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Electrical Characterization of Normal and Cancer Cells

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ABSTRACT In this paper, we characterize and discriminate between normal and cancer cells from three different tissue types, liver, lung, and breast, using capacitance–voltage-based extracted set of parameters. Cells from each type of cancer cell line were suspended in a liquid media either individually or as mixtures with their normal counterparts. Empirically, normal cells were observed to exhibit higher dielectric constants when compared to cancer cells from the same tissue. Moreover, adding cancer cells to normal cells was observed to increase the capacitance of normal cells, and the extent of this increase varied with the type of tissue tested with the lung cells causing the greatest change. This shows that the cancer cells of different cell origin possess their own signature electrical parameters, especially when compared with their normal counterparts, and that cancer cell seems to affect normal cells in a different manner, depending upon the tissue type. It was also noticed that the cells (both cancer and normal) exhibited a higher dielectric value as per the following order (from least to most): breast, lung, and liver. The changes in electrical parameters from normal to cancer state were explained not only by the modification of its physiological and biochemical properties but also by the morphological changes. This approach paves the way for exploring unique electrical signatures of normal and their corresponding cancer cells to enable their detection and discrimination.

INDEX TERMS Capacitance-voltage measurements, cancer cells, electrical detection, dielectric constant, dielectric properties, normal cells, polarization.

I. INTRODUCTION

Worldwide, cancer is considered as the second leading cause of death, affecting all ages and ethnicities. The literature is rich with data relating physiological changes with changes in the dielectric properties of tissues or cells, and this forms the basis for using dielectric properties in diagnostic medicine. By knowing that the major part of electric properties in cells is dependent on cell membranes (α- and β-dispersions) and cell composition (e.g., water, ions) [1], it is logical to suggest possible changes in these components in a diseased tissue. Therefore, a cancer cell is expected to have its own signature changes that are believed to affect its electrical properties. One of the earliest observations of such changes was the reduced transmembrane potential of cancer cells, which correlates well with their high mitotic activity [2]. Beech and colleagues to explain this change proposed several mechanisms. All of which suggested changes at the cell membrane, leading to increased electronegativity of the extracellular surface and thus reducing the membrane potential [3]. Another suggested mechanism for the increased electronegativity is disruption of electron homeostasis related to the transplasma membrane electron transport and electron flux which can transform a cell [4]. Moreover, cancer cells also have disrupted cell membrane permeability that affects their intracellular ionic composition since compared to normal cells, cancer cells were found to have higher concentrations of sodium and chlorine [5] and less concentrations of potassium, calcium, zinc and magnesium, as well as a higher water content [6]. Cell membrane composition alterations have also been reported in cancer cells where in one study both normal and tumor cells from the large intestine were analyzed [7]. In this study, cancer

cells were found to have a total increase in phospholipids and acidic/basic functional groups, and less free fatty acids. The general charge was also observed to increase over a pH range in cancer cells [7].

Similar conclusions have also been made in a study conducted on human bladder cells in which a reduction in the level of integral membrane proteins was also observed [8]. Studies conducted to compare the glycosylation level of glycoproteins on the plasma membrane have revealed increased level of sialic acid which is known to be negatively charged [9]–[11]. Interestingly, alterations in glycoprotein glycosylation were also observed in metastasized mammary carcinoma cells, implicating these changes in metastasis [12]. Beside all the above, cancer cells are known to have a disturbed pH profile since their extracellular space is usually acidic, while the intracellular environment is alkaline, unlike normal cells [13].

The work presented in this study utilized capacitance voltage measurements to extract a set of electrical-based parameters corresponding to the cell state, whether normal or cancer. Changes in the values of these electrical parameters should enable their characterization in a manner that should help differentiate normal from cancer cells.

