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Dielectric properties of human normal, malignant and cirrhotic liver tissue: *in vivo* and *ex vivo* measurements from 0.5 to 20 GHz using a precision open-ended coaxial probe

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Abstract

Hepatic malignancies have historically been treated with surgical resection. Due to the shortcomings of this technique, there is interest in other, less invasive, treatment modalities, such as microwave hepatic ablation. Crucial to the development of this technique is the accurate knowledge of the dielectric properties of human liver tissue at microwave frequencies. To this end, we characterized the dielectric properties of *in vivo* and *ex vivo* normal, malignant and cirrhotic human liver tissues from 0.5 to 20 GHz. Analysis of our data at 915 MHz and 2.45 GHz indicates that the dielectric properties of *ex vivo* malignant liver tissue are 19 to 30% higher than normal tissue. The differences in the dielectric properties of *in vivo* malignant and normal liver tissue are not statistically significant (with the exception of effective conductivity at 915 MHz, where malignant tissue properties are 16% higher than normal). Also, the dielectric properties of *in vivo* normal liver tissue at 915 MHz and 2.45 GHz are 16 to 43% higher than *ex vivo*. No statistically significant differences were found between the dielectric properties of *in vivo* and *ex vivo* malignant tissue (with the exception of effective conductivity at 915 MHz, where malignant tissue properties are 28% higher than normal). We report the one-pole Cole–Cole parameters for *ex vivo* normal, malignant and cirrhotic liver tissue in this frequency range. We observe that wideband dielectric properties of *in vivo* liver tissue are different from the wideband dielectric properties of *ex vivo* liver tissue, and that the *in vivo* data cannot be represented in terms of a Cole–Cole model. Further work is needed to uncover the mechanisms responsible for the observed wideband trends in the *in vivo* liver data.

1. Introduction

The liver is a common site for both primary and secondary malignancies. Colorectal (the most common secondary tumor) and hepatocellular (HCC) cancers are the third and fifth most common cancers worldwide, respectively, combined causing an estimated million deaths annually (Bosch *et al* 2005, Jemal *et al* 2004). Currently, the clinical standard of care and best chance for cure for both HCC and hepatic colorectal cancer metastases is liver resection; however, most patients (∼80%) have a disease that is not amenable to this procedure (Jamison *et al* 1997). To increase the number of patients who have a chance for cure, a number of technologies have been developed as alternatives to resection for the local control of liver tumors, such as radiofrequency ablation and cryoablation (Garcea *et al* 2003, Wright *et al* 2003). One novel alternative is microwave ablation (MWA), wherein a microwave antenna is inserted into the liver tumor and power is delivered to induce cellular coagulation necrosis of the tumor and a margin of the surrounding liver tissue (see, for example, Bertram *et al* (2006) and references therein).

Critical to the design and modeling of MWA antennas is an accurate understanding of the tissue dielectric properties at microwave frequencies. Previously published studies of the dielectric properties of liver tissue in the radio and microwave frequency ranges involve *in vivo* and *ex vivo* measurements of animal liver and *ex vivo* measurements of human liver. The survey of previous studies presented in table 1 shows that very little data exist on the dielectric properties of malignant human liver tissue, and no data exist on *in vivo* human liver tissue. The lack of *in vivo* data is a concern because physiological processes, such as perfusion, as well as temperature and water content changes, can impact the microwave dielectric properties of biological tissues (Foster and Schwan 1989).

To address these lingering questions, we have characterized the dielectric properties of human liver tissues *in vivo* and *ex vivo* in the microwave frequency range using an open-ended coaxial probe technique. This study provides important new insights on the differences in dielectric properties between *in vivo* and *ex vivo*, as well as normal and diseased, human liver tissues.

Our analysis includes a comparison of the narrowband (915 MHz and 2.45 GHz) and wideband (0.5 to 20 GHz) dielectric properties of normal and diseased human liver tissues. The narrowband results are relevant to current hepatic microwave applications which use ISM-band frequencies, namely 915 MHz and 2.45 GHz (Bertram *et al* 2006, Chin and Sherar 2001, Brace *et al* 2005, Wright *et al* 2005, Yang *et al* 2006). The wideband results inherently characterize important microwave dielectric relaxation processes, as well as provide dielectric properties data at a large number of frequencies for possible future applications.

We conducted measurements on normal, cirrhotic and malignant human liver tissues. Dielectric properties data for cirrhotic liver tissue were acquired and processed separately from normal tissue for several reasons. First, the cellular architecture of cirrhotic tissue is inherently different from that of normal hepatic parenchymal tissue due to the presence of fibrosis. Second, one of the major tumor types treated with MWA is HCC, which frequently arises in cirrhotic livers; thus, the knowledge of the dielectric properties of both normal and cirrhotic liver tissue is valuable for this application. For completeness, we also conducted similar measurements on porcine liver *in vivo* and *ex vivo*.

