

Revisiting the Wisconsin-Calgary Dielectric Spectroscopy Study of Breast Tissue Specimens

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Introduction

Breast cancer is the most common cancer in women worldwide and the second most common cancer overall. In 2013 alone nearly 1.7 million women around the globe were diagnosed with breast cancer (Breast Cancer Research Foundation, 2014). In United States it is the leading cause of cancer death among women (Centers for Disease Control and Prevention).

Previous reports of substantial contrast in the dielectric properties of normal and malignant breast tissues across portions of the electromagnetic spectrum have prompted a great deal of interest in non-ionizing electromagnetic techniques for breast cancer detection and treatment. Accordingly, researchers have begun to explore the feasibility of microwave techniques for breast cancer detection (Lazebnik et al, 2007). Clinical efficacy of such techniques depends on the dielectric contrast between different breast tissue types as well as the contrast between malignant and healthy tissue.

The large-scale collaborative experimental study at the University of Wisconsin-Madison and University of Calgary built an extensive database of ultrawideband dielectric properties of a variety of healthy and diseased breast tissue. Key findings of the study suggested a much lower contrast between healthy and cancerous tissues than previously understood (Lazebnik et al., 2007).

In recent years two key questions have been raised regarding the findings of the Wisconsin-Calgary study. The first question is how well the published Cole-Cole models fit the data specifically in the UHF band, as opposed to ultrawideband spectrum. The second question is whether the *in vivo* properties differ from the reported data on *ex vivo* tissue. These questions have risen from a single patient population study conducted at the Thayer School of Engineering developed a protocol to compare *in vivo* and *ex vivo* properties of malignant tissue in the UHF band (Halter et al., 2009). A later study at the Thayer School of Engineering used a procedure to integrate microwave tomography and magnetic resonance imaging in the UHF band (Meaney et al., 2013).

We revisited Wisconsin-Calgary data to address these questions. We developed Cole-Cole models specific to the UHF band (0.5-3 GHz) and compared them with previous models. We also conducted measurements to illustrate the inherent challenges of comparing *in vivo* and *ex vivo* breast tissue properties.

This report is organized in four sections. Section 1 is dedicated to the Wisconsin-Calgary dielectric spectroscopy study. It describes the procedures for obtaining tissue samples, processing the data, analyzing tissue composition, data fitting and statistical analysis. It then discusses the results of the study. Section 2 is dedicated to the first question and describes the new Cole-Cole models developed in the UHF band and the motivation for revisiting original study. It explains the methodology in data analysis and discusses the results obtained for UHF band. Section 3 is dedicated to the second question and describes the tissue-mimicking material construction. It explains the homogeneous and heterogeneous measurements and discusses the validity of comparing *in vivo* and *ex vivo*

measurements. Section 4 summarizes the conclusions of the experiments described in sections 2 and 3.

SECTION-1: Wisconsin-Calgary study (Lazebnik et al., *Phys. Med. Biol.*, 2007a, b)

The Wisconsin-Calgary study characterizes the dielectric properties of normal breast tissue obtained from breast reduction surgeries as well as the properties of malignant and normal breast tissue obtained from cancer surgeries and biopsies. 488 measurements from 93 patients undergoing breast reduction surgeries and 319 measurements from 196 patients undergoing lumpectomies, mastectomies and biopsies were conducted on freshly excised normal breast tissue obtained at UW and UC hospitals.

Measurements were conducted using a 3 mm aperture size, stainless-steel open-ended coaxial probe, which is designed for precision dielectric spectroscopy of biological tissue, such as breast tissue, over the 0.5-20GHz frequency range. A vector network analyzer and the two step post processing techniques described in Popovic et al., 2005 were used to convert the reflection coefficient measured at the probe's calibration plane to the tissue permittivity of the tissue specimen. After each measurement, the contact surface where the probe was placed on each tissue sample was marked with black ink. A medial cross-section of each tissue sample directly beneath the ink spot was processed to make a histology slide as shown in figure 1 (Lazebnik et al., *Phys. Med. Biol.*, 2007a, b).



Figure-1: Measurement technique and histological analysis of tissue composition (Lazebnik et al., *Phys. Med. Biol.*, 2007a, b)

Healthy breast tissue samples from reduction surgeries or tissue samples diagnosed as 'normal' from lumpectomies, mastectomies and biopsies were categorized by adipose tissue content. Group 1 contained all samples with 0–30% adipose tissue (the high-water-content group, glandular), group 2 contained all samples with 31–84% adipose tissue (fibroconnective) and group 3 contained all samples with 85–100% adipose tissue (the low-water-content group, adipose). The tissue samples diagnosed as 'cancer' were categorized in terms of percentages of invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS).

