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Review Article

A Review of Studies Investigating the Dielectric Properties of Biological Tissues for Application in Hyperthermia and Microwave Thermal Ablation

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Abstract. Heating of biological tissues beyond 40 °C has become an established method of treating a number of diseases, most notably tumours, where hyperthermia and thermal ablation are important modalities. In some interventions, tissue temperatures reached can even go beyond 100 °C, and demand precise knowledge of tissue dielectric properties and how these vary with frequency and temperature in order to facilitate accurate computational simulations for preclinical planning. This paper reviews the available literature concerning dielectric properties of biological tissues and their temperature dependence, focusing on the frequencies of 915 MHz and 2.45 GHz, at which most of the studies reviewed investigate predominantly liver tissue. In this review a comparative analysis of the results obtained by different research groups are presented in the different studies is also made, indicating possible limiting factors in the different studies. These studies propose a number of different models which could be used to describe temperature dependence. Due to the prevalence of liver investigations, it would be ideal to conduct further studies on different biological tissues.

Keywords: Dielectric properties, biological samples, temperature variation, hyperthermia, ablation

1 Introduction

Nowadays a number of medical conditions are treated through the use of localised heating beyond normal body temperatures. Two distinct temperature ranges are employed: between 40 and 45 °C for hyperthermia (Velazquez-Ahumada, Freire & Marques, 2011; Nguyen, Abbosh & Crozier, 2015; Strohbehn, 1983; Horsman & Overgaard, 2007), and between 50 and 100 °C for thermal ablation (Lopresto, Pinto, Farina & Cavagnaro, 2017; Cavagnaro, Pinto & Lopresto, 2015; Lopresto, Pinto, Lodato, Lovisolo & Cavagnaro, 2012; Rossmann & Haemmerich, 2014). In hyperthermic processes, the increased tissue temperature increases cellular metabolism, oxygenation and blood perfusion. In an ablative process, the high temperature destroys or modifies the tissue in an irreversible manner.

Hyperthermic and ablative procedures can be used to treat cancer, varicose veins, joint laxity, hyperopia, hyperplasia and other medical conditions (Rossmann & Haemmerich, 2014; Subwongcharoen, Praditphol & Chitwiset, 2009; Brace, 2010). These procedures can be performed during open surgery, laparoscopically, percutaneously or transcutaneously (Brace, 2010). Higher temperatures affect a number of tissue properties, such as electrical, mechanical, thermal and the rate of perfusion. These changes affect the rate at which the tissue absorbs heat.

The frequencies commonly used for medical procedures are 915 MHz and 2.45 GHz (Brace, 2010). The other frequency ranges used for medical applications include 433 MHz, and broad band pulses with the greatest spectral energy density between 1 GHz and 10 GHz.

The electrical interaction between electromagnetic fields and materials is best described by the permittivity and the permeability. In the case of biological tissues at 915 MHz and 2.45 GHz, the permeability is comparable to that of free space, and is not normally considered.

Knowledge of the dielectric properties and how these change with temperature is crucial for modelling the interaction of microwaves with the body tissues. The medical industry, specialists and patients would greatly benefit from patient-specific field simulation software for treatment planning prior to medical interventions. The

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effective implementation of this software relies on accurate knowledge of the dielectric properties of the target tissues at the treatment frequency and intended temperature range.

This review presents a detailed report on the dependence of the dielectric properties of biological tissues on frequency and temperature, with specific focus on the frequencies of 915 MHz and 2.45 GHz, these being at present the most common frequencies employed in the medical field.

2 Electromagnetic Interactions with Biological Tissues

Over the frequency range of interest for current medical applications, the main effect of an electromagnetic wave interacting with biological tissue is an increase in temperature. To date, the change in temperature of the biological tissue is best modelled using Pennes' Bioheat equation (Pennes, 1949)

$$\rho c_t \frac{\partial T}{\partial t} = k \nabla^2 T + Q - \rho_{bl} c_{bl} \left(T - T_{bl}\right), \qquad (1)$$

where, ρ is the tissue density $\left(\mathrm{kg\,m^{-3}}\right)$, c_t is the specific heat capacity $\left(\mathrm{J\,kg^{-1}\,K^{-1}}\right)$, k is the thermal conductivity $\left(\mathrm{W\,m^{-1}\,K^{-1}}\right)$, and Q is the heat supplied $\left(\mathrm{W\,m^{-1}}\right)$ from the heating modality (RF or MW energy). The quantity $\rho_{bl} c_{bl} \left(T - T_{bl}\right)$ is the term used to describe the heat being lost through blood perfusion.