A. PROPOSED MODELS OF CELL POLARIZATION

Living cells and tissues are composed of different types of molecules, ranging from the simple free moving ions and polar water molecules, to the more complex biomolecules such as carbohydrates, proteins, DNA and lipids [14]. Exposing cells or tissues to an external applied electric field affects the distribution of charges and other molecules in them, such that the ions tend to move over distances (thus, acting as conductors), while other molecules reorient themselves in space and get polarized. This makes cells a dielectric substance that has the ability to get polarized [15]. This polarization of dielectric substances creates an internal electric field that opposes and thus reduces the applied electric field with the extent of polarization, reflecting the ability to store energy, or what is usually referred to as electric permittivity of a material. The dielectric properties of substances are usually described by their conductivity or permittivity, with the later usually described by a dielectric constant or relative permittivity of a substance [16].

Living cells are not homogenous in nature; rather they are of high complexity. In addition to the different ions and biomolecules, the membranous organelles inside the cells add more interfaces within the cell. Interestingly, the dielectric properties of cells were always found to be frequency-dependent [1]. In another words, when relative permittivity was measured over a range of frequencies, the values were always high at very low frequencies, and by increasing frequencies, the values tended to suffer from stepwise decrements or dielectric dispersions that occur at specific range of frequencies. For example, one of the earlier dispersions noticed is α-dispersion which occurs at a few KHz. With increasing frequency, extra dispersions occur at a frequency range from tens of KHz to tens of MHz, referred to as the β-dispersion. Meanwhile, γ-dispersion occurs at the far end of the spectrum in the microwave frequency region [17]. These dielectric dispersions indicate that the polarization process in the cells is mediated by different mechanisms and that one mechanism is lost at a specific range of frequencies. As will be discussed later, the first two dispersions at low frequencies range are mainly caused by the structure of the cell, more specifically the cell membranes and the free ions within and outside the cell.

B. α DISPERTION AND β-DISPERTION

To understand these dispersions, it is useful to depict cells as highly conductive cytoplasmic spheres having free ions that are surrounded by insulating non-conductive cell membranes. These membranes separate the internal compartment from the external media which is also conductive. The highly negative charge of cell membranes is normally neutralized by an adsorbed cloud of counter ions forming an electric double layer [18] (Fig. 1 (a). Two mechanisms of polarizations of living cells have been proposed due to the presence of the cell membranes: the colloidal partial mechanism suggests the formation of a large dipole mediated by ionic movement within this double layer [19], or outside the electric double layer [20], as depicted in Fig. 1(a). Another suggested mechanism is through the bulk movement of ions

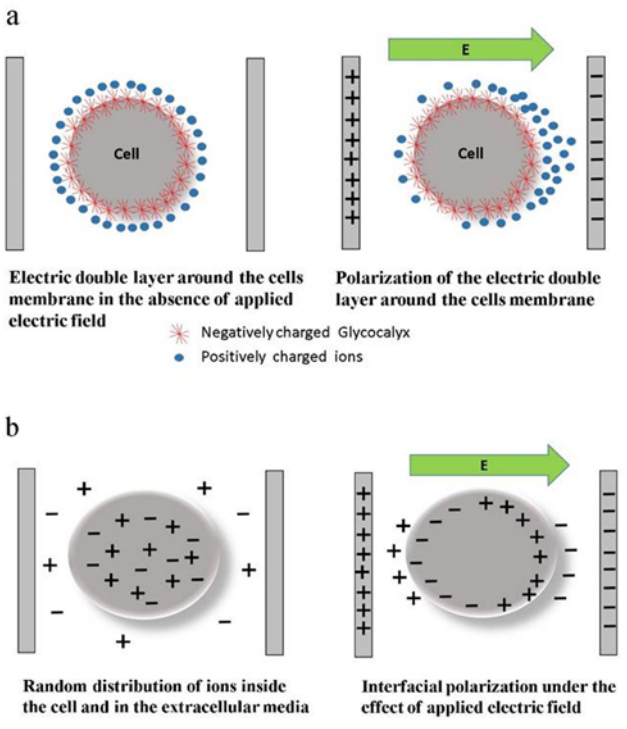

FIGURE 1. Illustration of two mechanisms of polarization of living cells due to cell membranes. (a) Electric double layer polarization, which accounts for α-dispersions. (b) Interfacial polarization, which accounts for β-dispersions. This results from trapping of ions against the ion impermeable cell membrane and the accumulation of counter ions on the extracellular space.