Exclusionary criteria were used to identify poor quality histology slides to minimize uncertainty in determining the tissue composition, and to ensure the correct relationship between the dielectric measurements and the histology information. 118 samples out of 488 measurements from breast reduction surgeries and 159 samples out of 319

measurements from lumpectomies, mastectomies and biopsies were excluded from further analysis. 370 quality breast reduction samples and 160 quality lumpectomy, mastectomy and biopsy samples remained after histology based exclusionary criteria were applied.

Cole-Cole models are commonly used as a representation of wideband frequency dependent dielectric properties (Gabriel et al 1996). The Wisconsin-Calgary study fit the following one-pole Cole-Cole model to each of the 370 and 160 complex permittivity data sets:

$$\epsilon^*(\omega) = \epsilon'(\omega) - j\epsilon''(\omega) = \epsilon_\infty + \frac{\Delta\epsilon}{1 + (j\omega\tau)^{1-\alpha}} + \frac{\sigma_s}{j\omega\epsilon_0}.$$

Parameter values for each complex permittivity data set corresponding to each tissue sample were obtained by minimizing the following normalized error function:

$$e = \frac{\sum_{i=1}^N \left(\frac{\epsilon'(\omega_i) - \hat{\epsilon}'(\omega_i)}{\text{median}[\epsilon'(\bar{\omega})]} \right)^2 + \sum_{i=1}^N \left(\frac{\epsilon''(\omega_i) - \hat{\epsilon}''(\omega_i)}{\text{median}[\epsilon''(\bar{\omega})]} \right)^2}{N},$$

The Kramers-Kronig relation between the real and imaginary parts was used to set an acceptability threshold for the fitting criterion, e, and any data set with a value for e that exceeds the threshold was further excluded from the study. After excluding 16 of the 370 and 5 of the 160 samples, 354 samples from breast reduction surgeries and 155 samples from cancer surgeries remained for final analysis.

Median dielectric constant and effective conductivity dispersion curves were obtained for each group by first calculating the fitted values for each group at 50 equally spaced frequency points. Second, the median value at each frequency point was calculated across samples within the group. Finally the Cole-Cole model from equation-1 was fit to these median values.

Histologically, the key finding of the Wisconsin-Calgary study is the high level heterogeneity of breast tissue on not only the macroscopic (centimeter) scale, but also the microscopic (sub-mm) scale. Figure 2 (Lazebnik et al., *Phys. Med. Biol.*, 2007a, b) shows the histograms of the distribution of tissue compositions across the entire 354 tissue samples from reduction surgeries. It shows that the composition of tissue samples varied greatly between low- and high-water content.