The remainder of this paper is organized as follows. Section 2 describes the methodology for obtaining tissue samples, conducting dielectric spectroscopy measurements and data analysis. Section 3 describes the results of the human and porcine tissue studies. Finally, section 4 summarizes the major conclusions of this study.

Table 1. Chronological summary of previously published studies on the dielectric properties of liver tissues in radio and microwave frequency ranges.

Tissue source	Tissue type	Frequency range	Reference
Bovine (*ex vivo*)	Normal	2, 3, 4 GHz	Brady *et al* (1981)
Feline (*in vivo*)	Normal	10 MHz–1 GHz	Stuchly *et al* (1981)
Feline (*in vivo*, *ex vivo*)	Normal	100 MHz–8 GHz	Kraszewski *et al* (1982)
Feline and rat (*in vivo*)	Normal	100 MHz–10 GHz	Stuchly *et al* (1982)
Bovine (*ex vivo*)	Normal	20 kHz–100 MHz	Surowiec *et al* (1985)
Bovine (*ex vivo*)	Normal	100 MHz–2.5 GHz	Tran and Stuchly (1987)
Human (*ex vivo*)	Normal, malignant	50 MHz–900 MHz	Joines *et al* (1994)
Ovine and human (*ex vivo*)	Normal	10 Hz–20 GHz	Gabriel *et al* (1996a)
Bovine (*ex vivo*)	Normal	915 MHz	Chin and Sherar (2001)
Rat (*ex vivo*)	Normal	130 MHz–10 GHz	Peyman *et al* (2001)
Human (*ex vivo*), bovine, canine, porcine (*in vivo, ex vivo*)	Normal, malignant	0.3 GHz–3 GHz	Stauffer *et al* (2003)
Bovine, porcine (*ex vivo*)	Normal	500 MHz–20 GHz	Lazebnik *et al* (2006)

2. Materials and methods

2.1. Source of tissue

The protocol for measuring the dielectric properties of *in vivo* and *ex vivo* human liver tissue was approved by the Institutional Review Board after it was reviewed by the University of Wisconsin–Madison (UW) Human Subjects Committee. Six patients with either HCC or hepatic metastases scheduled to undergo hepatic resection were included in the study. Patients were eligible if the tumor to be resected was on the surface of the liver. Patients with cirrhosis were not excluded. Exclusion criteria included prisoners, minors, adults with impaired decision making capacity, pregnant women and people with implanted pacemakers. All patients gave informed consent.

The protocol for measuring the dielectric properties of *in vivo* and *ex vivo* animal tissue was approved by the UW Institutional Animal Care and Use Committee. We conducted *in vivo* measurements on liver tissue in two animals and *ex vivo* measurements on excised tissue from two animals.

2.2. Data acquisition

Measurements of complex permittivity were performed using the custom designed, hermetically sealed, open-ended coaxial probe and associated techniques described in Popovic *et al* (2005). Our 3 mm diameter flange-free precision probe is particularly well suited for this application because (1) the small aperture size allows for excellent contact with the tissue sample, (2) the hermetic seal prevents fluid leakage into the aperture, and (3) the materials are chemically inert and thermally matched, resulting in very robust probe performance. Extensive prior characterization and validation studies (Popovic *et al* 2005) have demonstrated the reliable performance of this precision probe technique. The sensing depth of the probe is approximately 1 to 3 mm (Hagl *et al* 2003).

During each experiment, the tip of the probe was placed in contact with the tissue under test (see figure 1). An Agilent 8720ES vector network analyzer was used to record the frequency-

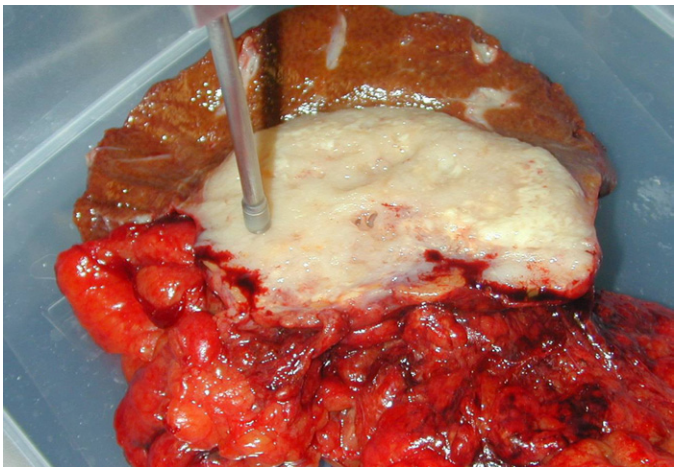

Figure 1. Dielectric spectroscopy of an excised liver tumor (light-colored mass), using a precision open-ended coaxial probe (shown with the tip making contact with the tissue).

(This figure is in colour only in the electronic version)

dependent complex reflection coefficient at the calibration plane of the probe. Measurements were performed over the frequency range of 0.5 to 20 GHz, with approximately 15 s required for a complete frequency sweep. Each measurement was performed with the probe held firmly in place by the surgeon (*in vivo*), or with the probe secured in a test jig (*ex vivo*) for the duration of the frequency sweep. Following the completion of all measurements, the reflection coefficient was converted into the tissue complex permittivity using the de-embedding and rational function models described in Popovic *et al* (2005).

