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Determination of Malignancy in Leukocytes with Micro Capacitive Sensor

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Abstract—*The paper presents a non-clinical method for the detection of cancerous cells in a given sample of leukocytes using MEMS capacitive sensor on the basic of dielectric permittivity. In case of malignancy, it has been observed that the dielectric permittivity of malignant White Blood Cell (WBC) is lesser than the healthy cells, as a result, a change in capacitance is reflected by the proposed sensor. The present work follows electrophoresis method where the blood cell plasma membrane is polarized to a transmembrane potential of about 0.5-1V with a supply of 1V which makes plasma membrane semi permeable in nature thus, producing a change in dielectric permittivity. In order to determine the polarized potential, a double shell electrical model of WBC is considered and analyzed in frequency range 20 kHz-10MHz. For this purpose, a MEMS capacitive sensor is fabricated virtually with a pair of rectangular electrodes in a FEM based platform. This change in dielectric permittivity consequences to change of output capacitance. The proposed sensor can accommodate on an average of 1000 cells at a time.*

Keywords*: Blood Cancer, Dielectric Permittivity, Cell Membrane, Electrical Model, Simulation, Electroporation,Polarization, MEMS, Electrostatic Capacitive Sensor.*

1. INTRODUCTION

Cancer also known as a malignant or cancer neoplasm involves unregulated cell growth. In cancer, cells divide and grow unusually, forming malignancy and invade nearby parts of the body [1]. According to 2014 World Cancer Report, there are 8.2 million cancer caused deaths with 14 million new cases in 2012 [2], therefore, early detection can considerably diminish the percentage of death due to cancer.

In case of malignancy, it has been observed in many published literatures that cancerous cell have lesser dielectric permittivity compared to normal one, therefore, detection of blood cancer can be done on the bases of dielectric permittivity [3-6]. In MEMS level, the standard method used for the detection of cancerous cell dielectric permittivity are (I) Electrophoresis, (II) Time Domain Dielectric Spectroscopy (TDDS) and (III) Electrorotation, whereas the most well-known technique is electrophoresis. Electrophoresis process can identify the change in dielectric permittivity of cell membrane in a range of frequency between 20 kHz-10MHz (called the β-dispersion)[3-5]. In TDDS technique, the dielectric permittivity of the cell is obtained by analyzing the response of the given sample according to the rising pulse of applied voltage. The drawbacks of TDDS method is development of electrical double layer and electrode polarization [4, 5] while the realization of electrorotation procedure is costly and difficult. The work deals with electrophoresis process and virtual fabrication of micro capacitive sensor for the detection of malignancy in leukocytes. Electrophoresis process depends on the polarization of cell membrane of a cell with an applied voltage of suitable magnitude and duration, thus inducing a transmembrane potential of about 0.5-1V in cell membrane making it porous for the exchange of electrons and ions, furthermore changes the dielectric permittivity of the sample.

This paper briefly explains the electrical modeling of leukocyte in Section 2 followed by section 3 describes the design of MEMS capacitive sensor. The two layer mask design and the virtual fabrication steps micro capacitive sensor are described in section 4 and section 5 provides results and discussion. Section 6 concludes with future scopes.

2. ELECTRICAL MODELING OF LEUKOCYTE

This segment illustrates an electrically model of leukocyte with respect to it double shell model, as the main consideration is to determine the transmembrane potential of a leukocyte and the desire magnitude and duration of applied voltage necessary for the polarization of cell. After getting acceptable outcome (verified with [6, 7]), the excitation voltage is considered as the primary parameters for the design and virtual fabrication of MEMS capacitive sensor. Figure 1 shows the electrical model of leukocyte with respect to it double shell model. The double shell model of leukocyte comprise of cytoplasm covering 60% cell volume confined by an external layer of cell membrane. In the electrical model, cell membrane is denoted by C_{m1} and C_{m2} with R_{cy} as cytoplasm, nuclear membrane and nucleolus as C_{nm1}, C_{nm2} and R_{nc}. Table 1 represents the numerical values of healthy blood cell structural parts [5-7]. The cell membrane act as a leaky dielectric due to the presence of lipid structure [7]. In electrophoresis method, cell membrane of a leukocyte is polarized with an applied voltage of 1V, as a result inducing a membrane potential of about 0.5V (threshold voltage for electroporation to occur) and above so that the pores in the cell membrane momentarily opens up for the exchange of ions and electrons [8, 9]. The equivalent impedance (Z) is represented Eq.1

$$Z = \frac{\omega^2 C_M R_{cy} C_{NM} R_n - R_{cy} - 1 - j\omega(C_{NM} R_n + C_M R_{cy})}{\omega^2 \mathrm{C_M C_{NM} R_n} - j\omega(1 + \mathrm{R_{cy}})\mathrm{C_M}}$$

(1)

Where $C_{m1} = C_{m2} = C_m$, $C_{nm1} = C_{nm2} = C_{nm}$, $\mathrm{C_M} = \frac{\mathrm{Cm}}{2}$

and $\mathrm{C_{NM}} = \frac{\mathrm{Cnm}}{2}$ and the cell natural frequency is $\omega_n = \sqrt{\frac{1+\mathrm{R_{cy}}}{C_M R_{cy} C_{NM} R_n}}$ (2)