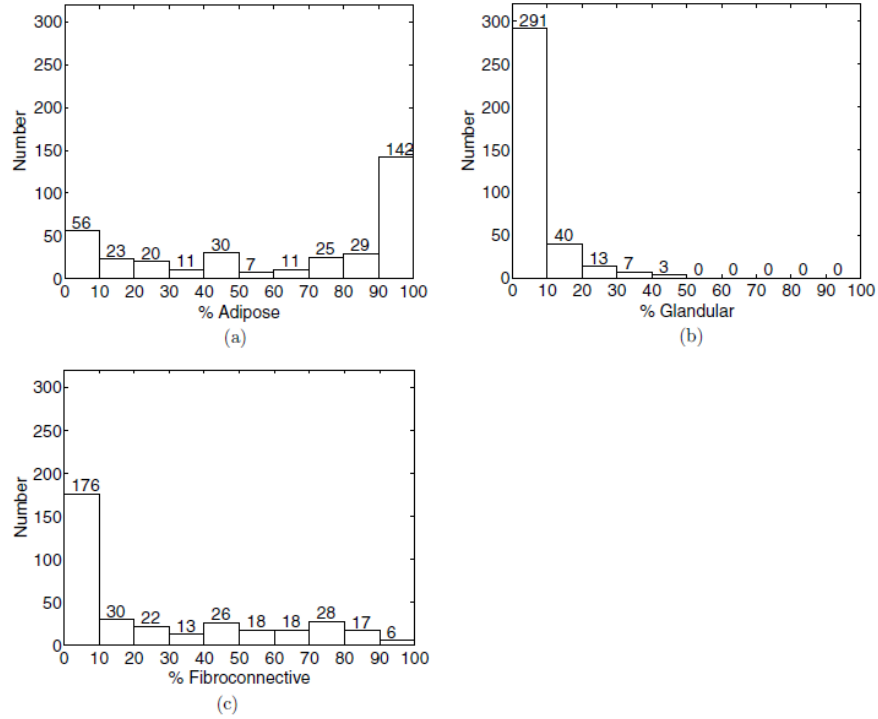


Figure-2: Histograms of the distributions of percentages of (a) adipose tissue, (b) glandular tissue and (c) fibroconnective tissue across the entire database of 354 tissue samples. The number of samples containing a given percentage of a particular tissue type is marked at the top of each vertical bar (Lazebnik et al., *Phys. Med. Biol.*, 2007a, b).

The Wisconsin-Calgary study also showed that the dielectric properties of healthy breast tissue are primarily determined by the adipose content of each tissue sample. Furthermore, analysis showed that the contrast in the ultrawideband frequency (0.5GHz to 20GHz) dielectric properties between malignant and normal adipose-dominated tissues in the breast is as large as 10:1, while the contrast between malignant and normal glandular tissues in the breast is no more than 10%. Figure 3 shows the dielectric properties of the three adipose-defined tissue groups (Lazebnik et al., *Phys. Med. Biol.*, 2007a,b). Each curve represents the median Cole-Cole fit, and the variability bars around the median represent the 25th-75th percentiles. Figure 4 shows the median curves of cancer samples (Lazebnik et al., *Phys. Med. Biol.*, 2007a,b).

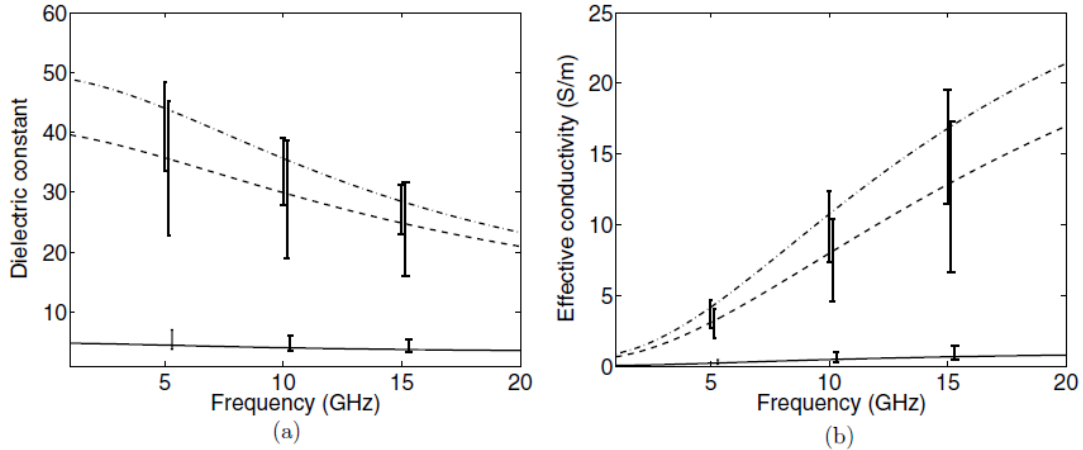


Figure-3: Median Cole-Cole curves, (a) dielectric constant and (b) effective conductivity, of the three tissue groups defined by percentage adipose tissue present in the sample. The variability bars show the 25th–75th percentiles of the fitted values. Dash-dot line: group 1 (0–30% adipose), dashed line: group 2 (31–84% adipose), solid line: group 3 (85–100% adipose) (Lazebnik et al., Phys. Med. Biol., 2007a, b).