2.2.1. Human liver tissue experiments. Prior to each experiment, the probe was gas sterilized as required for *in vivo* procedures. *In vivo* measurements were performed on each tissue type (normal, cirrhotic and malignant) identified by the surgeon in the operating room at the UW hospital. After resection, the sample was transported to the pathology suite at the UW hospital. Measurements were subsequently repeated *ex vivo* in the pathology suite approximately 30 min after excision. For *ex vivo* tissue measurements, full gas sterilization was not required, and instead the probe was cleaned with an alcohol wipe prior to every measurement. For both the *in vivo* and *ex vivo* procedures, the probe was placed at two or three different locations in a region of a given tissue type, and one frequency sweep was performed at each location. In the case of patient 5, we were able to collect more *ex vivo* measurements than for the other patients. Some of the measurement locations were marked and preserved for histological identification, with both tumor type and hepatic parenchyma margins evaluated. In addition, we recorded tissue temperature during the *ex vivo* measurements. We were not able to record temperature data during the *in vivo* measurements due to the hospital sterilization requirements.

2.2.2. Porcine liver tissue experiments. Baseline data acquisition from porcine tissue was performed following the same experimental protocol as in the human experiments. We collected three to five measurements during each experiment. We also conducted additional experiments to validate the experimental protocol and verify the integrity of our human data. For both *in vivo* and *ex vivo* porcine tissues, we performed measurements using an unsterilized probe cleaned only with an alcohol wipe, a probe that had been gas sterilized, and a gas

sterilized probe that was subsequently cleaned with an alcohol wipe (henceforth, these will be referred to as the 'unsterilized probe', 'sterilized probe' and 'wiped probe,' respectively). The 'sterilized probe' and 'wiped probe' represent the state of the probe during the *in vivo* and *ex vivo* human experiments, respectively. In addition, we tested two different probes of identical design to rule out any errors due to the probe itself. Finally, since all *in vivo* human data were obtained with a handheld probe, we also performed an *ex vivo* measurement on animal tissue with the probe held manually, without a stand.

2.3. Single-frequency data analysis

Since microwave applications in biomedicine commonly use either 915 MHz or 2.45 GHz, as discussed in section 1, we separately calculated the mean relative permittivity and effective conductivity at these two frequencies for *ex vivo* and *in vivo* malignant, cirrhotic and normal liver data from the raw data. We evaluated the differences in the dielectric properties between *in vivo* and *ex vivo* tissues, and between different tissue types (normal, cirrhotic and malignant) at 915 MHz and 2.45 GHz, using a likelihood ratio test. We accounted for the fact that some data were paired and some were unpaired by modeling the data with a random subject effect (Armitage *et al* 2002).

2.4. Wideband data analysis

Cole–Cole models are commonly used as physics-based compact representations of wideband frequency dependent dielectric properties (Gabriel *et al* 1996b). A MATLAB fitting function that performs the Nelder–Mead direct search optimization was used to fit the following single-pole Cole–Cole model to our data over the frequency range of 0.5 to 20 GHz:

$$\hat{\varepsilon}(\omega) = \varepsilon_\infty + \frac{\Delta\varepsilon}{1 + (\mathrm{j}\omega\tau)^{(1-\alpha)}} + \frac{\sigma}{\mathrm{j}\omega\varepsilon_0}.$$

In this model, ε_∞, $\Delta\varepsilon$, τ and σ are variable parameters chosen to fit the experimental data. We set α, which is an empirical parameter that accounts for the observed broad distribution of relaxation time constants in tissue, to 0.1. This choice is consistent with the value reported by Gabriel *et al* (1996b) for liver. Limits were set on the parameters in the fitting routine so that they would remain within physical ranges (i.e., $\varepsilon_\infty \geqslant 1$, $\Delta\varepsilon \geqslant 0$, $\sigma \geqslant 0$ and $\tau \geqslant 0$). In a previous study (Lazebnik *et al* 2006), it was shown that a single-pole model (with a ps time constant) is sufficient to model liver tissue dielectric properties data in the 0.5 to 20 GHz range.

3. Results and discussion

3.1. Human liver tissue properties

3.1.1. Overview. Table 2 presents a summary of the measurement details. We did not perform *ex vivo* measurements on patients 3 and 6, as widespread abdominal disease lead to the decision to cancel liver resection. In addition, we did not perform *in vivo* measurements on patient 4. Therefore, we obtained measurements on a total of five livers *in vivo* and four livers *ex vivo*. The cancer types were as follows: one primary HCC (patient 1) tumor and five metastatic [one squamous cell (patient 2), one pancreatic (patient 3) and three colorectal (patients 4, 5, 6)] tumors. The temperature of the *ex vivo* samples for all six patients varied between about 20 °C and 24 °C. Since the sample sizes for the individual tumor types are small, we decided to combine all cancer data into a single 'malignant' category. Furthermore,

Table 2. Summary of measurement numbers for the six patients.