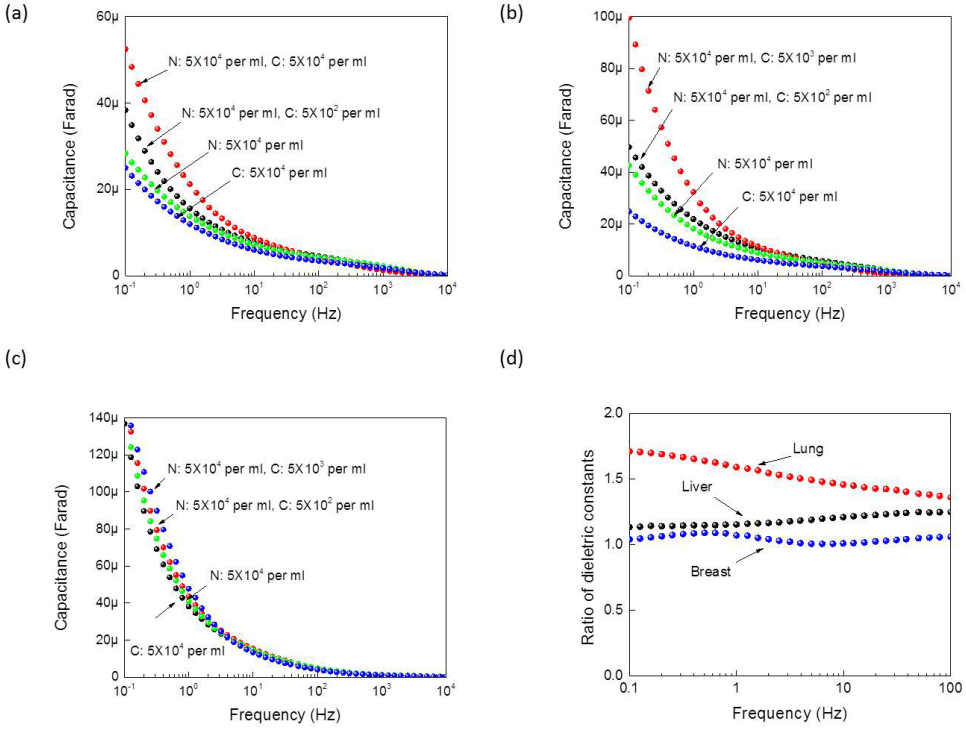

FIGURE 2. **Capacitance versus frequency curves for (a) liver, (b) lung, and (c) breast normal (N) and their cancer (C) counterparts. (d) Ratio of dielectric constants of normal to cancer cells for each cell type over a range of frequencies.**

in the electric double layer formed around membrane pores under the effect of an electric field [21], [22]; therefore, by increasing frequency, this mechanism seems to be lost, leading to α-dispersion.

Despite the freedom of ions inside cells, the movement is actually restricted by the insulating cell membrane, resulting in their accumulation at the interfaces. Thus, a cell acts as a big dipole. This type of polarization at interphases is also known as interfacial polarization, and it explains β-dispersions as seem in Fig. 1(b) [23].

With all these alterations in the cell membrane permeability, transmembrane potential, cell surface charge, and altered ionic concentration, it is expected that cancer cells will have different charge storage capacity. Most studies have focused on studying the electrical parameters of cancer cells compared to their normal counterparts or studying the dielectric properties of tumor tissue *in vitro* or *in vivo* and comparing it to the normal tissue. In the current study, we asked how the presence of cancer cells would affect the dielectric properties of their normal counterparts in cell suspension. In our method, a cell suspension was made by mixing normal and cancer cells where normal cells were maintained at a constant concentration and the suspension was doped with increasing concentrations of their corresponding cancer cells. This does not mimic the normal case of cancer were a tumor tissue is mainly made of cancer cells and surrounded my normal cells. Rather, cancer cells that are scattered in a normal tissue which can simulate tissue invasion by cancer cells before tumor growth or what is known as metastasis.