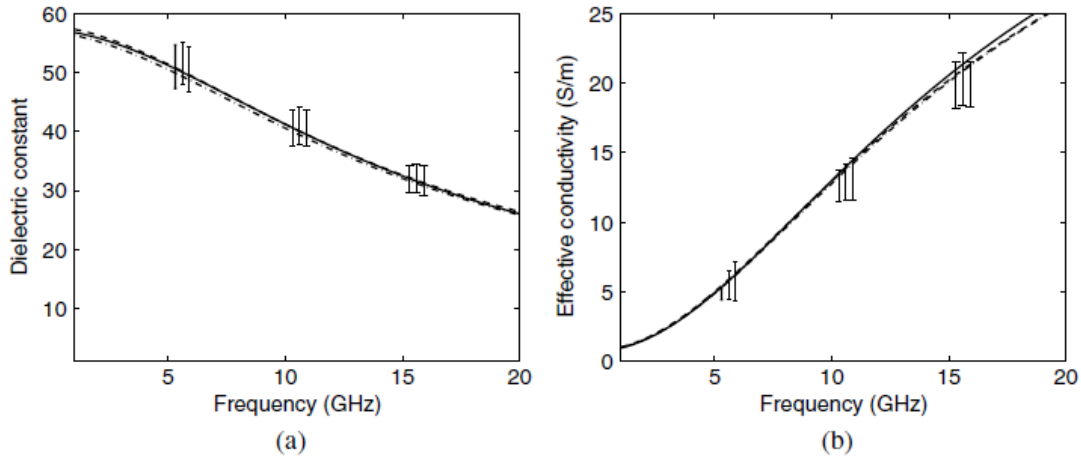


Figure-4: Median Cole-Cole curves, (a) dielectric constant and (b) effective conductivity, of cancer samples (Lazebnik et al., Phys. Med. Biol., 2007a, b).

SECTION-2: How well do the published Cole-Cole models fit the data specifically in the UHF band?

2.1. Motivation and overview

The large-scale Wisconsin-Calgary dielectric spectroscopy study (Lazebnik et al., *Physics in Medicine and Biology*, 52:6093-6115, 2007) reported measurements of the ultrawideband (0.5–20 GHz) microwave dielectric properties of freshly excised normal and malignant breast tissues obtained from breast reduction and cancer surgeries at the University of Wisconsin and University of Calgary hospitals. A one-pole Cole-Cole model was fit to the complex permittivity data set obtained from each measurement; each fit was performed over the entire measurement frequency range, e.g. 0.5–20 GHz. The analysis of dielectric-properties contrast between malignant and normal tissues was conducted using this compact Cole-Cole representation of the wideband measured data.

The dielectric properties of breast tissue are relevant to the development of microwave breast imaging techniques for several clinical applications, including density evaluation, cancer detection, and treatment monitoring. The techniques under development include qualitative radar-based imaging of scattering characteristics and quantitative inverse-scattering-based imaging of dielectric properties. Radar techniques typically make use of a wide frequency spectrum, while inverse scattering techniques typically use frequencies in the UHF band. In light of the promising nature of quantitative microwave breast imaging via inverse scattering, it is of interest to revisit the Wisconsin-Calgary data to obtain Cole-Cole fits specifically in the UHF band.

We apply the techniques reported by Lazebnik et al. to obtain one-pole Cole-Cole fits to the measured complex permittivity data for normal and malignant breast tissue, specifically over the 0.5–3 GHz frequency range. We compare the local error (0.5–3 GHz) in the Cole-Cole models obtained from a global fit (0.5–20 GHz) with the local error (0.5–3 GHz) in the Cole-Cole models obtained from a local fit (0.5–3 GHz). We show that, in the UHF band, the accuracy of the Cole-Cole fit to the measured complex permittivity is consistently improved when the range of the fit is limited to the UHF band. We evaluate the impact of this improvement in Cole-Cole parameters on our understanding of the dielectric-properties contrast between malignant and normal adipose-dominated tissues, and between malignant and normal glandular/fibroconnective tissues.

2.2. Definitions, Data Fitting and Reduction

We established the following error and curve fitting definitions to compare the quality of Cole-Cole models in the UHF band and ultra wideband:

- Global Fit : One-pole Cole-Cole fit to measured data in the 0.5-20 GHz range.
- Local Fit : One-pole Cole-Cole fit to measured data in the 0.5-3 GHz range.
- Local Error : The criterion given in equation (2) specific to 0.5-3 GHz range.

We compared the local error (0.5–3 GHz) in the Cole-Cole models obtained from a global fit (0.5–20 GHz) with the local error (0.5–3 GHz) in the Cole-Cole models obtained from a local fit (0.5–3 GHz).

The Wisconsin-Calgary study applied two sets of exclusionary criteria; histology and physics based, that reduced the number of datasets used in the final analysis from 488 to 354 tissue samples obtained from breast reduction surgeries and from 319 to 155 tissue samples obtained from cancer surgeries. We applied the same exclusionary criteria and used the identical 354 and 155 data sets in our local error calculations.

