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To cite this article: Atif Shahzad *et al* 2017 *Biomed. Phys. Eng. Express* **3** 045001

Biomedical Physics & Engineering Express

PAPER

Investigation of the effect of dehydration on tissue dielectric properties in *ex vivo* measurements

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Keywords: dielectric spectroscopy, electromagnetic interactions, biological tissue, bioimpedance, tissue dehydration

OPEN ACCESS

RECEIVED
8 February 2017

REVISED
5 April 2017

ACCEPTED FOR PUBLICATION
19 May 2017

PUBLISHED
26 June 2017

Abstract

This paper discusses the impact of tissue dehydration on the dielectric properties of excised tissue samples. The effect of dehydration on the tissue surface has been characterized as a function of time after excision on freshly excised mouse liver. The dielectric properties of liver were measured over the frequency range of 500 MHz–20 GHz using an open-ended coaxial probe. Tissue samples were obtained from 7 athymic BALB/c Nude mice, and measurements were performed over the first 3.5 h post-excision at the tissue surface and in the middle of the sample (accessed via a small incision). The samples were kept in sealed containers between measurements to avoid excessive dehydration. The measured dielectric data show a change of more than 25% in both the real and imaginary parts of complex permittivity over 3.5 h after excision. Results indicate the impact of tissue dehydration on the dielectric properties, and signify the importance of considering controls in the experimental design of *ex vivo* dielectric measurements.

Background

The dielectric properties of biological tissue are of significant importance in modeling and evaluating the energy deposition in a body exposed to radio-waves. Applications involving tissue dielectric properties range from the safety assessment of telecommunication systems to the characterization of medical diagnostic and therapeutic systems. Dielectric spectroscopy of biological tissue has been an active field of research over the past four decades, starting from the early studies by Schwan and Foster (1980). There has been a large number of studies reporting dielectric properties of various animal and human tissue over a wide frequency range of 10 Hz–100 GHz. In one of the most comprehensive studies, Gabriel *et al* (1996) reported the dielectric properties of a large number of biological tissues including freshly excised bovine and porcine tissue, human autopsy material, and human skin and tongue over a frequency range of 10 Hz–20 GHz. Dielectric data for various human and animal tissues reported in other studies (Foster *et al* 1979, Surowiec *et al* 1987, Peyman *et al* 2001, Schmid *et al* 2003, Lazebnik *et al* 2006, Abdilla *et al* 2013, Sasaki *et al* 2014) align with the data presented in (Gabriel *et al* 1996), which is widely used in electromagnetic modeling and assessment of specific absorption rate. Stuchly *et al* (1982) studied inter-species differences in dielectric properties of skeletal muscle, brain cortex, spleen, and liver tissue between 0.1 and 10 GHz, and reported a very small difference (within system uncertainty) between the same tissues of different species, which led researchers to believe that the data from animal studies can be generalized and used for human tissue modeling. In addition to healthy biological tissue, the dielectric properties of a wide range of cancerous tissue has also been dielectrically characterized. For example, a number of studies, (Chaudhary *et al* 1984, Surowiec *et al* 1988, Joines *et al* 1994, Lazebnik *et al* 2007, O'Rourke *et al* 2007, Sugitani *et al* 2014) characterized the dielectric properties of cancerous tissues that are being used in the development of medical diagnostic and therapeutic applications.

Most of the data on dielectric characterization of tissue are based on excised samples, where the time of measurement varies between 5 min and 5 h after excision from the donor body. These measurements provide dielectric data of tissue which is far removed from the normal physiological state. The data from *ex vivo*

measurements therefore does not account for factors such as blood perfusion, temperature, tissue dehydration, and ischemic effects (Foster and Schwan 1995). The factors influencing the dielectric measurements can be divided into two categories based on two stages of the tissue excision process: (1) bio-physiological impact of death on the tissue; (2) other factors affecting the physiological state of the tissue during and after excision, e.g. tissue dehydration, temperature variations, or any physical damage to tissue sample. The impact of death has been studied by Lofgren (1950) in the low frequency range (2 kHz–15 MHz) on rat kidney, where the electrical impedance of the kidney was measured *in situ* before and after the death of animal. A decrease of 50% of the baseline value in conductivity was observed 1 h after animal death. In the most recent study on rat liver by Farrugia *et al* (2016), the dielectric properties of rat liver over the microwave range of frequencies (0.5–40 GHz) were measured *in situ* before and after animal death. In this carefully designed experiment, no statistically significant difference was observed in the dielectric properties of liver before and immediately after animal expiry (within the first 6 min). In contrast to the results from Lofgren experiments, Farrugia *et al* measured the dielectric properties at the high frequency range which is mainly driven by water content in the tissue. A drop in conductivity at low frequency can be associated with flaccidity of tissue, especially in the low kilo Hertz range. Farrugia *et al* concluded that the differences in the *in vivo* and *ex vivo* dielectric properties cannot be associated with blood perfusion, so the other factors including temperature and tissue dehydration may contribute to these variations. In other studies (Kraszewski *et al* 1983, Lazebnik *et al* 2006, Peyman *et al* 2009), similar observations have been reported.