Many biological tissues, including cancerous have a relatively high-water content (Allen, Krzywicki & Roberts, 1959). When the incident electromagnetic field interacts with the water molecules' dipole moments, it causes them to realign periodically with the incident time-dependent field. This constant realignment of the dipoles increases the thermal energy, as a result of which the tissue temperature increases.

The microwave heat source can be modelled by

$$Q = \frac{\sigma}{2} |E|^2. \qquad (2)$$

In Eq. (2), σ is the effective conductivity $\left(\mathrm{S\,m^{-1}}\right)$ and $|E|$ is the applied electric field intensity $\left(\mathrm{V\,m^{-1}}\right)$.

In biological tissue, the heat generated by absorption of electromagnetic waves is determined by the material dielectric properties, which are described by the complex (relative) permittivity

$$\varepsilon^\star = \varepsilon' - j\varepsilon'', \qquad (3)$$

where ε' represents the real part of the relative permittivity of the material and ε'' represents the imaginary part of the permittivity. ε'' represents both the ionic conduction as well as the dipole rotation. The imaginary part of the permittivity is sometimes represented using the effective conductivity (σ), in the rest of the paper this is referred to as conductivity, as this is how it has been referred to in cited papers. Both ε' and ε'' depend on frequency, temperature, tissue type and water content.

To date many studies on a range of tissue types (see for example Farrugia, Wismayer, Mangion & Sammut, 2016; Gabriel, Lau & Gabriel, 1996; Lazebnik et al., 2007) have been carried out over the frequency range 10 kHz to 10 GHz. However, the temperature variation of dielectric properties still leaves a substantial gap in knowledge. The subsequent paragraphs provide an overview of the pertinent available literature on the subject.

In two separate studies performed by Chin and Sherar (2001, 2004), they report on the temperature coefficients of dielectric properties bovine liver and rat prostate. In both works measurements, were conducted at 915 MHz using the open-ended coaxial probe technique, and the permittivity calculated using a two-capacitor model. The samples were heated using a water bath and the temperature ranged from room temperature to 75 °C.

In the first study (bovine liver), Chin and Sherar (2001) report that during the heating process, there is an initial decrease of 5% in ε', followed by a 10% increase, eventually resulting in a 5% overall increase in ε' after 40 minutes. When examining σ, Chin and Sherar report a sharp initial increase which then stabilises to about twice the initial value after about 30 minutes (Fig. 1). The temperature coefficients reported for ε' and σ were $-0.13\,\%\,°\mathrm{C}^{-1}$ and $1.82\,\%\,°\mathrm{C}^{-1}$, respectively.

In the second study by Chin and Sherar (2004), measurements were conducted a day after excision. The tissues were stored in phosphate-buffered saline, which is shown to minimally affect the native ionic content. Despite stating that the effect of the phosphate-buffered saline was minimal, the study does not quantify this effect. This study on the temperature variation of tissue dielectric properties revealed an increase in the tissue conductivity with temperature, while the relative permittivity decreased with temperature. The study goes on to point out that, as the temperature increased, the tissue shrunk in dimensions. This would have been due to desiccation of the tissue while it was being heated, but the change in size was identified as a possible reason for the increase in measurement uncertainty at high temperatures (Chin & Sherar, 2001, 2004). The dielectric temperature coefficients for rat prostate were reported to be $-0.31\,°\mathrm{C}^{-1}$ for ε' and $1.10\,\%\,°\mathrm{C}^{-1}$ for σ.

Chin and Sherar (2004) report that, as opposed to rat prostate, the dielectric properties of bovine liver do not return to their native values on cooling. For bovine liver, Chin distinguishes between reversible and irreversible changes occurring with tissue temperature increase, where the initial decrease observed in the relative permittivity for bovine liver occurs due to reversible changes, and the increase in ε' occur due irreversible structural changes. Chin and Sherar (2004) state that "liver exhibits a more organized architecture compared with prostate" and that this is a possible explanation for the different behaviours of liver and prostate with temperature.

On comparing the two studies, it is evident that different tissues react differently to an increase in temperature. Therefore, there is a need to measure dielectric properties of different tissues at different temperatures and to see how they behave in order to construct reliable models of different tissue types for medical intervention planning.