We fit the Cole-Cole model given in equation (1) in 0.5-20GHz and 0.5-3GHz frequency ranges using the same data set; and calculated the normalized local error value given in equation (2). We observed that the accuracy of the Cole-Cole fit to the measured complex permittivity is consistently improved when the range of the fit is limited to the UHF band. Figure 4 shows two representative examples of the raw measurement data (black dashed

lines) along with globally and locally fitted Cole-Cole curves (solid lines and green or red dashed lines) Figures 4(a) and (b) show an example of an adipose tissue sample with 100% adipose content, while figures 4(c) and (d) show an example of a glandular tissue sample with 10% adipose content. The measured data were fit with better accuracy in UHF band for both low water content and high water content breast tissues.

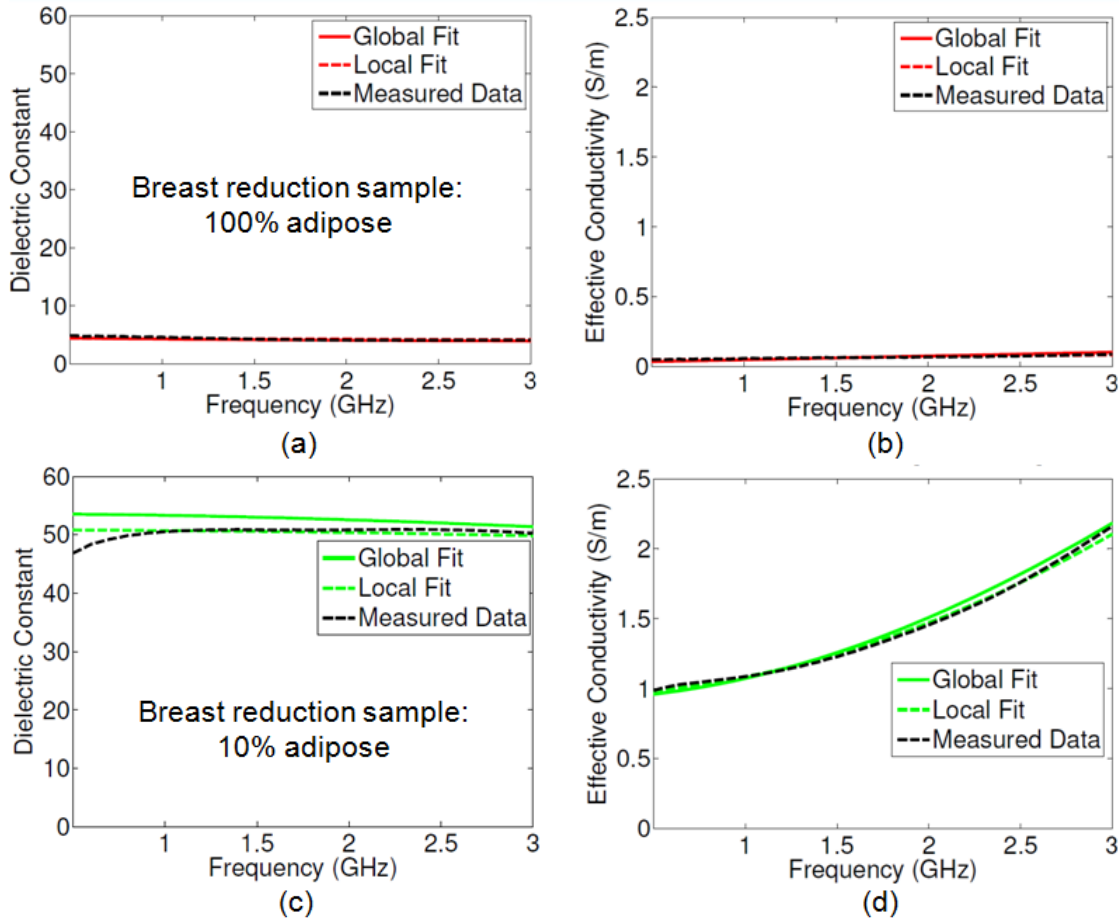


Figure-4: Examples of Cole-Cole fits to two representative experimental data sets. (a) Dielectric constant and (b) effective conductivity as a function of frequency for a data sample with 100% adipose content and (c) dielectric constant and (d) effective conductivity as a function of frequency for a data sample with 10% adipose content. Black-dashed line: Measured data, color-dashed line: Local fit, color-solid line: global fit

2.3. Results and discussion

To quantify the improvement achieved in local fits, we calculate the total local error values across all data samples obtained from global and local fits. Using the 354 breast reduction tissue specimens, we observed a total local error reduction of 7.20 to 1.28. Similarly, across 155 cancer tissue specimens, we observed a reduction of 0.73 to 0.024. Table 1 shows the local error matrix for both studies.