	In vivo measurements			*Ex vivo* measurements			
Patient no.	Normal	Malignant	Cirrhotic	Normal	Malignant	Cirrhotic	Cancer type
1	0	3	3	0	3	3	Primary HCC
2	3	3	0	4	3	0	Squamous cell
3	3	3	0	0	0	0	Pancreatic
4	0	0	0	4	3	0	Colorectal
5	3	3	0	12	15	0	Colorectal
6	2	2	0	0	0	0	Colorectal
Total	11	14	3	20	24	3	

Table 3. Average and standard deviation values for the relative permittivity and effective conductivity for *in vivo* samples at 915 MHz and 2.45 GHz.

	Normal ($n = 11$)		Malignant ($n = 14$)		Cirrhotic ($n = 3$)	
	ε_r	σ (S m^{-1})	ε_r	σ (S m^{-1})	ε_r	σ (S m^{-1})
915 MHz	59.94*	1.16*, †	64.09	1.34*, †	61.77	1.38
	±3.05	±0.14	±3.78	±0.13	2.58	±0.15
2.45 GHz	57.55*	1.95*	62.44	2.18	61.26	2.21
	±3.92	±0.18	±3.18	±0.13	±2.70	±0.17

n: number of data samples.
* $p < 0.05$ in a comparison of the *in vivo* and *ex vivo* tissue properties at the same frequency.
† $p < 0.05$ in a comparison of the normal and malignant tissue properties at the same frequency.

Table 4. Average and standard deviation values for the relative permittivity and effective conductivity for *ex vivo* samples at 915 MHz and 2.45 GHz.

	Normal ($n = 20$)		Malignant ($n = 24$)		Cirrhotic ($n = 3$)	
	ε_r	σ (S m^{-1})	ε_r	σ (S m^{-1})	ε_r	σ (S m^{-1})
915 MHz	48.11*, †	0.81*, †	57.09†	1.05*, †	51.60	0.94
	±7.67	±0.15	±3.00	±0.07	±2.69	±0.07
2.45 GHz	45.79*, †	1.68*, †	54.88†	1.99†	50.16	1.83
	±7.53	±0.27	±3.10	±0.11	±2.36	± 0.11

n: number of data samples.
* $p < 0.05$ in a comparison of the *in vivo* and *ex vivo* tissue properties at the same frequency.
† $p < 0.05$ in a comparison of the normal and malignant tissue properties at the same frequency.

since the sample size for cirrhotic liver tissue was much smaller than for other tissue types, we elected not to make any general statements about the dielectric properties differences between cirrhotic and other liver tissues.

3.1.2. Comparison of single-frequency in vivo and ex vivo data. Tables 3 and 4 summarize the dielectric properties of *in vivo* and *ex vivo*, respectively, normal, malignant and cirrhotic human liver tissues at 915 MHz and 2.45 GHz. The mean and standard deviation values for both the relative permittivity and effective conductivity were computed for five patients for *in vivo* tissue (table 3), and for four patients for *ex vivo* tissue (table 4). In addition, the p values are shown for comparisons of *in vivo* and *ex vivo* properties as well as for normal and malignant tissue properties, at the same frequency.

Analysis of the data at 915 MHz and 2.45 GHz reveals statistically significant ($p < 0.05$) differences between the *in vivo* and *ex vivo* normal tissue dielectric properties. The *in vivo* relative permittivity for normal liver tissue is 25% higher at 915 MHz and 2.45 GHz than *ex vivo* relative permittivity; the *in vivo* effective conductivity for normal tissue is 43% higher at 915 MHz, and 16% higher at 2.45 GHz than the *ex vivo* effective conductivity. Furthermore, the effective conductivity of *in vivo* malignant tissue is 28% higher than the effective conductivity of *ex vivo* malignant tissue at 915 MHz. These findings suggest that when modeling the *in vivo* performance of hepatic MWA antennas, particularly those that are highly sensitive to the dielectric properties of the tissue into which they are inserted, the use of dielectric properties data obtained from *ex vivo* studies may result in inaccurate simulation results. This is true at both 915 MHz and 2.45 GHz.

3.1.3. Comparison of single-frequency normal and malignant tissue data. Table 3 shows that there are almost no statistically significant differences between the *in vivo* normal and malignant tissue dielectric properties. However, a comparison between *ex vivo* normal and malignant tissue (table 4) reveals statistically significant differences ($p < 0.05$) for both relative permittivity and effective conductivity at both 915 MHz and 2.45 GHz. At 915 MHz, *in vivo* effective conductivity for malignant tissue is about 16% higher than for normal tissue, *ex vivo* relative permittivity for malignant tissue is 19% higher than for normal tissue, and *ex vivo* effective conductivity for malignant tissue is 30% higher than for normal tissue. At 2.45 GHz, *ex vivo* relative permittivity for malignant tissue is 20% higher than for normal tissue, and *ex vivo* effective conductivity for malignant tissue is 18% higher than for normal tissue. These findings emphasize the importance of accounting for the tissue state when incorporating dielectric properties data into numerical models of MWA.