In another study carried out by Stauffer, Rossetto, Prakash, Neuman and Lee (2003), the dielectric properties of liver tissue were studied. The samples were obtained from four different species - human, bovine, canine and porcine. The temperature variation aspect of this study is however focused on porcine and bovine liver. In the case of porcine liver, the freshly excised tissue was allowed to cool down from body to ambient temperature prior to measurements, which were carried out between 15 and 37 °C. Bovine liver measurements were conducted between 10 and 90 °C. The temperature coefficient for ε_r was $-0.2\,\%\,°\mathrm{C}^{-1}$ for porcine liver and $-0.04\,\%\,°\mathrm{C}^{-1}$ for bovine liver while σ increased steadily at approximately $1.1\,\%\,°\mathrm{C}^{-1}$ (porcine liver) and $2\,\%\,°\mathrm{C}^{-1}$ (bovine liver), as shown in Fig. 2. This study focused on a number of other aspects and as a result did not analyse the reasons for the differences in the measured increase in σ of bovine and porcine liver.

Lazebnik, Converse, Booske and Hagness (2006) measured the dielectric properties of porcine and bovine liver over the frequency range 0.5 to 20.0 GHz while

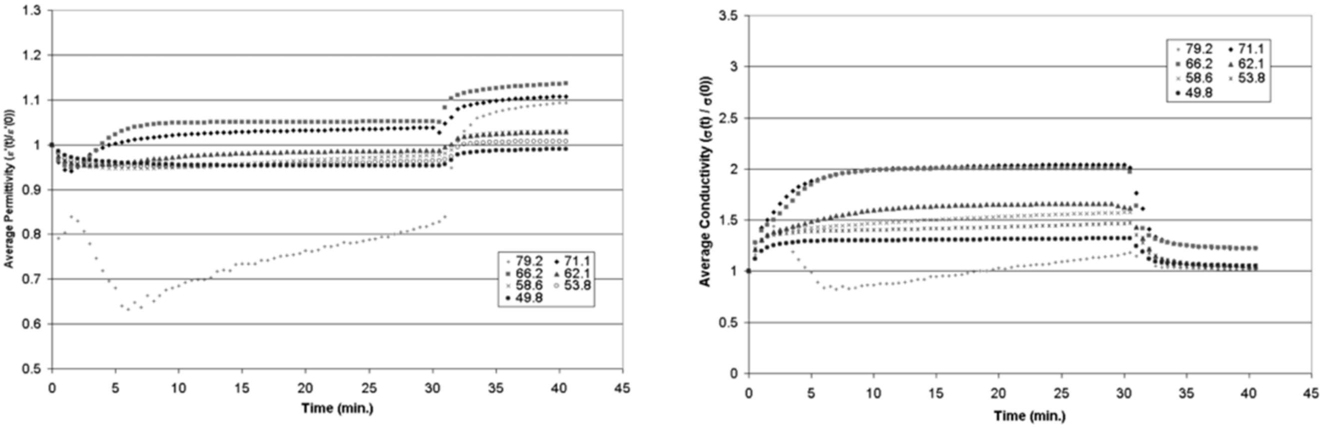

Figure 1: Changes in normalized bovine liver permittivity and conductivity, as a function of heating time for a range of target temperatures (49.8–79.2 °C). Plots obtained from Chin and Sherar (2001).