Study	Global Fit (0.5-20GHz)	Local Fit (0.5-3GHz)	Error Reduction
Breast reduction tissue specimens (354 datasets)	7.20	1.28	~5x
Cancer tissue specimens (155 datasets)	0.73	0.024	~30x

Table-1: Local Error Matrix

To summarize the fits in the UHF band we formed three groups of tissue samples. The three divisions were based on the percentage of adipose tissue in each sample. Group 1 contained all samples with 0-30% adipose tissue (the high water-content group), group 2 contained all samples with 31-84% adipose tissue, and group 3 contained all samples with 85-100% adipose tissue (the low water content group). Median dielectric constant and effective conductivity dispersion curves were obtained for each group by first calculating the fitted values for each sample in the group at 50 equally spaced frequency points. Second, the median values at each frequency point were calculated across samples within the group. Finally the Cole-Cole model was fit to these median values.

We compared the median curves obtained in the UHF band to the median curves obtain by the Wisconsin-Calgary study in the ultrawideband frequency range. We found no statistically significant differences between the median dielectric constant and effective conductivity dispersion curves obtained for each group. The impact of the improvement in the quality of the Cole-Cole models in the UHF band is statistically insignificant. Conclusions reported by Lazebnik et al. (PMB 2007 a,b) hold for the UHF band. Those conclusions show a considerable contrast in the microwave-frequency dielectric properties between malignant and normal adipose tissues in the breast, as large as 10:1. On the other hand, the contrast in the microwave-frequency dielectric properties between malignant and normal glandular tissue in the breast is no more than 10%.

Figures 5(a) and (b) show the median Cole-Cole curves of the three adipose-defined groups for normal breast tissues obtained from reduction and cancer surgeries in the UHF band (dashed lines) and in the ultrawideband frequency range (solid lines). Similarly, figures 5(c) and (d) show the median Cole-Cole curves for the dielectric constant and effective conductivity of malignant samples obtained from cancer surgeries in the UHF band (dashed lines) and in the ultra wideband (solid lines).

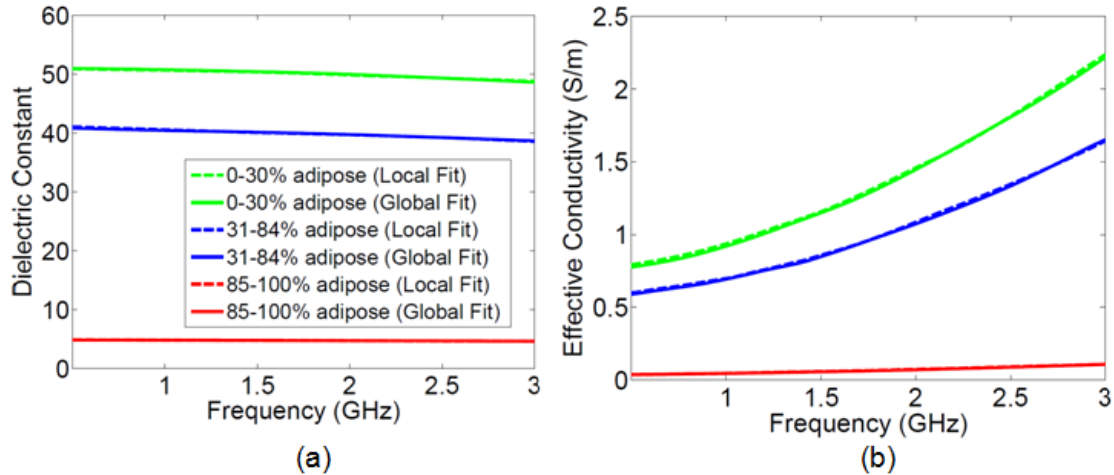


Figure-5: (a) Median dielectric constant and (b) effective conductivity of the three tissue groups defined by percentage adipose tissue present in the sample. Green lines: group 1 (0–30% adipose), blue lines: group 2 (31–84% adipose), red lines: group 3 (85–100% adipose). Solid lines: Median values obtained from Cole-Cole fits in the ultrawideband frequency range, dashed-lines: Median values obtained from Cole-Cole fits in the UHF band.