3.1.4. Comparison with previous studies at 915 MHz and 2.45 GHz. Figure 2 shows a comparison between the dielectric properties of human liver tissue in this study with previously published results at two discrete frequencies. The *ex vivo* relative permittivity and effective conductivity found in this study are consistent with those reported by Stauffer *et al* (2003) and Gabriel *et al* (1996a) at 915 MHz and 2.45 GHz. These two studies were chosen for comparison because they report results for human liver tissue in the same frequency range as our data. It should be noted that Gabriel *et al* (1996a) only report data for normal liver tissue at 37 °C, and the temperature range in the Stauffer *et al* (2003) study is 21 to 34 °C.

3.1.5. Wideband analysis. Figure 3 shows the *in vivo* and *ex vivo* relative permittivity and effective conductivity as a function of frequency for patient 5. The results for the other patients were very similar to these, and are not shown. Each curve in figure 3 represents an average across the different measurement locations for a given tissue type. Comparing figures 3(a) and (b), as well as 3(c) and (d), it is evident that the wideband trends generally follow the single-frequency trends discussed in sections 3.1.2 and 3.1.3, except for the cross-over in the normal and malignant *in vivo* tissue properties above about 15 GHz.

Figure 4 shows an example of a single-pole Cole–Cole fit to normal *ex vivo* human liver data from 0.5 to 20 GHz for patient 5. The results for the other patients are similar, and are not shown. Table 5 shows the mean and standard deviation values of the Cole–Cole parameters calculated across four patients where *ex vivo* data (normal, malignant, cirrhotic) were available. For comparison, we include the Cole–Cole parameters for normal animal liver tissue reported in Lazebnik *et al* (2006) at 20 °C. Figure 4 illustrates the excellent fit of the single-pole Cole–Cole model to the *ex vivo* data over the entire 0.5 to 20 GHz frequency

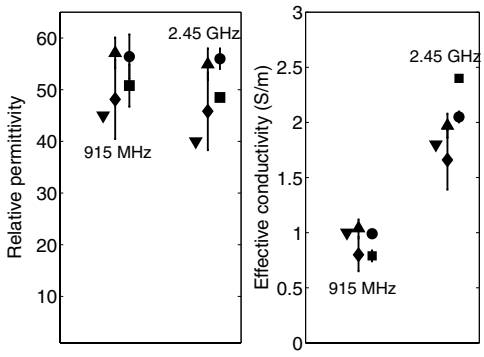

Figure 2. Comparison of the relative permittivity and effective conductivity (S/m) of *ex vivo* data in this study (normal (♦), malignant (▲)), with data reported in Stauffer *et al* (2003) (normal (■), malignant (●)), and Gabriel *et al* (1996a) (normal (▼)). The error bars for this study correspond to the standard deviation. The error bars for the Stauffer *et al* (2003) study correspond to the range of data given. No range is provided in Gabriel *et al* (1996a).

Table 5. Cole–Cole parameters for *ex vivo* data for normal, malignant and cirrhotic liver tissue at ∼20 °C. Also shown for comparison are the Cole–Cole parameters for normal animal liver tissue at 20 °C as reported in Lazebnik *et al* (2006). In both studies, α was set to 0.1 and was not considered as a fitting parameter.

	Normal ($n = 20$)	Data from Lazebnik *et al* (2006)	Malignant ($n = 24$)	Cirrhotic ($n = 3$)
ε_∞	5.32 ± 1.47	6.73	4.60 ± 1.24	6.09 ± 1.37
$\Delta\varepsilon$	44.23 ± 7.64	45.09	54.26 ± 4.15	46.81 ± 2.63
τ (ps)	11.55 ± 0.99	11.54	10.82 ± 0.51	10.45 ± 0.42
σ (S/m)	0.25 ± 0.04	0.65	0.21 ± 0.03	0.74 ± 0.06

n: number of data samples.

range. In addition, the Cole–Cole parameters calculated in this study for *ex vivo* normal liver data generally agree with the previously published data very well (table 5). The value of σ reported in Lazebnik *et al* (2006) is closer to the value for σ found for cirrhotic liver tissue in this study, although we do not have an explanation for this finding.

3.2. Porcine liver tissue properties

While characterizing the animal tissue properties, we compared the results obtained using two precision probes that are identical in design. Our results were very similar with both probes. In addition, we compared the results obtained by varying the probe cleaning procedure. Figure 5(a) shows representative relative permittivity curves obtained for each of the three cases ('unsterilized probe', 'sterilized probe' and 'wiped probe') tested during the *in vivo* porcine tissue measurements. Each curve represents an average of 3–5 measurements. For comparison, we include an *in vivo* human normal liver measurement for patient 5 (the same as in figure 3). Figure 5(b) shows the corresponding relative permittivity curves for the *ex vivo* case. Figures 5(c) and (d) show the effective conductivity curves for *in vivo* and *ex vivo* measurements, respectively. Note that the 'sterilized probe' and 'wiped probe' data were acquired from the same animal, while the 'unsterilized probe' data were acquired separately from a different animal.