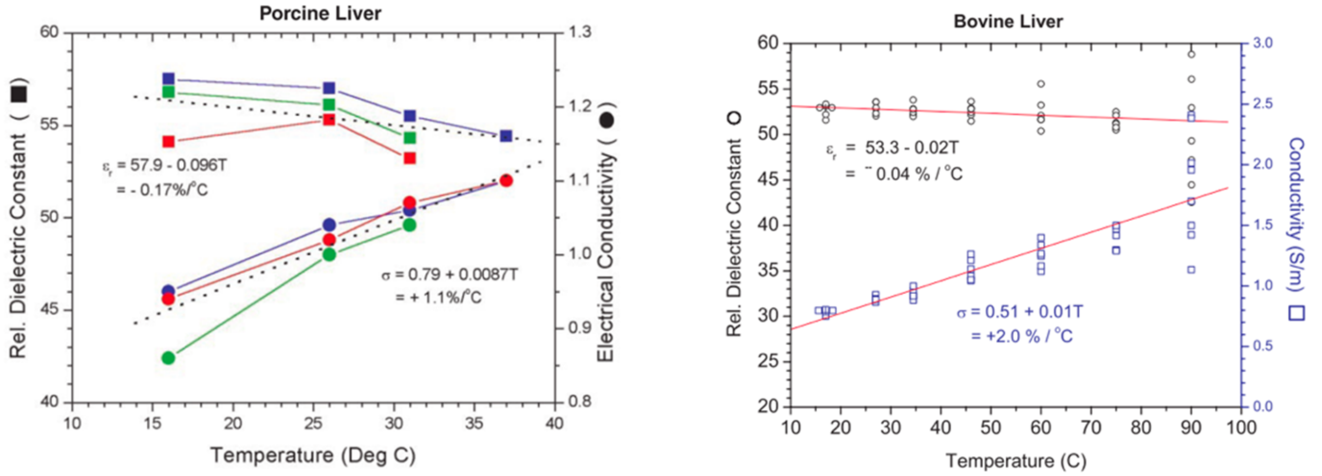

Figure 2: Dielectric properties of liver tissue at 915 MHz as a function of temperature. Plots taken from Stauffer, Rossetto, Prakash, Neuman and Lee (2003).

warming the tissue samples in an oven up to a temperature of 60 °C. They observed that the variation of the dielectric constant and conductivity are also frequency dependant, with a cross-over point at around 4 GHz, observed for the dielectric constant. There were two cross-over points for the conductivity at 3 and 15 GHz (Fig. 3). The temperature coefficients obtained at 915 MHz are $-0.20\,\%\,^{\circ}\mathrm{C}^{-1}$ and $1.33\,\%\,^{\circ}\mathrm{C}^{-1}$ for ε and σ, respectively during heating, and $-0.13\,\%\,^{\circ}\mathrm{C}^{-1}$ and $1.16\,\%\,^{\circ}\mathrm{C}^{-1}$ during cooling. At 2.45 GHz the temperature coefficients obtained were $-0.17\,\%\,^{\circ}\mathrm{C}^{-1}$ and $0.20\,\%\,^{\circ}\mathrm{C}^{-1}$ for ε and σ, respectively during heating, and $-0.090\,\%\,^{\circ}\mathrm{C}^{-1}$ and $0.008\,\%\,^{\circ}\mathrm{C}^{-1}$ during cooling.

Also highlighted in this study are the differences observed between the measurements recorded during the heating and cooling cycles. The heating cycle showed repeatable anomalies when compared to the cooling cycle. The reason given for these anomalies are non-equilibrium effects. This was consistent with Chin and Sherar's work (2001, 2004) where it was also stated that during the heating cycle there are irreversible changes taking place in the tissues. Lazebnik et al. (2006) unfortunately do not explain the phenomena which occur during the heating cycle, which would be of particular interest to medical practitioners. In Lazebnik et al. (2006) also reports non-linear dielectric coefficients, especially notable for the conductivity at 2.45 GHz. This result is similar to that reported by Sipahioglu, Barringer and Bircan (2003). Lazebnik et al. (2006) also present four quadratic equations to model the variation of dielectric properties of the material under study with temperature and frequency.

Another relevant study carried out by Brace (2008), where *ex-vivo* bovine liver tissue samples were ablated using a commercial multi-probe RF ablation system operating at 500 kHz, allowing dielectric measurements to be carried out by the open-ended coaxial probe reflection technique over the frequency range 500 MHz to 5 GHz while the tissue was being heated. The temperature coefficients obtained in this study are $-0.22\,\%\,^{\circ}\mathrm{C}^{-1}$ for ε_r and $1.29\,\%\,^{\circ}\mathrm{C}^{-1}$ for σ at 915 MHz. The variations in conductivity at 915 MHz and 2.45 GHz are shown in Fig. 4. At 2.45 GHz, the coefficients obtained were $-0.18\,\%\,^{\circ}\mathrm{C}^{-1}$ for ε_r and $-0.2\,\%\,^{\circ}\mathrm{C}^{-1}$ for σ, in contrast with the positive coefficient obtained by Lazebnik et al. (2006). Brace explains that the heating method could be a possible reason for this difference, as in this study, on the contrary to previous studies, there was no attempt at limiting water loss from the samples under test. Consequently, tissue properties were observed to vary rapidly and irreversibly when approaching 100 °C. It would prove useful to carry out further measurements on similar tissues in order to obtain a more reliable data set.