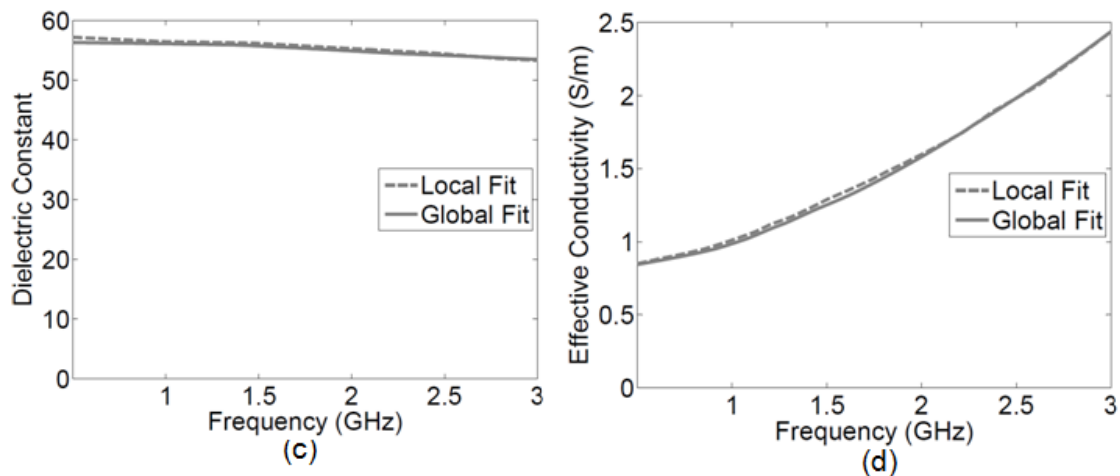


Figure-5: (c) Median dielectric constant and (d) effective conductivity of the malignant tissue samples from cancer surgeries. Solid line: Median values obtained from Cole-Cole fits in the ultrawideband frequency range, dashed-lines: median values obtained from Cole-Cole fits in the UHF band.

2.4. Additional discussion

The Wisconsin-Calgary study investigated the contrast between the dielectric properties of cancer samples (containing 30% or more malignant tissue) with the dielectric properties of normal samples obtained from cancer surgeries. The results indicate that the microwave-frequency dielectric-properties contrast between malignant breast tissues and normal glandular breast tissue is considerably low, no more than approximately 10% (Lazebnik et al 2007b).

While 30% or more malignant tissue content was used in the contrast analysis, the Wisconsin-Calgary study also compared the median dielectric properties of cancer samples

with a minimum 30%, 50% and 70% malignant tissue content. The median Cole-Cole curves of samples with higher minimum malignant tissue content (e.g. 50% or 70%) were indistinguishable from the median Cole-Cole curves of samples with minimum malignant content of 30%. 49 samples contained 30% or more malignant tissue content while the number of samples included with higher malignant tissue content was 33 or 14 respectively. For better reliability, minimum malignant tissue content was set to 30%.

We further analyzed the Wisconsin-Calgary data to show if the contrast between malignant and normal glandular breast tissues varies based on the tissue composition of samples. We specifically focused our analysis on tissue samples that contained almost pure malignant or normal glandular breast tissue. We used cancer samples containing 85% or more malignant tissue content, instead of 30% or more. We used the 6 cancer samples that fit the criterion. For normal glandular breast tissue, we looked into three different cases that included 15% or less, 5% or less and 0% adipose content. Restricting the maximum adipose content allowed us to focus our analysis on high-water content samples. Thus 29, 21 and 12 samples included in this analysis, are composed primarily of normal glandular tissue, while the 6 cancer samples are composed primarily of malignant glandular tissue. By malignant tissue content we mean the sum of percentages of all cancer types (IDC, DCIS, ILC and LCIS) considered in Lazebnik et al.

Figure-6 (a) and (b) present the contrast between healthy breast tissue with 15% or less adipose content (29 samples) and malignant breast tissue with 85% or more malignant tissue content (6 samples).

