Permittivity measurements of brain cancer cell solutions: towards the electriccharacterisation of single Cancer Stem Cells

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***Abstract*— The dielectric properties of human glioblastoma and medulloblastoma cell lines with a relatively pure population of brain cancer stem cells (CSCs) were measured in the frequency range of 500 MHz to 3 GHz. The complex permittivity was measured using an open-ended coaxial probe (Keysight Technology 85070E dielectric probe kit) and a Keysight network analyzer. These measurements represent the first step towards the electrical characterization of single cancer stem cells. Reliable estimation of CSCs dielectric parameter is of interest for an effective computation of electromagnetic (EM) field distribution within a single or group of cells which is essential for our novel CMOS-based micro-optofluidic lab-on-chip (LOC) platform. Our LOC will enable the fast isolation and neutralization of CSCs through electromagnetic wave stimulation.**

Keywords—Permittivity; Cancer Stem Cells; Electromagnetic Stimulation

I. INTRODUCTION

Cancer stem cells (CSCs) are a subpopulation of tumour cells that have been identified in various solid tumours including glioblastoma, melanoma, ovarian, gastric and lung cancers [1]. Stem-like properties of CSCs such as self-renewal, differentiation and their ability to migrate are believed to play a role in tumour initiation, invasion and recurrence. Drug resistance is another feature of CSCs that is behind the failure of conventional cancer therapies in many cases [1]. There is therefore a vital need for novel therapeutic strategies that can target and eradicate CSCs. The first challenge however remains the recognition and separation of CSCs from the rest of the tumour mass, before the application of a tailored therapy. We propose a novel CMOS-based micro-optofluidic lab-on-chip (LOC) platform for the isolation and neutralization of CSCs through electromagnetic wave stimulation. We have previously shown the efficiency of a quadruple electrode structure in discriminating glioblastoma CSCs [2, 3]. The non-uniform electric field gradient generated by the quadruple structure allowed for cell trapping and characterisation based on their dielectrophoretic signatures in the UHF frequency range (above 50 MHz); at which the dielectric properties of the cell internal structures dominate. Additionally, the microwave intermodulation technique used for high sensitivity dielectric spectroscopy, allows for label-free monitoring of intracellular processes as well as cellular manipulation such as on-chip electroporation [4]. Other electrode microchambers are currently being developed, providing a uniform electric field for the sensing, stimulation and neutralization of CSCs to modulate their differentiation processes, and ultimately increase their sensitivity to anticancer treatments. These platforms using both planar and 3D electrode architectures, can be used for on-chip electroporation using pulsed electric fields. They will also allow for real-time stimulation and monitoring of cell growth under the effect of continuous wave signals up to the millimeter-wave frequency range.

An accurate dielectric model of CSCs is an essential requirement for identifying cells physical properties and arriving at a reliable estimation of the electromagnetic (EM) field distribution within a single cell and small cell clusters [5]. Studies characterizing the dielectric properties of abnormal tissues is however very limited, especially for brain cancer cells [6]. Furthermore, there are no dielectric models of human brain CSCs due to the difficulty in their isolation and culture. Here, we present novel permittivity measurements of human brain cancer cells which represents a first step towards the construction of an electric model for CSCs. Complex permittivity measurements have been performed for human glioblastoma (U87) and medulloblastoma (D283) cell lines which, after our validation using flow cytometry, have been shown to constitute of a relatively pure CSCs population. Cell electrical parameters can then be extracted and modelled using non-linearEffective Medium Theory (EMT) fitting of the measured permittivity of cell solutions as in [5] .

II. METHODS AND EXPERIMENTAL SET UP

The glioblastoma cell line (U87) and the medulloblastoma cell line (D283) were obtained from ATCC. U87 were cultured in complete Dulbecco's Modified Eagle Medium (DMEM) with 10%FBS while D283 were cultured in complete Minimum essential Medium (MEM). Cells were incubated at 37°C in humidified atmosphere with 5% CO_2.