Ji and Brace (2011) investigated the dielectric properties of fresh liver in an effort to establish an empirical model to improve simulations at high temperatures. In this study, Ji and Brace used a microwave ablator operating at 2.45 GHz to heat the tissue and measured the dielectric properties with the open-ended coaxial probe technique over the frequency range 500 MHz to 6 GHz. Although the liver samples were placed in containers with normal saline, Ji and Brace do not comment on the effect that this solution had on the measured dielectric properties. The experimental outcome of this study below 70 °C was similar to that of previous studies by Lazebnik et al. (2006) and Stauffer et al. (2003).

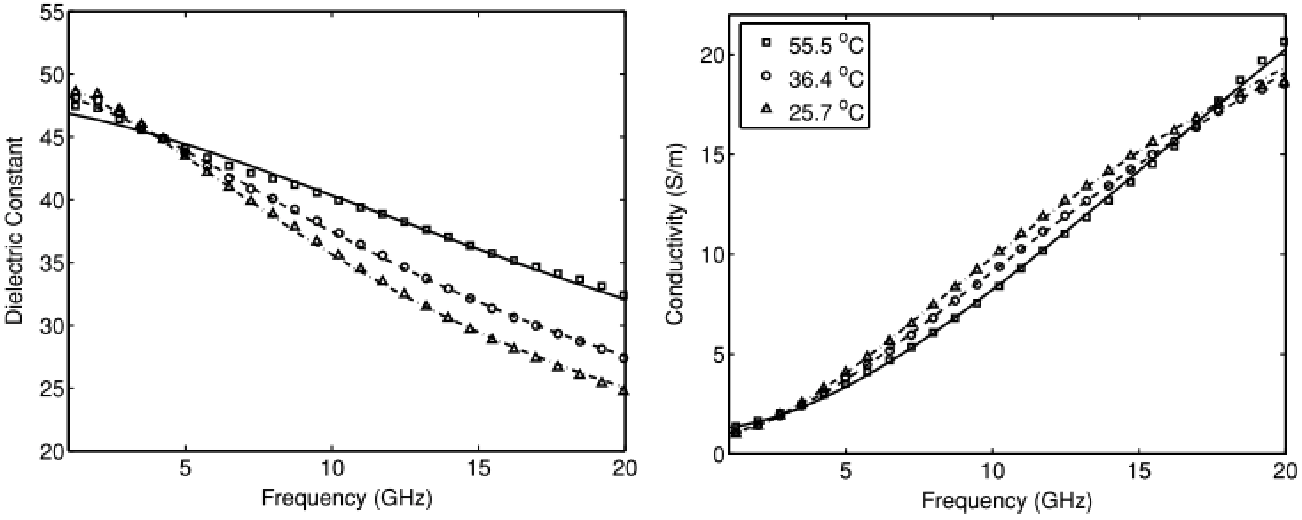

Figure 3: Example of dielectric constant and conductivity of liver tissue as a function of frequency at three distinct temperatures. Reproduced from Lazebnik, Converse, Booske and Hagness (2006).