The impact of temperature on tissue dielectric properties has been well characterized in the literature. Lazebnik *et al* (2006) studied the effect of temperature on dielectric properties of bovine and porcine liver obtained from a local abattoir, and developed a temperature dependent model of the dielectric properties of animal liver. In another study (Chin and Sherar 2001), the effect of temperature on dielectric properties at 915 MHz was studied on bovine liver. The changes in the biological tissue due to external heating were observed and categorized as reversible and nonreversible. The temperature coefficients for reversible changes and the critical energy that activates the nonreversible changes were reported. Chin and Sherar also studied the temperature effects on rat prostate at 915 MHz, and presented the temperature coefficients in (Chin and Sherar 2004). Stauffer *et al* (2003) reported temperature coefficients of porcine, bovine, and human liver tissues over the frequency range of 0.3–3 GHz. Early studies by Schwan and Kay (1957), Johnson and Guy (1972), Schwan and Foster (1980) discussed the temperature effects on various biological tissue over the microwave frequency range, predominantly 0.3–10 GHz. Ji and Brace (2011) used a microwave ablation system to heat the liver tissue up to 100 °C, and measured the dielectric properties from 0.5 to 6 GHz using an open-ended coaxial probe. The temperature at various distances was measured and a sigmoidal model was fitted to the data. In summary, the temperature coefficient of various tissue over a broad frequency range has been evaluated and reported in literature.

The effect of tissue dehydration is the other most influential factor in the dielectric spectroscopy of tissue, and is perhaps the most challenging to characterize for biological tissue. There can be large variations in the tissue hydration state due to varying experimental conditions. Various factors such as, ambient temperature, exposure to air, temperature control techniques (to heat or cool), and time between excision and measurements can affect the hydration state of the tissue. The impact of tissue dehydration can mostly be observed on the surface of the tissue, while the inner structure remains well protected from the external conditions. One of the most commonly used measurement techniques in the microwave frequency range is based on the use of the open-ended coaxial probe, which is put into contact with tissue to measure the reflection coefficient of the material under test. Therefore, the dehydration of the tissue surface being measured has a larger impact on the measurements in the open-ended coaxial technique.

In this article, the impact of tissue dehydration over time is studied in the frequency range of 0.5–20 GHz. Dielectric measurements were performed using an open-ended coaxial probe on seven freshly excised mouse liver samples at time $T0$ (which is taken as 8 ± 3 min after excision due to slight differences in the excision and transportation time), 30 min (0.5 h), 90 min (1.5 h), 150 min (2.5 h), and 210 min (3.5 h). Four different sites on the liver sample were randomly selected for measurements, and two sets (or groups) of measurements were carried out on each site: (1) at the tissue surface; and (2) deep under the surface (accessed via a small incision). The data from the surface group are compared with those from the interior group. A comparison with *ex vivo* data on rat liver from Peyman *et al* (2001) and *in vivo* data from Farrugia *et al* (2016) is also presented.

The remainder of the paper is organized as follows: section 2 describes the source and handling procedures for the tissue samples, the measurement system, sample size and sensing volume, and uncertainty analysis of the measurement system. Section 3 presents the results and comparison with existing studies, while the conclusion and future work are presented in section 4.

Materials and methods

Tissue samples

All *in vivo* work was approved by the institutional Animal Ethics Committee (National University of Ireland, Galway) and Health Products Regulatory Authority of Ireland. Female athymic BALB/c Nude mice (Charles River Laboratories, $n = 7$), aged 6–8 weeks, weighing 25.6 ± 1.1 g (mean ± SEM) were used for this experiment. Animals were placed under terminal inhalation anesthesia and a terminal bleed performed by cardiac puncture. The liver was excised within 5–10 min using a 'Y' incision. The intact liver was removed by handle of the diaphragm, to avoid tissue damage. The dry liver was then placed in a snug-fitting sterile sealed container.