Table 1: Arithmetical value of different structural parts of cell

C_{1m} (pF)	C_{2m} (pF)	R_{cy} (k)	C_{nm1}(pF)	C_{nm2}(pF)	R_{nplm}(k)
2.493	2.493	12.7	1.247	1.247	12.7

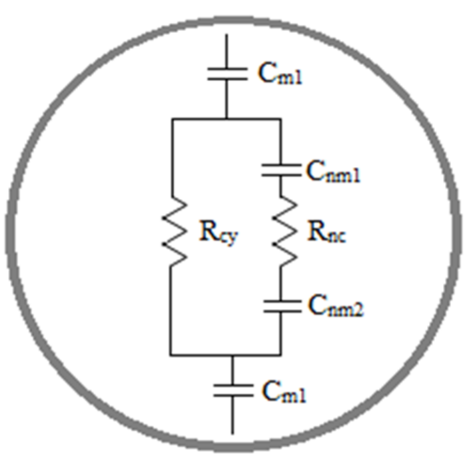

Fig. 1: Electrical modeling of Leukocyte

3. DESIGN OF MEMS CAPACITIVE SENSOR

An electrostatic micro capacitive sensor is virtually fabricated keeping cell thickness as 10 nm and radius as 3.5µm [6-8]. The sensor is planned or designed as comb geometry, where one side of the electrodes is connected to 1V supply while the other side is grounded. The space between the electrodes is to be filled with leukocyte sample for the detection of malignancy. The electrodes position, distance between them and the area of the electrodes are kept constant as the sensor output in terms of capacitance is a function of dielectric permittivity of the cancerous cell membrane. The material used for the fabrication of plates is polysilicon doped with boron. The property of polysilicon is presented in Table 2.

Table 2: Properties of microfabrication materials

Properties	Material	
	Poly Silicon	SiO_2
Young's Modulus	160e-09 Pa	61 GPa
Poisson's Ratio	0.22	0.26
Density	2.32 g/cm^3	2.2g/cm^3
Thermal Expansion	2.6e-6 K^{-1}	5.6e-7 K^{-1}

4. VIRTUAL FABRICATION OF MEMS SENSOR

The proposed sensor is virtually fabricated using surface micromachining technique with silicon (Si) Czochralski 100 as base material. The electrodes are fabricated by conformal low pressure chemical vapor deposition (LPCVD) of PolySi whereas PolySi is implanted with boron. Photolithography, also known as optical lithography, is a technique used in micro fabrication to produce desire pattern on a substrate. The desired prototype are printed on light transparent mask and placed above the substrate which is coated with thin film of photo resistive material. Photolithography is done by depositing positive photoresist PR-SPR2 and the necessary pattern is produced by allowing UV ray to pass through the mask. A two layer mask is designed which is shown in Fig. 2. The PSG material is used to create the gap in-between the electrodes while copper and titanium is used for essential connection. Later the base material and the other unnecessary materials are removed by the process of etching (partial etching or sacrifice). Figure 3 shows the virtually fabricated MEMS capacitive sensor for the detection of malignancy.

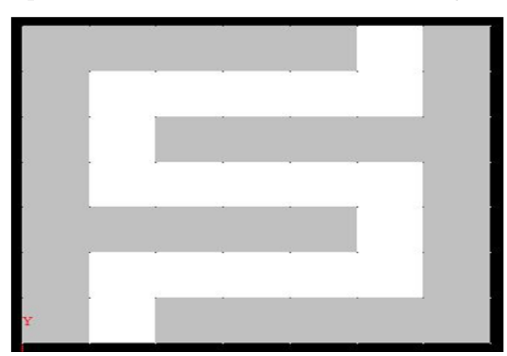

Fig. 2. Two layer mask used for virtual fabrication

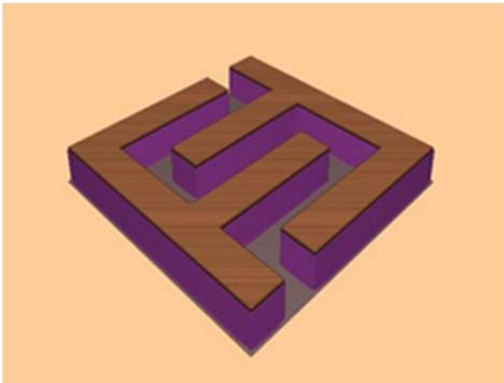

Fig. 3: Virtually fabricated MEMS capacitive sensor

5. RESULTS AND DISCUSSION

The simulation of electrical model of leukocyte is studied for specific range of dielectric permittivity between 7.119 F/m - 12.814 F/m. The simulation of electrical model of WBC cell is shown in Fig. 4. For a cell or plasma membrane, electrophoresis method can occurs at low frequency as the total external voltage applied to the leukocyte is received by the cell membrane therefore inducing transmembrane potential of about 0.5-1V [11, 12]. At higher range of frequency, electrophoresis can occur in the internal organelles of a cell or else it act as an insulator [11-13]. Figure 5 and Fig. 6 demonstrate the said fact for the structural parts of the cell which depends upon the magnitude and duration of the applied voltage. The proposed micro capacitive sensor is non-invasive in nature; a leukocyte sample of unknown permittivity is placed inside the sensor and the resultant is in term of capacitance, shown by Table 3. The equivalent response of the senor output is represented in Fig. 7.

