Electrical Impedance measurement as biomarker for brain tumors

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***Abstract*— Each day, nearly 45 deaths occur due to brain and central nervous system tumors, in the US. Glioblastoma Multiforme (GBM), a fatal form of brain tumor, kills nearly two individuals each hour and has an average 5-year survival rate less than 3%. This indicates that the existing therapies are inadequate. There is a critical need for alternate therapies. Towards this, we propose a simple, straightforward method of using electrical impedance as a biomarker. This could be harnessed to detect tumors at an early stage. A recent study demonstrated the ablation of spontaneous brain tumors in canine patients using irreversible electroporation with minimally invasive electrodes and short duration, high voltage electric pulses. Such electrical treatments hold immense potential for early detection and treatment of malignant tumors. This study explores electrical impedance as a potential biomarker for brain tumors. We measured an average impedance of 20.463 kΩ in *ex vivo* bovine brain. We also measured current between 0.2 and 0.3 mA in *ex vivo* brain, under an applied potential of 5V DC between inserted electrodes. Knowing these values gives an estimate of the voltages to apply and the range of impedance and current to expect when trying to distinguish tumor-affected tissue from healthy tissue. The insights obtained from this study will allow the evaluation of electrical impedance as a biomarker for early tumor detection and aid in developing realistic brain phantoms for testing new electrotherapies and drugs.**

I. Introduction

Of all brain tumors, the malignant forms are the most fatal and among malignant brain tumors, 80% are gliomas [1]. Glioblastoma Multiforme (GBM) is a deadly malignant brain cancer having a poor prognosis of only 2 to 3 years. Because it is difficult to surgically remove the entire infiltrating tumor without affecting normal brain functions, glioblastoma treated with chemo and radiation therapy gives a median survival of 14.6 months [2]. The invasive nature of GBM tumors causes recurrence and complicates treatment, ultimately making them fatal. Hence, novel treatment modalities that complement existing options of surgery, radiation and chemotherapy are necessary. Harnessing the potential of electrotherapies for GBM requires understanding the dielectric properties of the brain and identifying which ones could be used as biomarkers. This will facilitate the development of novel treatment using devices such as electroceuticals. According to a study in 1957 by

Schwan and Kay [3], the dielectric properties of tissues are frequency dependent. A study of dog brain's grey matter (GM) and white matter (WM) showed the brain has a temperature dependent conductivity between 0.01 and 10 GHz frequency [4].

Novel electric field-based treatment modalities, such as Tumor Treating Fields (TTF) [5], now in clinical use for GBM treatment, and upcoming treatments like intratumoral modulation therapy [6] call for a holistic understanding of the electrical nature of tumors and dielectric properties of the brain tissue. Studies have shown that low-intensity, intermediate frequency alternating electric fields disrupt cancer cell proliferation, which is key to controlling cancer [5]. A recent study showed the tumor ablation of spontaneous brain tumors in canine patients using Irreversible Electroporation [7]. Applying ninety 50 μs pulses at 4 Hz maximixed the area of tumor destroyed, while minimizing the damage to surrounding healthy tissue.

Given the immense potential for electrical treatments, knowledge of electrical properties of the brain would reveal new insights about the causes of GBM, which is key for early detection. Measurement of electrical properties could form a basis for understanding the origins of brain tumors, which is currently a topic of research [8] [9]. Impedance spectroscopy was used as a biomarker for label-free real-time distinction between *in vivo* brain tumors and brain tissue [10]. Several other studies have reported different electrical impedance between tumorous and healthy tissue in both *in vivo* and *ex vivo* measurements [11-15]. In this research, we measure two electrical properties of *ex vivo* bovine brain samples. Measuring electrical impedance and current from applied dc voltage in *ex vivo* specimen could provide insight into creating a more comprehensive brain phantom for electrical property studies and exploring impedance measurements as biomarkers of GBM tumor tissue.