At the time of first measurement (8 ± 3 min after excision), the sample temperature was dropped to room temperature (~22 °C), and all the measurements were performed at room temperature. The ambient temperature is well-controlled in the Lambe Institute for Translational Research at National University of Ireland, Galway where the research was carried out; therefore, the sample (tissue) temperature during the measurements had relatively small variability. The temperature of the tissue samples was measured using an infra-red [Precision Gold N85FR] thermometer at each measurement, and recorded as 22 ± 0.8 °C.

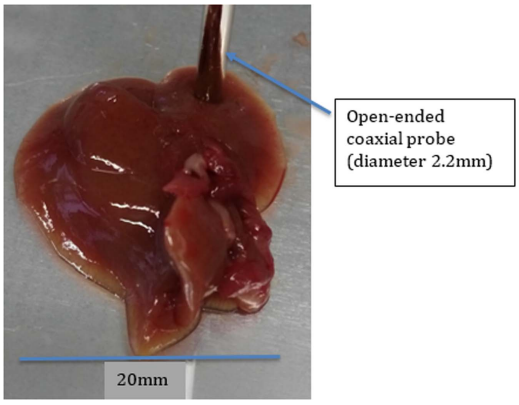

Figure 1. Freshly excised mouse liver sample during surface measurements using open-ended coaxial probe.

Dielectric measurements

Measurements were performed using a slim-form dielectric probe (Keysight 85070E, Santa Rosa, CA, USA) connected to a vector network analyzer (Keysight E8362B), and reflection coefficient (S_{11}) was recorded at 201 discrete frequency points over 500 MHz–20 GHz. The S_{11} parameters were converted to complex permittivity using Keysight material measurement software suite (Keysight N1500A). The open-ended coaxial probe is the most common method to measure the broadband dielectric properties of the biological tissue (Surowiec *et al* 1987, Gabriel *et al* 1996, Peyman *et al* 2001, Chin and Sherar 2001, Stauffer *et al* 2003, Schmid *et al* 2003, Lazebnik *et al* 2006, Ji and Brace 2011, Abdilla *et al* 2013, Sasaki *et al* 2014). In order to measure the reflection coefficient of the tissue sample, a lift table (lab jack) was used to lift the sample under the open-ended coaxial probe. The tissue sample was pressed against the probe to achieve proper contact for surface measurements. The samples were kept in snug-fitting sterile sealed container during the measurements, and the container was opened only to perform a measurement at time *T*0, 30 min, 90 min, 150 min, and 210 min, and kept closed otherwise. For each tissue sample, the following two sets of measurements were performed at four randomly selected sites over the time (30 min, 90 min, 150 min, and 210 min after excision): (1) three repeated measurements at the surface of the liver tissue on selected site; (2) three repeated measurements just below the surface at the same site. An additional three measurements at the surface of each sample was carried out at time *T*0 (8 ± 3 min after excision). This measurement pattern resulted in a total of 189 broadband measurements. Figure 1 shows one of the liver samples during the measurements, where open-ended dielectric probe is put into firm contact with the tissue surface for measurements.

Sample size and sensing volume

Open-ended coaxial probes were originally designed for dielectric measurements of liquids and powders, where the probe must be immersed in the material under test for accurate results. A minimum immersion depth is often reported for a probe to achieve specified accuracy (Keysight 85070E—5 mm immersion depth) for a liquid. Considering the advantages of broadband measurements and being useful for *in vivo* measurements, the open-ended probe has become the preferred choice in broadband dielectric spectroscopy of biological tissue. The effective sensing volume of the open-ended coaxial probes for tissue measurements has been widely studied for various applications. A number of studies (Hagl *et al* 2003, Meaney *et al* 2014, Meaney *et al* 2016) assessed the sensing depth of the slim probe (2.2 mm diameter) for tissue measurement applications and reported minimum sample thickness of less than 2 mm for accurate measurements. The average sample size in the study presented in this paper was 20 mm (minor axes) by 25 mm (major axis). The thickness of the sample varied from 3 to 9 mm from edges to the center. Repeated measurements on various randomly chosen cites on the tissue sample at a given time were found consistent, which can be seen in the results.