II. RESULTS TEST OF THE PROPOSED MODELS

Normal and cancerous cells from different tissue origins (liver, lung, and breast) were subjected to electrical measurements either individually or as mixtures in order to determine how malignancy can affect the dielectric properties of cells and whether this effect is similar in cells of different tissues. The Gamry instrument was used to collect the electrical responses from these cells suspended in appropriate tissue culture medium either alone or as mixtures of normal and corresponding cancer cells.

A. NORMAL LIVER AND LUNG CELLS HAVE HIGHER CAPACITANCE VALUES THAN THEIR CANCER COUNTERPARTS

Figure 2 shows the capacitance-frequency profiles of the normal (N) and cancer (C) cells from the three tissue types: a) liver, b) lung, and c) breast. As can be seen, overall, the capacitance profile exhibited a smooth behavior over the frequency range (0-10^4 Hz) and appropriate calibration ensured noise removal from the cables (Fig. 2). The capacitance also showed an exponential decaying behavior versus frequency: as the frequency increased, the capacitance decreased rapidly. Interestingly, all normal cells of different tissue origin displayed higher capacitance values compared to cell suspensions containing equal concentrations of their

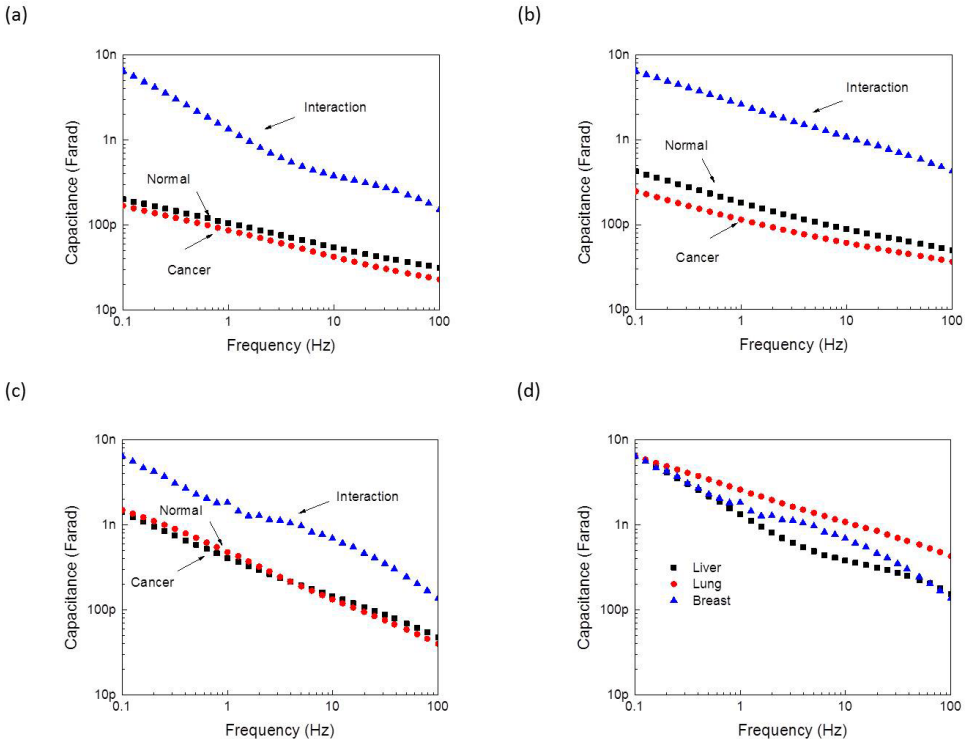

FIGURE 3. Capacitance per cell versus frequency and interaction curves for normal and cancer cells of (a) liver, (b) lung, and (c) breast origin. (d) Comparison of the interaction capacitances between the normal and cancer cell mixtures for each tissue type shown in panels a), b), and c) over a range of frequencies. The data for interaction curves was used from the mixture of cell representing 10^4 N cells with 10^4 C cells.

cancer counterparts, as observed in Fig. 2(a), Fig. 2(b) and Fig. 2(c) for liver, lung and breast cells, respectively.