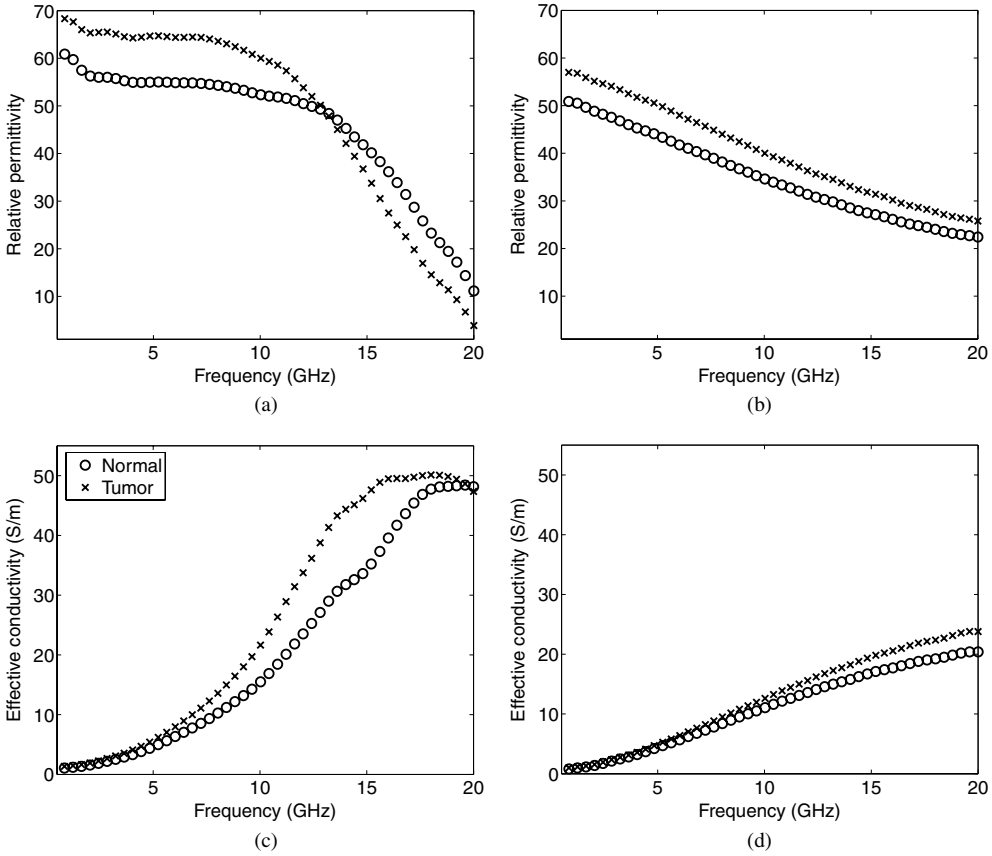

Figure 3. Measured wideband (0.5 to 20 GHz) dielectric properties of malignant and normal human liver tissue *in vivo* and *ex vivo* (patient 5). (a) *In vivo* relative permittivity, (b) *ex vivo* relative permittivity, (c) *in vivo* effective conductivity, and (d) *ex vivo* effective conductivity. Normal tissue: o, malignant tissue: x.

Figure 5 demonstrates that the 'unsterilized probe,' 'sterilized probe' and 'wiped probe' curves for both the *in vivo* and *ex vivo* porcine data are very similar. The small differences observed between the curves are most likely due to differences in measurement locations, as well as inherent between-animal variability in the dielectric properties. In addition, the results between the two identically designed probes are consistent with each other. Finally, when we collected *ex vivo* measurements with a handheld probe, the resulting relative permittivity and effective conductivity curves were not only similar in terms of frequency-dependent trends but also in terms of absolute values, within experimental uncertainty, to the *ex vivo* measurements taken with a stand.

3.3. Trends observed in both human and porcine liver tissue properties

The differences we observe in the *in vivo* and *ex vivo* liver tissue dielectric properties below approximately 10 GHz are quantitative in nature; namely, at any given frequency in this range, the *in vivo* properties are higher than the *ex vivo* properties. There are no significant qualitative differences in the dispersion trends observed over this range. In general, quantitative