Table 1. Summary of uncertainty assessment results on 0.1 M NaCl solution at 22 °C, reference data is obtained from Cole–Cole model in Peyman *et al* (2007).

Uncertainty	Dielectric constant (%) 0.5−20 GHz	Conductivity (%) 0.5−20 GHz
Repeatability (standard deviation of mean)	0.22	0.69
Accuracy (deviation from reference)	0.53	1.18
Drift (systematic drift over time)	0.04	0.07
Cable movement	—	—
Combined uncertainty	0.58	1.37

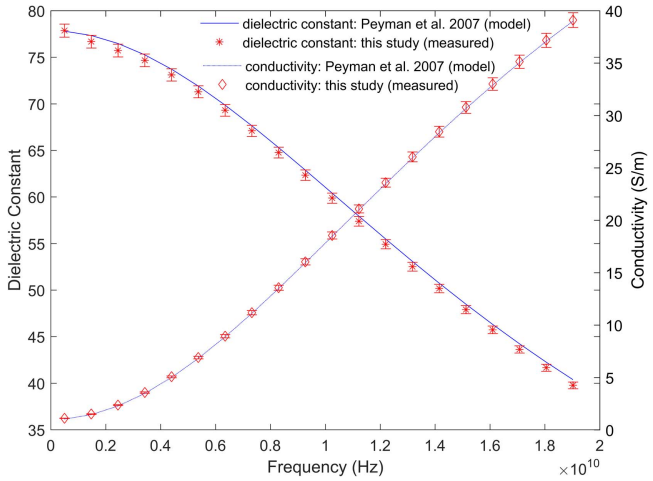

Figure 2. Comparison of measured dielectric constant and conductivity of 0.1 M saline (verification liquid) with data from Cole–Cole model in Peyman *et al* (2007). The error bars show standard error of the measured data.

Uncertainty analysis

The slim form coaxial probe was connected directly to the VNA to avoid error due to cable movement. One port calibration was performed at the tip of the probe using three standards: a short (shorting block in Keysight 85070E kit); open (air); and load (de-ionized water). Accuracy of the measurement system was evaluated on 0.1 M NaCl solution (Honeywell chemicals, Fluka 35275), using the standard analysis technique described in (Gabriel and Peyman 2006). In the estimation of total uncertainty of the measurement system, repeated measurements were performed on a standard liquid to assess random and systematic errors. The error was calculated for each discrete frequency point in the measurement and averaged over the band. Table 1 lists the random and systematic errors in the system, assessed over 0.1 M NaCl solution at 22 °C. The accuracy was calculated as deviation from the reference data obtained from the Cole–Cole model presented in Peyman *et al* (2007). Repeatability in table 1 is a measure of the standard deviation of the mean. A relatively large error was observed in the imaginary part of the complex permittivity, resulting in a larger contribution to the combined uncertainty. Figure 2 shows a comparison of dielectric properties of 0.1 M NaCl solution measured in this study and the reference data from Cole–Cole model in (Peyman *et al* 2007). In order to produce a less cluttered plot, only 21 frequency points out of 201 (every tenth point) are shown over 500 MHz–20 GHz in figure 2. Measured data is found to be in agreement with the reference data with average error less than 2%. The average value of dielectric constant is slightly lower than the reference data, while it is higher in conductivity.

Results and discussion

The measured data (189 broadband measurements) were divided into two groups: (1) data from measurements at the surface of tissue at time *T*0, 30 min (0.5 h), 90 min (1.5 h), 150 min (2.5 h), and 210 min (3.5 h) for all tissue samples (105 broadband measurements); (2) data from measurements in the middle of the samples for all measurement sites and for all tissue samples (84 broadband measurements). The tissue was fresh and well hydrated at first measurement (*T*0), so only three measurements at the surface of the tissue were performed at three randomly selected sites. Table 2 summarizes the data distribution in the two groups. Data from the interior group was found to be stable over time with very small variation over time, and it is treated as reference. The surface group is further divided into five sub-groups, each representing the dielectric properties of tissue at various time instances which is affected by tissue dehydration.

Table 2. Categorization of data from measurements on 7 mice liver samples.