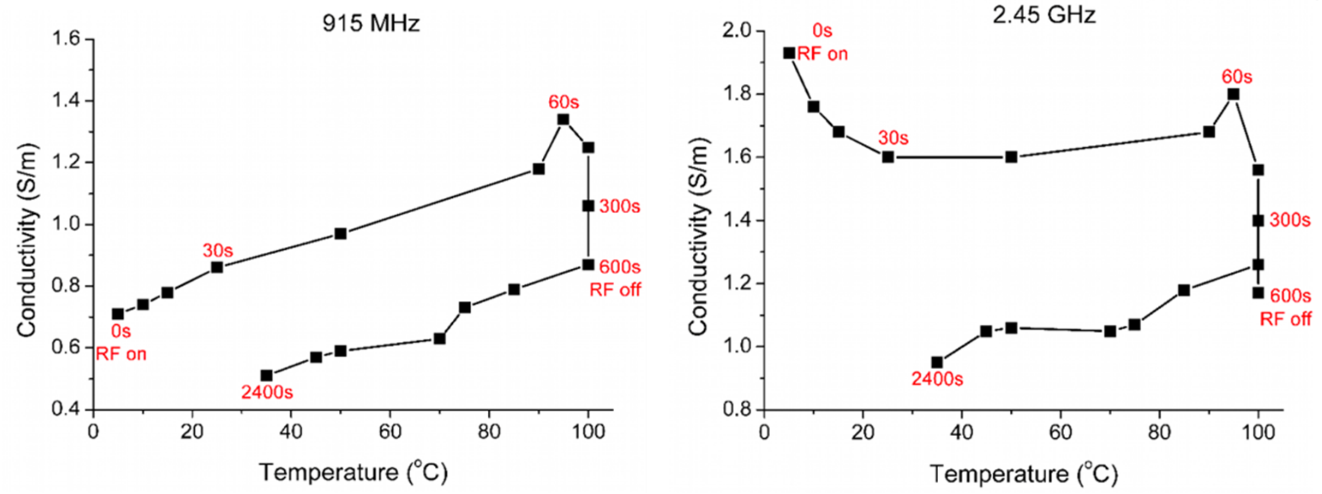

Figure 4: Plots showing changes obtained at 915 MHz and 2.45 GHz in measured conductivity of *ex-vivo* bovine liver with temperature. Reproduced from Brace (2008).

In a study performed by Ji and Brace (2011), it was established that once the 70 °C mark is surpassed, both the relative permittivity and the conductivity decrease significantly as seen from Fig. 5. In addition to the experimental results, this work also performs numerical simulations. Ji and Brace also modelled a time-temperature curve for both the relative permittivity and effective conductivity, and compare their models to others, concluding that sigmodal models better model the temperature-dependence of tissue dielectric properties. Finally, Ji and Brace note that the simulations slightly underestimated the temperatures reached when compared to experiment but these are more accurately determined with sigmodal models.

Lopresto, Pinto, Lovisolo and Cavagnaro (2012) also used a microwave ablator to heat excised bovine liver and determined the dielectric properties at 2.45 GHz. The difference between this study and that of Brace (2008) is that in Lopresto, Pinto, Lovisolo and Cavagnaro (2012) the operating frequency of the ablator was in the frequency range being investigated, and the ablator and the dielectric measurement probe were positioned at 90 °C to each other to avoid electromagnetic coupling between the two (Lopresto, Pinto, Lovisolo & Cavagnaro, 2012; Lopresto et al., 2011). Lopresto et al. compared dielectric measurements when heating the sample tissue with the ablator and in a water bath, and concluded that the heating method was not responsible for any significant differences in the measured values. The final part of their study incorporated computer simulations that compared reasonably well with the measurements.

A further contribution of Lopresto, Pinto, Lovisolo and Cavagnaro (2012) was that they reported on the dependence of the variation of dielectric properties with temperature on the size of the thermal lesion caused by the ablator. The importance of being able to predict the extent of the thermal lesion cannot be overstated in any planned treatment, as the goal is always to extend this to just beyond the tumour region, in order to ensure the destruction of the entire tumour region, while restricting as much as possible the thermal damage to the surrounding healthy tissue. This work also confirms the findings of Brace (2008) that there is a decrease

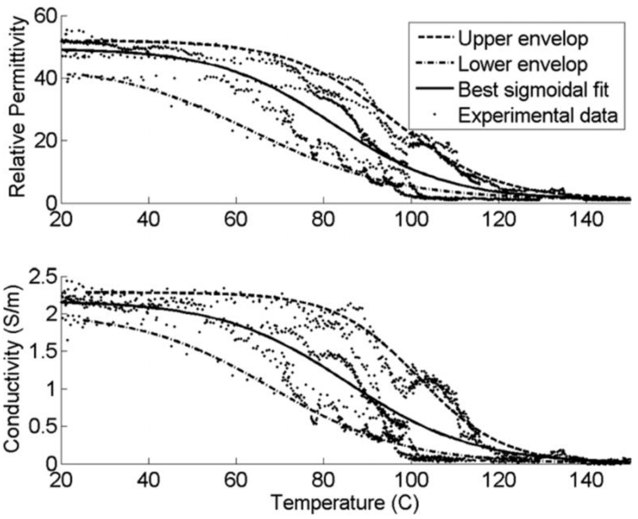

Figure 5: Experimental results (dots) of relative permittivity and conductivity at 2.45 GHz versus temperature during microwave ablation. Also shown are the best-fit sigmoidal curves (solid lines), along with the upper and lower envelops (dashed lines) used for numerical simulation. Plots taken from Ji and Brace (2011).

in the tissue permittivity and conductivity with temperature, as opposed to what was reported by Stauffer et al. (2003). The differences could be due to the fact that Stauffer et al. report on measurements at 915 MHz, whereas in the work of Lazebnik et al. (2006) a turning point is reported between 915 MHz and 2.45 GHz.