Such a common trend indicates that malignant changes in cells can affect their capacitive behavior in a negative way. Interestingly, this difference was much bigger in lung and liver cells when compared to breast cells for which the difference in capacitance between normal and cancer cells was much lower.

Since all malignant cells experienced a decrease in their capacitance value, we next asked whether increasing concentrations of cancer cells in suspensions containing a fixed number of their normal counterparts will affect normal cells capacitive behavior. Therefore, interactions between normal and cancer cells of each tissue type were tested by adding increasing concentrations of cancer cells into a suspension of normal cells that were maintained at a concentration of $5x10^4$ cells/ml. The three independent curves in Fig. 2 (a, b and c) clearly show that adding increasing concentrations of cancer cells to normal cells led to an increase in the overall cell suspension capacitance of the three cell types. Figure 2(d) shows the ratios between the dielectric constants of normal to cancer cells over a range of frequencies for each cell type. The figure reveals that the ratio was close to 1 for breast cells, while it increased in liver and lung cells, respectively, over the frequency range, confirming the results obtained in Figure 2 (a), (b), and (c) that overall, the normal cells of liver and lung had more capacitance than their cancer counterparts. However, the capacitance of the normal and cancer breast cells was about the same.

B. LUNG CANCER CELLS EXHIBIT HGHER INERTERACTION VALUES THAN BREAST AND LIVER CANCER CELLS

Next, the background noise was eliminated from the dynamic interactions between the normal and cancer cells by de-embedding the effect of the media to reveal the net effect of the cell-to-cell interactions. This was followed by normalizing the curves to cell numbers to obtain capacitance values per cell, a more sensitive indicator of the capacitance-bearing capacity of each cell type (Fig. 3). As can be observed from the bottom curves in Figure 3 (a)-(c), the normal cells overall had higher capacitance over the frequency range tested compared to their cancer counterparts for liver and lung cells, while the curves essentially overlapped for the breast cells, indicating that the normal and cancer cells had very close capacitance in the breast cells. Furthermore, the capacitance of the normal lung cells was much higher compared to the cancer cells. Together, these results confirmed the observations made in Fig. 2 earlier.

For cell suspensions made of normal and cancer cell mixtures, the corresponding interaction curves measuring their net capacitances are depicted in Fig. 3(d). As can be seen, the interaction curves for both breast and liver cancer cells were much steeper, since they had recorded lower