	*T*0 [8 ± 3 min] (3 randomly selected sites)	0.5 h (site 1)	1.5 h (site 2)	2.5 h (site 4)	3.5 h (site 4)
Interior-group	—	7 × 3	7 × 3	7 × 3	7 × 3
Surface-group	7 × 3	7 × 3	7 × 3	7 × 3	7 × 3

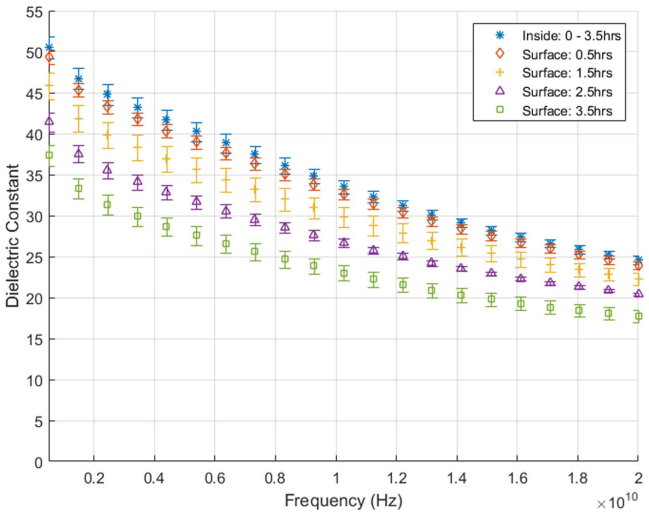

Figure 3. Comparison of dielectric constant measured at surface and under the surface. Plot shows mean and standard error of data from measurements.

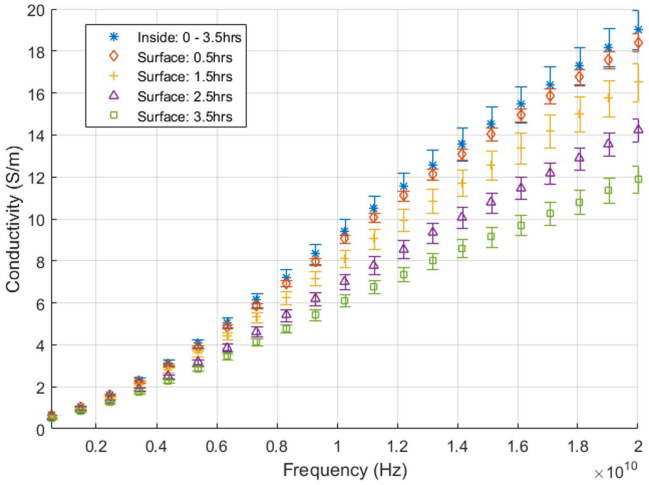

Figure 4. Comparison of conductivity measured at surface and under the surface. Plot shows mean and standard error of data from measurements.

Measured dielectric properties at *T*0 (8 ± 3 min after excision) from the surface group has been found to be within standard error of the mean of the reference data (interior-group); therefore, it is excluded from analysis. Effectively the change in dielectric properties at *T*0 with respect to the mean of reference data was within the standard error, that leads to a conclusion that there is no statistical difference between dielectric properties at the surface of freshly excised liver tissue and the properties in the middle of the sample.

Effect of tissue dehydration on dielectric properties

The dielectric constant and conductivity of the liver tissue from the interior group (inside: 0–3.5 h) are compared with the data from the surface group (0.5, 1.5, 2.5, and 3.5 h), and mean and standard error are shown in figure 3 (dielectric constant) and figure 4 (conductivity). A significant change in both the dielectric constant (average >25%) and conductivity (average >30%) of the tissue has been observed as a function of time after excision.

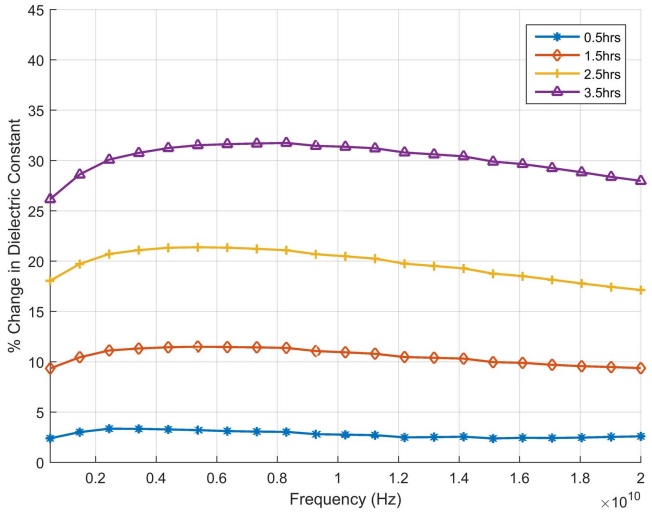

Figure 5. Percentage difference in dielectric constant of measurements at 0.5, 1.5, 2.5, and 3.5 h with reference (interior group).