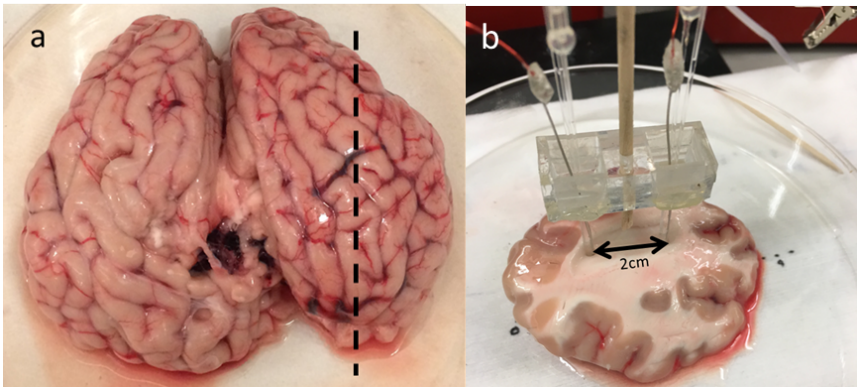

Fig. 1. a) Region of the brain used to obtain a flat slice exposing GM (peripheral) and White Matter (central) b) Sample preparation for measurement of *ex vivo* electrical impedance and current monitoring

II. Materials and Methods

A. Sample preparation

We obtained an intact bovine brain from the Animal Science Department at Purdue University. Fig. 1a shows the brain specimen used for the experiment. It was preserved in a bag containing tissue homogenate and PBS in a temperature-controlled ice box and used

within 70 minutes of removal from the animal to preserve the tissue's initial state. Prior to the experiment, the specimen was thoroughly washed with PBS to remove any tissue covering the brain surface for placement of electrodes. Fig. 1a shows the section of the brain used to obtain a flat slice of 7 cm for measurements. A medical grade scalpel was used to expose the grey and white matter. Measurement position of electrodes in the WM was chosen to ensure homogeneous tissue composition around the tip. We assume a constant contact area between the electrode and tissue.

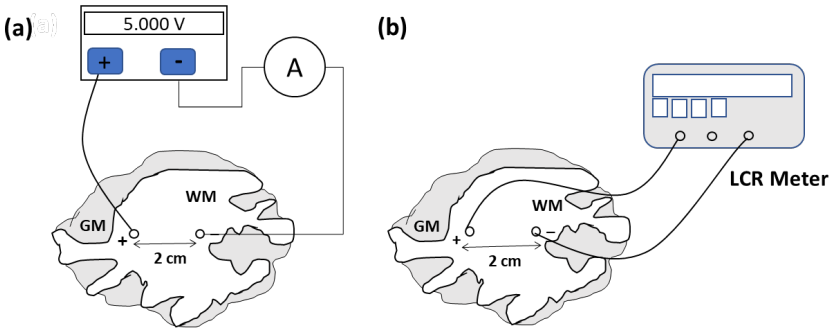

Fig. 2: Experiment setup used for (a) current output measurement and (b) impedance measurements (WM: White matter, GM: Grey matter)

B. Experimental setup

Fig. 1b shows the experimental setup with 5 V dc applied from a standard power supply between platinum coated electrodes (Anomet products, 0.5 mm diameter) spaced 2 cm apart. A capillary embedded electrode setup made of glass capillaries (internal diameter: 2 mm) placed within micromachined acrylic wells allowed platinum electrodes to be fixed within the tissue at same depth. Fig. 2a shows setup where voltage applied to the electrodes using a standard laboratory power supply, varying in steps of 500 mV to measure the current output, using an ammeter. Experiments were conducted at room temperature (21^0C). Fig. 2b shows the setup used for measuring the electrical impedance. The ends of the platinum electrodes placed in the WM were connected to LCR meter (LCR-821, GW Instek) to read its electrical impedance at a frequency of 1kHz.

III. Results and Discussion

Fig. 3 shows the current profile through the brain specimen continuously monitored when 5 V dc was applied between 2 cm distance for a period of 30 minutes. Beyond 30 minutes there was no observable variation in current. The measured current followed a linearly increasing trend from 0.2 mA to 0.3 mA. A linear fit to the measured current (R^2 =0.9467) indicates that the specimen behaves as a resistor.

Fig. 4 shows variation of measured current with applied dc voltage between 0 and 10 V. Current varied linearly with applied voltages for voltages less than 5.7 V, after which the behavior is non-linear. To accurately represent this full range, we used a fifth-degree polynomial curve to closely fit to the data (R^2 =0.9742). The equation of fit line is $y = 0.0001x^5 - 0.0022x^4 + 0.0134x^3 - 0.0151x^2 - 0.0075x + 0.0097$ where x is the applied dc voltage in volts and y is the current in mA. The measured output current increases until an

applied voltage of 7.5 V, where there is a sudden drop, followed by steady decrease. This may indicate temporal changes in the brain post-mortem due to absence of blood supply and ion exchange between cells. To our knowledge, this is the first study where current profile was measured over time in *ex vivo* brain tissue. Measured average impedance of the brain specimen using LCR meter at 1 kHz at room temperature was 20.463kΩ, a resistive load (as the phase angle was zero).