Table 3: capacitive mems sensor output

Conditions	Permittivity of WBC (F/m) [5,7]	Sensor output in (fF)
Normal cell	11.86-12.81	5.71-5.97
Transforming cell	10.28-11.38	5.28-5.58
Cancer cell	7.12-9.88	4.39-5.17

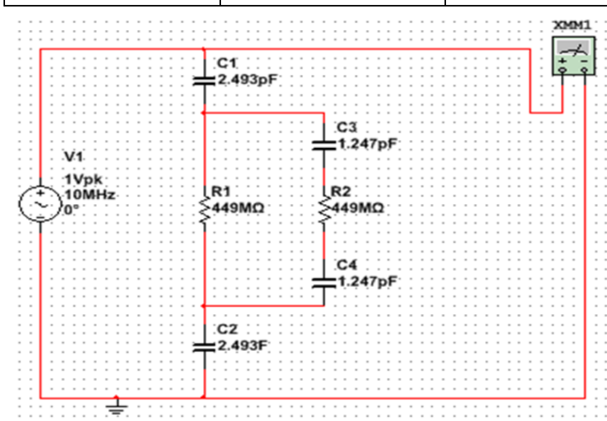

Fig. 4. Simulation of electrical circuit of WBC cell

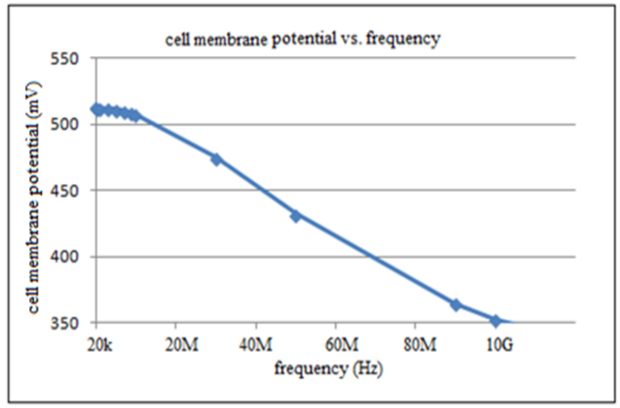

Fig.5. Cell membrane frequency response

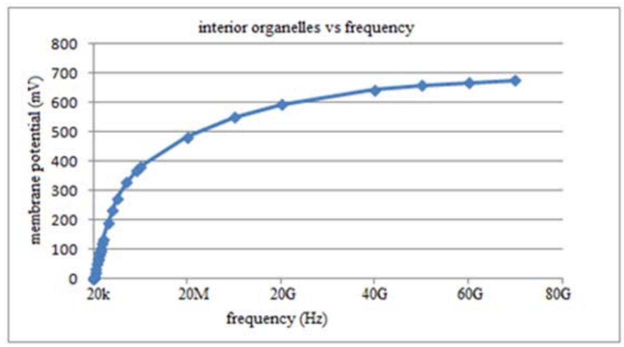

Fig.6. Frequency response of cytoplasm and nucleus

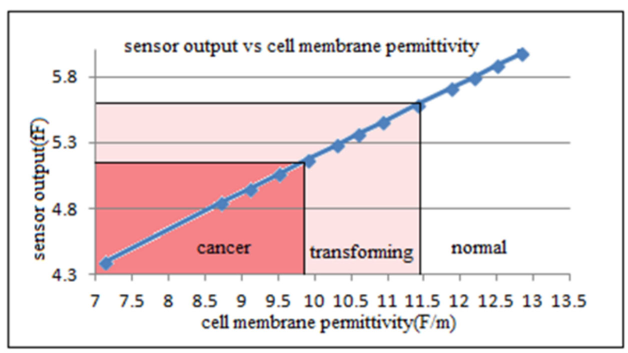

Fig.7. Response of capacitive sensor

6. CONCLUSION

Though this work is based on simulation but all the simulated outcome and response is confirmed with other published literatures [3-6, 14]. Additional study of electrical model of a leukocyte cell shows that at higher frequency above 20MHz internal organelles can be electroporated. Further fractional derivation of Eq.1 will lead to Cole-Cole impedance model which can provide additional physiological details. The Cole-Cole model is the simplest mathematical model for relating the behavior of biological cell [21]. The proposed capacitive sensor is an alternative approach for real-time, non-invasive and cost effective capacitive sensor for easy-to-adopt non-clinical method for detection of blood cancer at early stage whose sensitivity depends on it geometry, mainly on number of electrodes used.

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