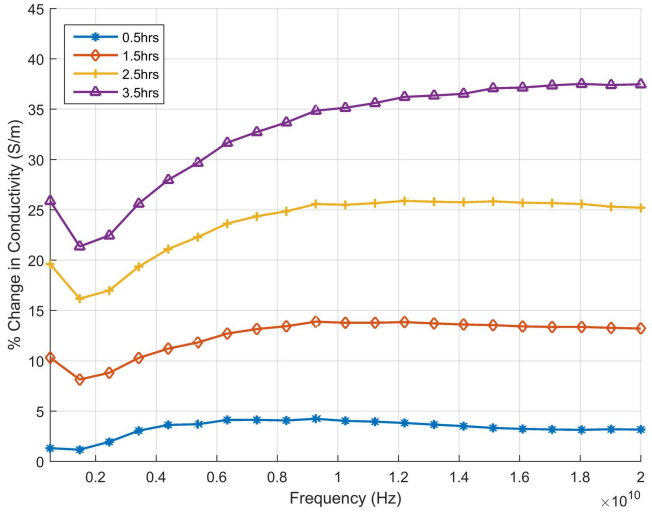

Figure 6. Percentage difference in conductivity of measurements at 0.5, 1.5, 2.5, and 3.5 h with reference (interior group).

Figures 5 and 6 show the percentage change relative to the interior group in dielectric constant and conductivity at time; 0.5, 1.5, 2.5, and 3.5 h. Although a general decreasing trend has been observed, the change in dielectric properties after 0.5 h is within measurement uncertainty (<3%). However, a significant change in both the dielectric constant and conductivity can be seen in the follow-up measurements at 1.5, 2.5, and 3.5 h. A decrease of >25% has been observed after 3.5 h. As the tissue temperature was well controlled during this experiment, these variations can be attributed to the loss of moisture (water content) in the tissue which is most evident at the surface of the tissue. It is important to note that the effect of surface dehydration can vary based on many factors, including but not limited to, ambient temperature, size of tissue sample, amount of water content in the tissue, tissue handling procedures, and exposure to air. Therefore, the results cannot be generalized to other biological tissue and experimental conditions. However, the results signify the extent of expected error in the *ex vivo* dielectric measurements due to tissue dehydration.

Comparison with previous studies

The data from the interior group was consistent over time with the average standard error being less than 7.5% in both dielectric constant and permittivity. No significant difference has been found between the data from the interior group and first measurement taken at the surface of tissue at time *T*0, which was performed on freshly excised tissue. In order to understand the relevance of the data from this study in terms of tissue moisture, a comparison has been made with dielectric data of rat liver from *in vivo* measurements (Farrugia *et al* 2016) and *ex vivo* measurements (Peyman *et al* 2001). Figures 7 and 8 show a comparison of dielectric constant and conductivity of reference data (this study: interior group) with Farrugia *et al* (2016) and Peyman *et al* (2001).

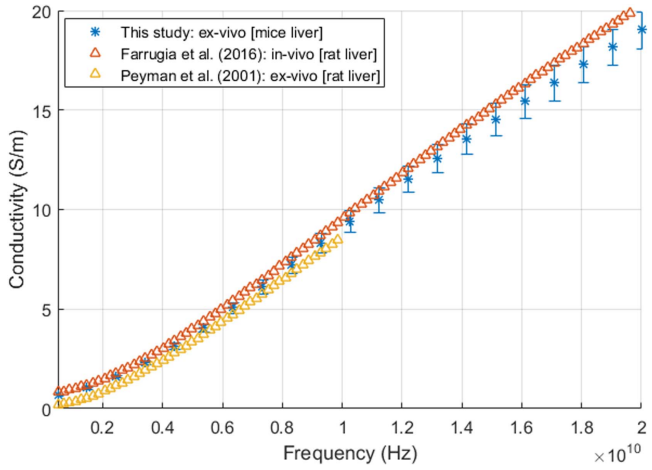

Figure 7. Comparison of measured conductivity (this study: interior group) with rat liver data from *in vivo* measurements by Farrugia *et al* (2016) and *ex vivo* measurements by Peyman *et al* (2001).