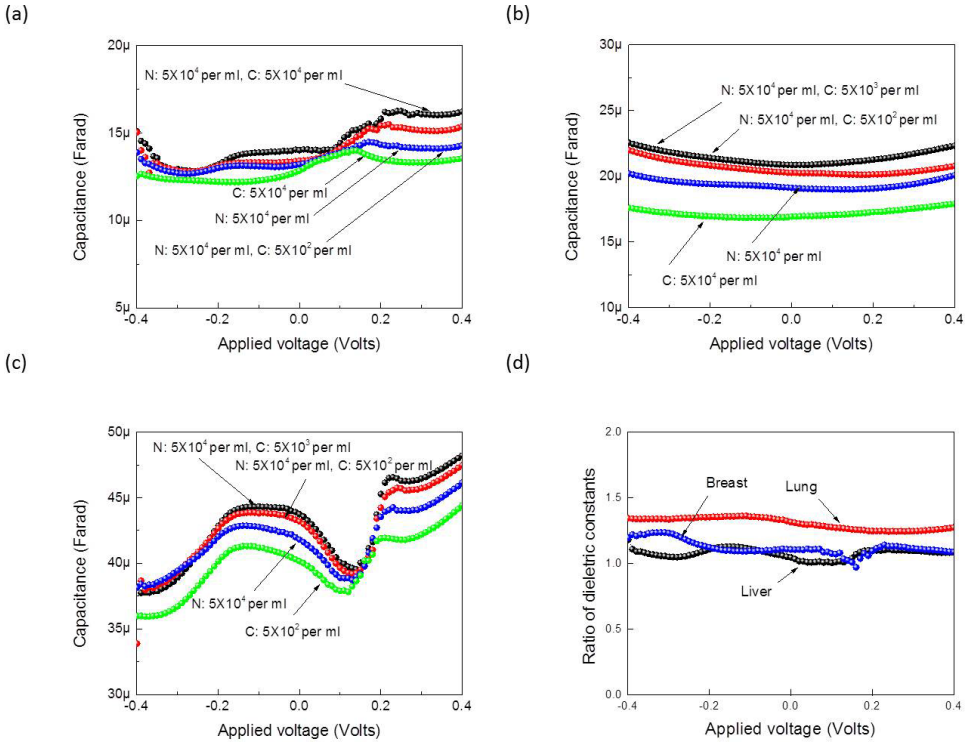

FIGURE 4. Effect of DC bias on the electrical behavior of normal and cancer cells. Capacitance versus voltage measurements for combinations of normal (N) and cancer (C) cells alone or as mixtures with their own counterparts: (a) liver, (b) lung, and (c) breast. (d) Ratio of dielectric constants of normal to cancer cells for each cell type over a range of voltages.

capacitance values compared to lung cells. These interaction capacitances could be considered as a measure of the change in medium electrical properties due to possible cells cargo when they are mixed with each other.

C. LUNG CELLS EXHIBIT HIGER CAPACITANCE/VOLTAGE VALUES THAN BREAST AND LIVER CLELS

The electrical behavior of cells was further explored under applied DC bias voltage conditions. With the application of DC bias, an effective interface layer is formed on the cells surface which builds an electrical field across the surrounding media. Hence, the cells get electrically polarized, enabling their electrical detection and identification.

Figure 4 displays curves of capacitance values measured over a range of voltages (−0.4 −0.4 V) at a fixed frequency of 1 Hz. The capacitance versus voltage curves thus obtained for each cell type revealed higher voltages for normal cells than cancer cells for all the three cell types tested, Fig. 4 (a, b and c), respectively. Similar to the capacitance-frequency profile, mixing increasing concentrations of cancer cells into fixed number of normal cells caused a step-wise increase in capacitance. Figure 4(d) displays plotted ratios between the dielectric constants of normal to cancer cells over a range of voltages at 1 Hz for each cell type. The liver and breast cells showed overlapping curves with a ratio close to 1, while the lung cells showed much higher dielectric constants over the range of voltages shown. Overall, this data shows that the capacitance/voltage measurements can also be used to differentiate between normal and cancer cells in the three cell lines, but they may not be as valuable in differentiating between the three types of cells

III. DISCUSSION

This study was conducted to electrically characterize the behavior of normal and cancer cells from three different tissue types to determine if they could be distinguished from each other. Breast cells were found to have the highest capacitance value followed by liver and then lung cells (Fig. 2). This shows that cells from different tissue origins possess different electrical properties. Generally, and independent of cell type, normal cells exhibited higher capacitance values when compared to their cancer counterparts. This trend was conserved when capacitance was measured over a range of frequencies as in Fig. 2 (a, b and c)), or over a range of voltages at a fixed frequency of 1 Hz as seen in Fig. 4 (a, b and c). This shows that malignant changes do affect the capacitance behavior of cells by reducing it. This observation is supported by other studies in the literature which similarly show a decline in capacitance in cancer cells. For example, in one study, the bio-impedance of cervical cancer cells in suspension measured over a frequency range of 100 Hz-1 MHz was found to be three orders less than the normal cervical cells [24]. In two other studies, the dielectric property measurements conducted on normal breast cells

and three breast cancer cell lines from different stages of malignancy in suspensions revealed higher capacitance of normal cells compared to cancerous cells [25], [26]. They also showed that the stage of cancer could be deduced from the relaxation frequency which tended to increase with a more developed stage of cancer. Furthermore, although the numbers in the two studies were different, the whole trend was preserved.