Permittivity measurements were performed for cell suspensions using an open-ended slim form coaxial probe (Keysight Technology 85070E dielectric probe kit) with its tip immersed in the liquid under test. The probe is connected to a

Keysight network analyzer which measures the frequency-dependent reflection coefficient at the coaxial probe connector and converts it to a complex permittivity spectrum through the measurement software provided with the dielectric probe kit [7]. The measurements were conducted in the frequency range between 500 MHz and 3 GHz at a temperature of 27 ^{0}C. Inverse application of the Effective Medium Theory (EMT) was used to estimate singlecell electrical parameters. Estimations have been performed using a three-layered Maxwell–Wagner formulation. The measurements were performed for U87 and D283 cell lines at three different cell concentrations (5, 10 and 20 million cells). For each of these concentrations, 5 measurements were conducted. Repeated measurements were performed to maximize the robustness of the successive estimation procedures. Permittivity measurements of the pure culture medium were also performed.

III. Results

An example of the relative permittivity measurements for U87 human glioblastoma cell line is shown in Fig.1. Fig.1(a) shows the real part of the measured complex permittivity for each of the three cell concentrations (5, 10, 20 million cells) as well as for the culture medium whereas Fig.1(b) shows the imaginary part as a function of frequency.

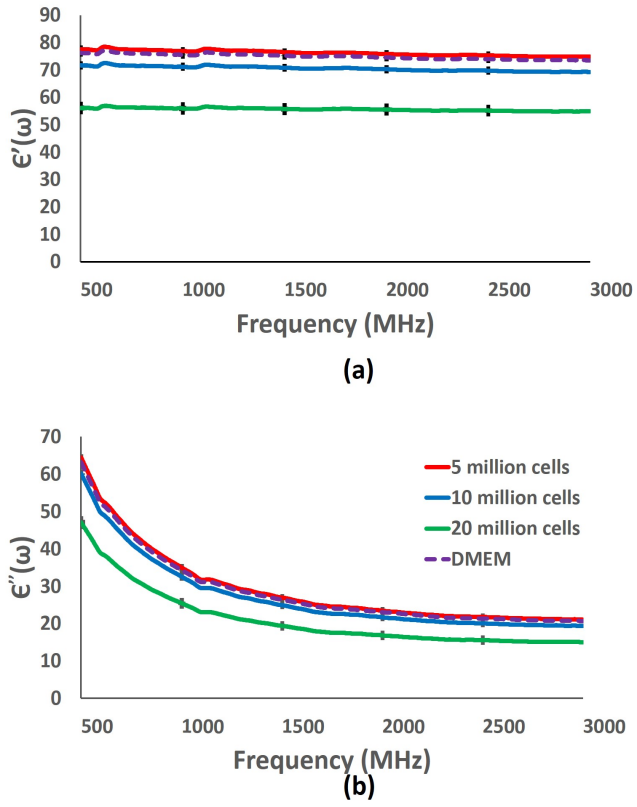

Fig. 1. Dielectric Measurements of U87 glioblastoma cells. (a) real part of complex permittivity as a function of frequency. (b) Imaginary part of complex permittivity as a function of frequency.

Both the real and imaginary parts of the complex permittivity were found to increase with decreasing the cell concentration towards a higher permittivity cell free medium. These results depend on the cell conductivity, dielectric properties of the bilipid membrane as well as the cell size. It has to be noted that there is a measurement uncertainty of around 5%. Matlab curve fitting procedures of the measured data sets are currently underway for the estimation of cellular parameters from both real and imaginary parts to make the assessment of cell electric parameters as reliable as possible.

IV. Conclusion

We present a first step towards a novel study of the dielectric properties of brain CSCs. These measurements will help arrive at an accurate dielectric model of CSCs and a reliable estimation of the electromagnetic (EM) field distribution within a single or group of cells which is essential for our novel CMOS-based micro-optofluidic lab-on-chip (LOC) platform. Our LOC will enable the isolation and neutralization of CSCs through electromagnetic wave stimulation.. In vitro and in vivo studies will validate the LOC approach toestablish the foundation of future therapies and the development of electrosurgical tools that are capable of CSCs neutralization in tissues.

Acknowledgment

This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 737164 SUMCASTEC. Bangor University also gratefully acknowledges the financial support provided by the Welsh Government and Higher Education Funding Council for Wales through the Sêr Cymru National Research Network in Advanced Engineering and Materials.

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