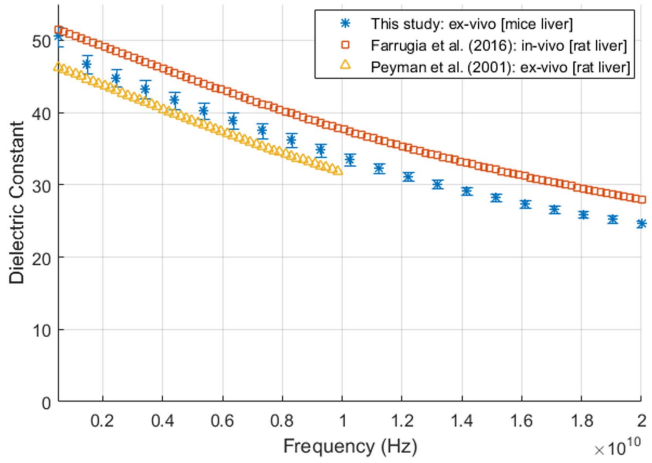

Figure 8. Comparison of measured dielectric constant (this study: interior group) with rat liver data from *in vivo* measurements by Farrugia *et al* (2016) and *ex vivo* measurements by Peyman *et al* (2001).

The graphs shown are based on the data derived from Cole–Cole models presented in (Farrugia *et al* 2016) and (Peyman *et al* 2001) at body temperature (37 °C). Farrugia *et al* studied the correlation between *in vivo* and *ex vivo* dielectric properties and reported no significant difference immediately after animal expiry (if the temperature is kept constant). A decrease in both the dielectric constant and conductivity in this study compared to *in vivo* data from (Farrugia *et al* 2016) can be seen in figures 7 and 8. This difference can be attributed to tissue temperature differences in the studies (Farrugia *et al* 37 °C, this study 22 °C). Data from *ex vivo* measurements in (Peyman *et al* 2001) corresponds to mean values of dielectric constant and conductivity of rat liver tissue between 2 and 4 h after excision at 37 °C. As the temperature in both studies (Peyman *et al* 2001, Farrugia *et al* 2016) is the same, the decrease in the dielectric properties of rat liver is evidently due to loss of tissue moisture. The difference in dielectric properties of freshly excised tissue in this study and Peyman *et al* (2001) can be associated with tissue dehydration over time. It must be noted that this comparison ignores the temperature differences, which can effectively result in an increase in the dielectric properties and shift the data from this study up closer to that of (Farrugia *et al* 2016).

It is found that the interior of the tissue remains well hydrated and protected for a relatively long duration compared to that at the surface. Therefore, the measurements carried in the middle of tissue sample can be a better estimate of the true dielectric properties assuming that all other factors are well compensated.

Conclusion

In this study, the effect of dehydration on the dielectric properties of biological tissue has been characterized as

function of time. Dielectric properties of freshly excised liver samples from 7 athymic BALB/c Nude mice were measured at time 0, 30 min (0.5 h), 90 min (1.5 h), 150 min (2.5 h), and 210 min (3.5 h). The samples were kept in sealed containers to avoid excessive loss in tissue moisture, and temperature was kept controlled at 22 ± 0.8 °C. The measurements were performed on the surface of tissue at four randomly selected sites, and under the surface at the same points. The data from measurements inside the tissue samples were combined and used as reference for comparison with data from four time instances. An average decrease of >25% in both the dielectric constant and conductivity has been observed after 3.5 h of excision, which can be associated with tissue dehydration. Results of this study are in line with the established understanding of the dehydration effects, and a comparison with *in vivo* and *ex vivo* data from the literature shows the magnitude of expected error in the *ex vivo* data. The results indicate a significant decrease in dielectric properties with tissue dehydration, and signify the importance of considering proper controls in experimental design of the *ex vivo* dielectric measurements.

Acknowledgments

The research leading to these results has received funding from the European Research Council under the European Union's Horizon 2020 Programme/ ERC Grant Agreement BioElecPro n. 637780. SK was funded by Irish Cancer Society Grant CCRC13GAL. The travel was funded by Irish Research Council New Foundations Award.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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