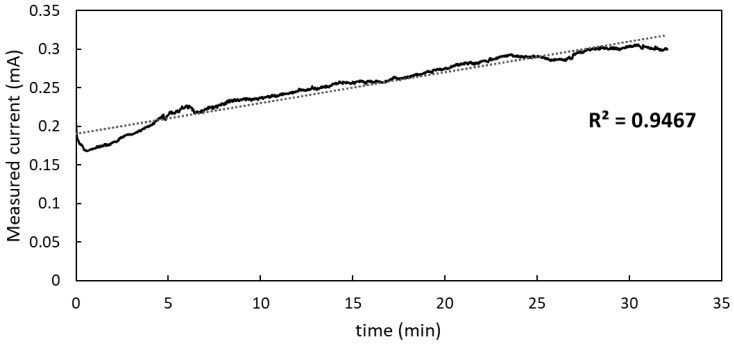

Fig. 3: Current profile measured in *ex vivo* brain specimen with time, showing a good linear fit (R^2= 94.67%)

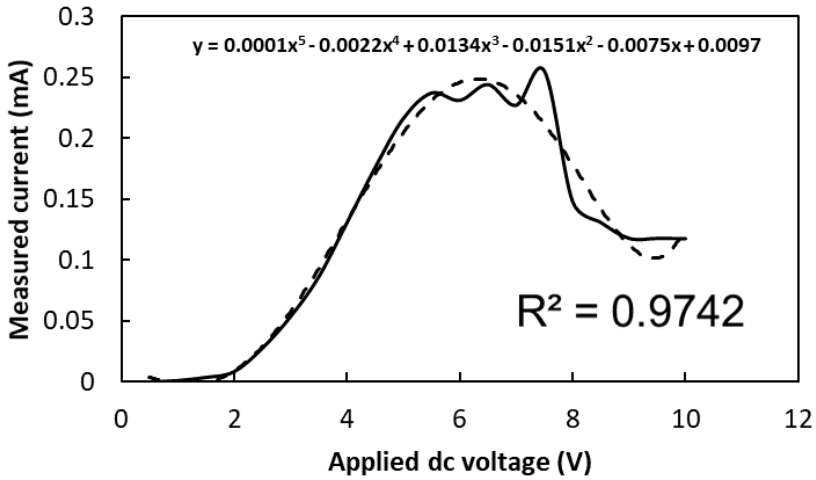

Fig. 4: Current variation with applied dc voltage in the *ex vivo* brain specimen

Electrically characterizing the brain is useful for exploring electrical treatments for GBM treatment. A hypothesis that charged drugs may be moved in the brain to increase their local concentration after brain tumor removal surgery has been explored by Ammirati et al. using *in vivo* brain electrophoresis [16]. The variation of current with applied dc voltage in the brain specimen suggests the possibility of using *ex vivo* measurements to predict the range of voltages surgeons could apply to *in vivo* experiments. However,

limitations exist, calling for a systematic examination of electrical effects under realistic brain conditions [17]. A comprehensive *in vitro* gel model based on *ex vivo* tissue measurements could help understand brain's electrical characteristics as biomarkers but *in vivo* methods are still going to be the benchmark that provide relevant results for applicability to humans [18]. Thus, future work correlating *ex vivo* and *in vivo* studies is crucial to develop clinically relevant electrotherapies for GBM.

IV. Conclusions

The current study provides a rationale for conducting electrical property measurements to characterize brain tissues under applied dc voltage and the importance of using electrical impedance measurements as biomarkers for GBM. The authors believe this study is a first attempt to understand the electrical nature of brain under dc conditions and could open several research possibilities for development of electrotherapies in the future. Human brain tissue dielectric properties, such as electrical impedance, electrical conductivity at dc and electrical conductivity at ac frequencies, permittivity and ionic diffusion coefficient are important parameters to determine the nature of neural activity that could pave way for developing novel electrotherapies for GBM and other brain pathologies.

- In this study, *ex vivo* bovine brain specimen was used towards measurement of electrical impedance and electrical current.
- Measured current under an applied dc bias of 5 V (electrodes placed 2 cm apart) varied between 0.2 and 0.3 mA.
- Electrical impedance measured in the white matter was 20.463kΩ.
- A variation in current with applied dc bias between 0 and 10 V showed a linear trend until 5.7 V after which it showed a non-linear behavior.
- This measurement is useful to develop novel electrotherapies for GBM treatment such as electrically charged drug delivery through electrophoresis and for providing a realistic range of electric current and impedance to expect during surgical procedures.

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