We also analyzed how normal cells and their cancer counterparts interact with each other electrically, mimicking a simplistic model of metastases. Our data revealed that spiking increasing concentrations of cancer cells into a fixed number of normal cells led to an incremental increase in the capacitance values for the three types of normal cells ((Fig. 2(a, b and c)). This was expected since any additional cells will increase the polarizing capacity of the suspension. However, we observed differences between the three cell types in the magnitude of these increments, where the greatest changes were observed in lung, followed by liver and breast cells, the latter of which had the least change.

Availability of data on the critical biochemical differences between normal and cancer cells or tissues has encouraged researchers to look for concomitant changes in the dielectric properties of these cells. In fact, there are many studies that link the two changes together as will be discussed later. Such studies can help in the continuous improvement of screening and diagnostic tests, treatment approaches, and effective prevention strategies. Impedance measurements in the biological field are usually performed on either tissues or cells. However, both are not similar in complexity. Tissues excised from organisms are usually nonhomogeneous, containing different types of cell of various sizes, shapes and functions. Moreover, different architecture and organizations of cells in tissues can impose anisotropic effects, complicating the dielectric measurements. The whole image is further complicated with the composition of the extracellular matrix that can vary from one tissue type to another [16]. Therefore, it is obvious that performing measurements on cells is easier and helps in evading all the above complications presented by tissue samples despite the difficulty in extrapolating tissues properties from cells suspension. Furthermore, measurements conducted on cells are especially useful when one needs to study the response of a single cell type to malignant transformation, cell dynamics, or different treatments. Impedance measurements on cells can be done not only on cells in suspension, but at a single-cell level. Difficulty in manipulating the cells during single cell measurements in addition to inconsistency in results due to cell-to-cell variations makes measurements in cell suspensions more favorable [25].

Capacitance values can vary from one experimental setup to another due to unavoidable factors that are hard to control. Therefore, capacitance measurements can only give qualitative information and not a signature electrical parameter that can be used; however, the difference in capacitance between normal and cancer cells should be constant, which can make this difference a good candidate as an electrical signature. To extract such a parameter, the ratio of the dielectric constant of normal to cancer cells was calculated over a range of frequencies (Fig. 2(d)) or voltages (Fig. 4(d)). A common trend was observed in which the ratio for lung cells was always higher than that for liver and breast cells, which exhibited values closer to or slightly above one, as seen in Figs. 2(d) and 4(d). This value indicates that lung cancer cells have reduced capacitance values than other cancer cells when compared to their normal counterparts. A similar conclusion can be made from capacitance per cell values calculated for all cells, in which similar values for normal and cancer cells for both breast and liver cells were observed, while lower values for lung cancer cells, as seen in Fig. 3 (a,b and c).

To find a possible explanation for such an observation, we compared the diameter of normal and cancer cells of the three cell types tested. By referring to the literature, it was found that breast and liver cancer cells (CC) were smaller in diameter than their normal counterparts (NC) (breast: 10 μM CC [27], 14.1 $\pm$ 2.4 μM NC [28]; liver: 18 μM CC [29], 20-30 μM NC [30] which can explain the drop in capacitance in these two types of cells. However, the lung cells showed the opposite pattern where the cancer cells possessed larger diameter compared to their normal counterparts (19.6 μM CC [31], 16.25 μM NC [32]) which disputes the first notion as a rule. Thus, it seems that increased size does not explain the increase in capacitance of the normal cells compared to the cancer cells; rather, this reduction seems to result from alterations in the intrinsic properties of the cell, such as cell membrane permeability, intracellular granularity and/or density, interior cell chemistry that affects the capacitive behavior of the cells, etc. Thus, the increase in diameter may or may not accompany the changes observed in their electrical parameters. This assertion is supported by many studies in literature that correlate changes in cell membrane properties with malignant changes [2]–[11]. Interaction curves in Fig. 3(d) were shown to be steeper in normal and cancer mixes of breast and liver cells mixes, while it was less steep in lung cells mix, which might explain the higher increments in capacitance/frequency values upon adding lung cancer cells. This observation suggests greater alterations in either cell biochemistry or perhaps bigger differences in the physical properties of lung cancer cells compared to other cells.