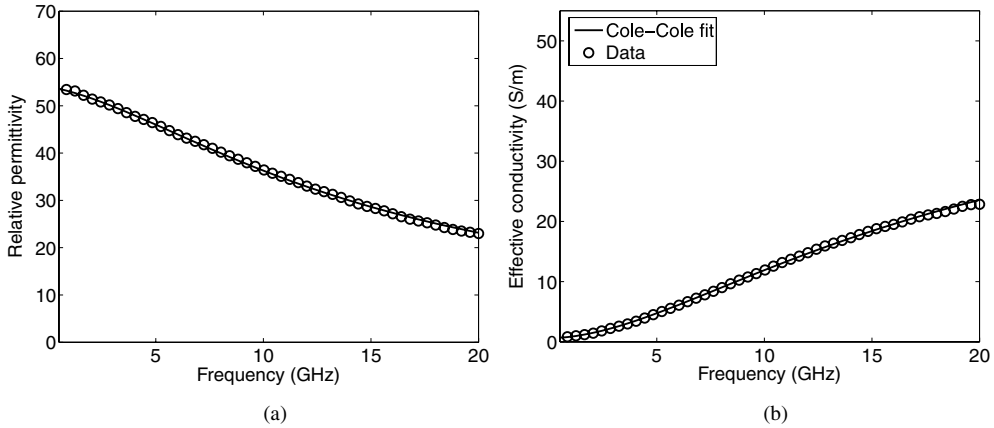

Figure 4. Example of Cole–Cole fit for (a) *ex vivo* relative permittivity and (b) *ex vivo* effective conductivity for normal liver data from patient 5.

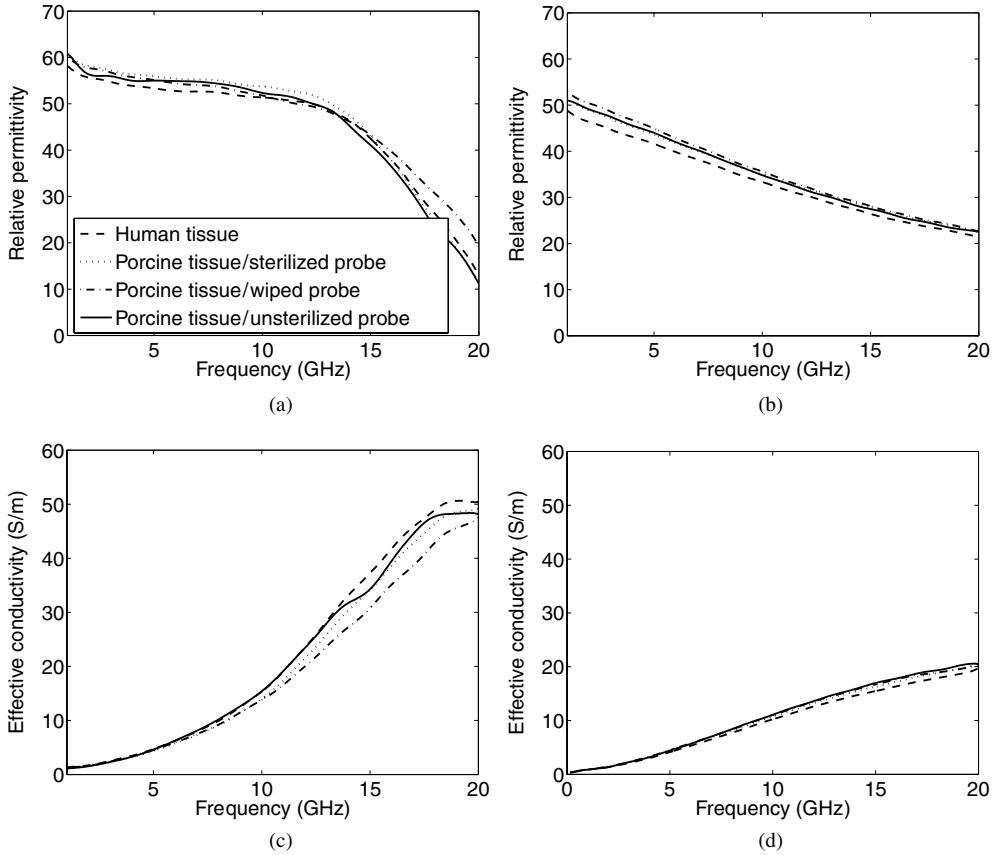

Figure 5. Comparisons of dielectric properties data for normal human liver tissue and various probe measurement scenarios with porcine liver. (a) *In vivo* relative permittivity, (b) *ex vivo* relative permittivity, (c) *in vivo* effective conductivity and (d) *ex vivo* effective conductivity.

differences between *in vivo* and *ex vivo* tissue properties are commonly attributed to variation in tissue temperature and water content. Our previous work (Lazebnik *et al* 2006) has shown that, below about 4 GHz, the relative permittivity of *ex vivo* liver tissue decreases and effective conductivity increases as tissue temperature increases. If we assume that the *in vivo* tissue temperature is close to 37 °C, then based on temperature changes alone, we expect the relative permittivity of *in vivo* tissue below 4 GHz to be lower than that of the *ex vivo* tissue. This is the opposite of the observed effect. On the other hand, the effective conductivity does follow the expected temperature-dependent trend. In addition, we have previously shown that the dielectric properties of animal liver tissue at 915 MHz and 2.45 GHz change about 1% $^{\circ}C^{-1}$ (Lazebnik *et al* 2006). In this study, the temperature of the *ex vivo* tissue samples for all six patients varied between about 20 and 24 °C. Therefore, due to temperature alone, the differences between the *ex vivo* and *in vivo* tissue properties (at 915 MHz and 2.45 GHz) should be no more than about 17% since the maximum variation in *ex vivo* and *in vivo* tissue temperature is about 17 °C. Yet the observed differences between *in vivo* and *ex vivo* data are as large as about 40%. Thus, we conclude that temperature alone does not explain the observed *in vivo* and *ex vivo* dielectric properties differences below 10 GHz.

