hypotheses, Vol. 52, No.5, May 1999, pp. 367-372.