A study reported by Jaspard, Nadi and Rouane (2003) investigated the temperature dependence of the dielectric properties of blood, measured with an electrical impedance analyser in the frequency range from 1 MHz to 1 GHz. The conductivity is reported to be sensitive to tissue temperature increases at a rate of 1 % °C^{-1}. In contrast, the variations measured for the permittivity were reported to be around 0.3 % °C^{-1} at 1 MHz and −0.3 % °C^{-1} at 1 GHz, with a change in gradient at 50 MHz. The permittivity increased with temperature till 50 MHz and then decreased with temperature.

The frequency ranges used in interventions related to magnetic resonance image-guided focused ultrasound surgery (MRgFUS) are from 42.58 MHz to 468 MHz. The work reported by Fu, Xin and Chen (2014) measured the dielectric properties of porcine uterus, liver, kidney, urinary bladder, skeletal muscle and fat from 36 °C to 60 °C in this frequency range. They reported the highest positive temperature gradients at 42.6 and 64 MHz for all tissues except fat.

Zhuang, Nelson, Trabelsi and Savage (2007) measured the dielectric properties of chicken breast over the temperature range of 5 °C to 85 °C from 10 MHz to 1.8 GHz. They conclude that below 100 MHz the increase in both the dielectric constant and loss factor are constant with temperature. Zhuang et al. (2007) also show that the change in dielectric properties with temperature also depends on the type of muscle under study and note that there is no difference in both the loss factor and dielectric constant resulting from time following deboning.

Some other studies which examined the variation of dielectric properties with temperature were those of Macchi, Gallati, Braschi and Persi (2014), Ryan, Platt, Dadd and Humphries (1997) and Zurbuchen et al. (2010). However, all these studies were conducted at or below 0.5 MHz and hence fall outside the remit of interest of this review.

From the studies at 915 MHz, tissue dependence can be noted in temperature coefficients of dielectric properties. Chin and Sherar report a −0.13 % °C^{-1} for bovine liver (Chin & Sherar, 2001) and −0.31 % °C^{-1} for rat prostate (Chin & Sherar, 2004). The temperature gradients also depend on temperature range, as indicated by Stauffer et al. (2003), who obtained a temperature gradient of −0.04 % °C^{-1} in ε', which is lower than the values reported in Stauffer et al. (2003) over a wider temperature range, and those reported in Chin and Sherar (2004) and Lazebnik et al. (2006).

At 2.45 GHz, studies by Brace (2008) and Lopresto, Pinto, Lovisolo and Cavagnaro (2012), Lopresto et al. (2011) report a negative temperature gradient of ε' while Lazebnik temperature gradient reported is positive. The main difference between the studies was the tissue heating, as in Lazebnik et al. (2006) the tissue was heated in an oven while in Brace (2008), Lopresto, Pinto, Lovisolo and Cavagnaro (2012) and Lopresto et al. (2011), tissue samples were either heated with a thermal ablator or in a water bath. A decrease in dielectric properties with temperature is most likely due to decreasing tissue water content with temperature, as water content is the major factor affecting dielectric properties in biological tissue. These observations are confirmed by measurements we conducted on freshly excised tissues which in the process for publication.

3 Conclusion

This work reports on studies of the variation of dielectric properties of biological tissue at super physiological temperatures. It is established that the dielectric properties of biological tissues of all types vary with temperature. There is consensus that tissues heated to temperatures exceeding 60 °C undergo irreversible physiological changes. In experiments carried out by our research group resulted in negative temperature gradients of tissue permittivity and conductivity, in line with those reported by other groups. This continues to strengthen the view that tissue desiccation during heating is the main reason for the observed changes.

Finally, we note that the majority of published studies focus on the dielectric properties of liver, which is an organ with a high-water content. It would be useful for further studies of the behaviour of dielectric properties with temperature to be conducted on different tissues.

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