Previous studies have reported that above about 100 MHz, tissue dielectric properties change only slightly within a few hours after tissue excision. For example, Kraszewski *et al* (1982) and Stuchly and Stuchly (1984) found that the dielectric properties of cat skeletal muscle do not change (within experimental uncertainty) above 100 MHz, while the relative permittivity decreases somewhat at 100 MHz. Surowiec *et al* (1985) found that the relative permittivity and effective conductivity of the kidney and spleen decrease as a function of time following the animal's death at frequencies below 100 MHz. Other studies found that the relative permittivity and effective conductivity of brain tissue decline slightly (less than 15%) within the first hour after tissue death (Burdette *et al* 1986, Schmid *et al* 2003) even at higher frequencies (greater than approximately 1 GHz). This effect is partly attributed to the decrease in tissue water content due to stopped blood circulation within the tissue. In general, it has been found that changes between *in vivo* and *ex vivo* properties of biological tissues can be minimized as long as the measurements are performed within several hours after excision so that minimal liquid loss takes place (Foster and Schwan 1989). In contrast, our data suggest that the changes for liver tissue are almost immediate. We hypothesize that this effect was not noted in previously-published studies of liver tissue because the frequency range used in this study is much broader than in previously published data.

The differences we observe in the *in vivo* and *ex vivo* liver tissue dielectric properties above approximately 10 GHz are more significant than simple quantitative differences. Specifically, we observe an unexpected but repeatable dispersion trend in the high-frequency *in vivo* human and porcine liver tissue dielectric properties, as shown in figures 3 and 5. The shape of the frequency-dependent curves for both relative permittivity and effective conductivity are very different from their *ex vivo* counterparts. We were not able to fit a Cole–Cole model (single- or multi-pole) to these *in vivo* curves. These unexpected trends are either due to experimental artifacts that arise in the *in vivo* procedure or some underlying biophysical mechanism in liver tissue that we cannot presently explain. We made every effort to rule out all possible experimental artifacts as the causes of the differences. The open-ended coaxial probe technique that we used for both the *in vivo* and *ex vivo* experiments has been rigorously validated using reference liquids (Popovic *et al* 2005), and the *ex vivo* liver data obtained with this technique is consistent with previously published *ex vivo* human liver data, as discussed in section 3.1.4. Furthermore, the porcine experiments eliminated probe type, sterilization procedures and probe positioning (handheld versus secured in a stand) as possible explanations for the

observed differences. Thus, all protocol features that were unique to the *in vivo* measurements have been ruled out as possible confounders.

Finally, we note that a qualitatively similar dispersion trend was observed in the *ex vivo* breast tumor data presented in figure 2 of Choi *et al* (2004). Choi *et al* (2004) conducted measurements on breast and lymph node tissue in the frequency range of 0.5 to 30 GHz using an open-ended coaxial probe. They reported the discovery of 'another strong dielectric relaxation between 15 and 30 GHz in both cancer tissues and metastasized lymph nodes' whereby the relative permittivity dropped off suddenly above about 15 GHz, while the effective conductivity rose sharply and then leveled off at about 20 GHz. They noted that the mechanisms underlying the observed properties are not presently understood.

4. Conclusions

In this paper, we reported the results of characterizing the *in vivo* and *ex vivo* dielectric properties of human and porcine normal, malignant and cirrhotic liver tissues. The dielectric spectroscopy measurements were conducted over a wide frequency range of 0.5 to 20 GHz with a custom-designed, precision open-ended coaxial probe that is particularly well suited for *in vivo* measurements. To the best of our knowledge, this is the first study to characterize the wideband microwave-frequency dielectric properties of human liver tissue *in vivo*.

The results of this study indicate that statistically significant differences exist in the dielectric properties of *ex vivo* normal and malignant liver tissue, as well as *in vivo* and *ex vivo* normal liver tissues at 915 MHz and 2.45 GHz. These differences need to be taken into account in electromagnetic and thermal models for hepatic MWA, and should allow for the design of improved antennas.

Finally, we have shown that the wideband trends in the dielectric properties of *in vivo* and *ex vivo* liver tissues, both human and animal, are very different. There is no previously published wideband *in vivo* liver data with which to compare our unexpected results. There are two possible explanations for the trends noted in the *in vivo* liver measurements in this study—experimental artifacts and biophysical phenomena. We performed a number of investigations to rule out experimental artifacts as causes of the observed differences. Further work must be carried out to uncover any possible biophysical mechanisms responsible for these differences.

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