Although the results obtained from cell suspensions can be informative, it is hard to extrapolate them to tissue level since measurements done on tissues can be reversed and complicated by the extra cellular matrix and other parameters. For example, dielectric properties of prostate cancer cells in tissues were found to have less conductivity and higher permittivity compared to normal cells when measurements were conducted over a frequency range of 0.1-100 kHz [33]. The higher permittivity was suggested to arise from increased cell density and higher level of cell membranes in cancerous tissue [33]. In breast cancer, dielectric property measurements done *in vivo* and *in vitro*

have shown that cancerous tissues have higher capacitance and conductivity than surrounding normal tissue [34]. Similarly, measurements done on both excised normal and cancer breast tissues over a frequency range from 0.5 to 50 GHz revealed higher relative permittivity of cancer breast tissues when compared to normal breast tissues [35]. This was explained by the difference in composition between the two tissues since normal breast tissues is mostly made of adipose tissue, while cancer tissues has a higher water content due to higher vasculature [35]. Despite the differences in results obtained from cell suspensions of one cell type or in tissues, the previous method still presents a great potential of studying effects of malignant cell transformation on homogeneous cell suspensions, and test treatments, which can be very valuable in research area. Our results, support previous results where electrical signature can be deduced for normal cells and their cancer counterparts beside the interaction between them, which we show for the first time to be different between different cell types. This suggests that cells of different cell types interact differently in the presence of their cancer counterparts which might highlight differences in the effect of malignancy on different cell types.

IV. CONCLUSION

In this study we have explored the ability to detect differences between normal and cancer cells by characterizing their electrical properties. In general, we confirmed findings in previous studies showing reduced ability of cancer cells to store potential energy compared to their normal counterparts. Furthermore, we could extract electrical parameters that can help identify different types of cancer cells based on differences in interaction with their normal counterparts. These results show that cancerous transformations can affect different cells in different ways despite a general reduction in capacitance. These observations imply diverse mechanisms of transformation that can provide more insight into the understanding carcinogenesis.

APPENDIX: MATERIALS AND METHODS

A. CELL LINES USED AND THEIR CULTURE

All cell lines were purchased from the American Tissue Culture Collection (ATCC), http://www.atcc.org/. The cell lines used were BEAS-2B ATCC® CRL-9609™, HCC827 ATCC® CRL-2868™, THLE-2 ATCC® CRL-2706™, Hep G2 (HEPG2) ATCC® HB-8065™, MCF 10A ATCC® CRL-10317™ and MDA-MB-231 ATCC® HTB-26™. Cells were cultured in their specific media, as recommended by ATCC. All the cells were maintained under humidified air with 5% CO_2 at 37 °C.

B. PREPARATION OF SINGLE AND MIXED SUSPENSIONS

To prepare the cell suspensions, cells were trypsinized and resuspended in DMEM media at the appropriate concentrations. For mixed suspensions, the normal cells were diluted in DMEM media at a final concentration of 10^5 cells per ml. The cancer cells were resuspended in DMEM media at a concentration of 10^6 cells per ml and further diluted with DMEM media to obtain the following concentrations: 10^5, 10^4, 10^2, and 10^1 cells per ml. For mixing, a volume of 250 μl was taken from the diluted suspension of each cancer cell line and combined with 250 μl from its respective normal cell suspension.

C. ELECTRICAL MEASUREMENTS

The electric measurements were carried out by loading 500 μl of each cell suspension in a coaxial capacitor adaptor linked to *Gamry* 3000 equipment (USA) [36]. The Gamry equipment has the ability to measure current ranges from 3 amps to 300 pico-amps over a range of frequency from 100 MHz to 100 KHz. The instrument is controlled through user interface software to measure and record the corresponding responses, namely capacitance-frequency and voltage profiles. The Gamry equipment is capable of measuring capacitance of high precision (up to zepto-Farad).

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