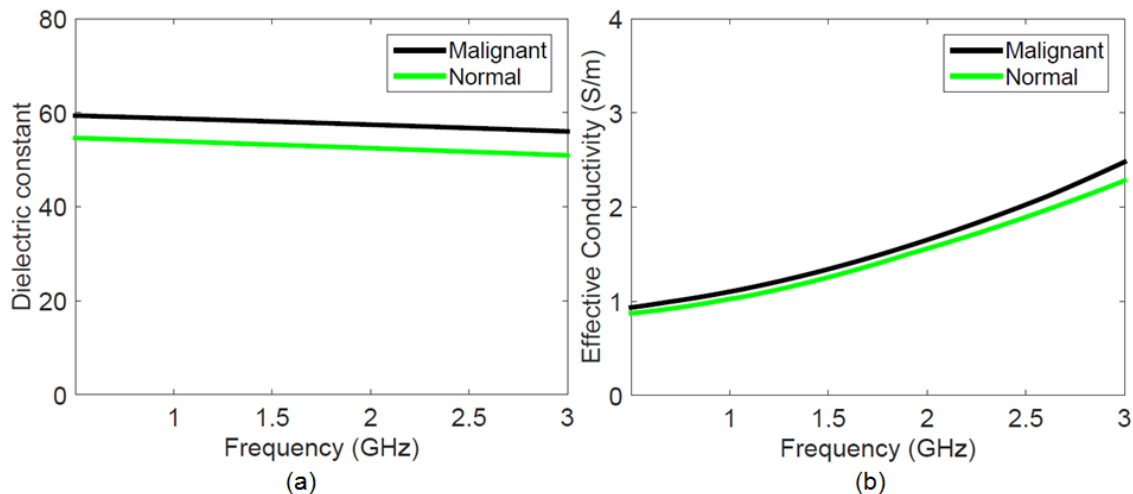


Figure-6: Contrast between healthy and malignant breast tissue: (a) Median dielectric constant and (b) effective conductivity; solid red line malignant tissue with 85% cancer content (6 samples), solid blue line healthy glandular tissue with 15% or less adipose content (29 samples).

Figure-7 (a) and (b) present the contrast between healthy breast tissue with 5% or less adipose content (21 samples) and malignant breast tissue with 85% or more malignant tissue content (6 samples).

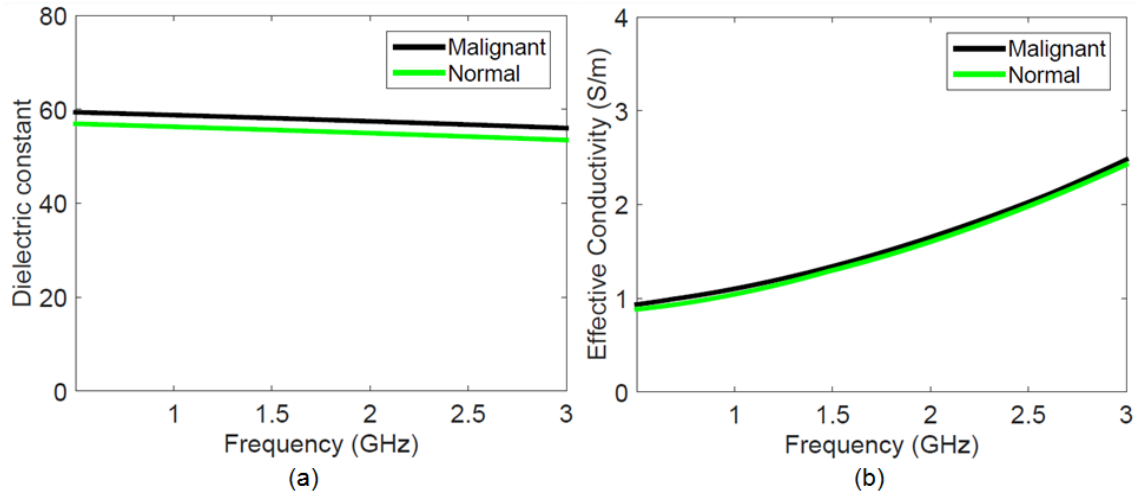


Figure-7: Contrast between healthy and malignant breast tissue: (a) Median dielectric constant and (b) effective conductivity; solid red line malignant tissue with 85% cancer content (6 samples), solid blue line healthy glandular tissue with 5% or less adipose content (21 samples).

Figure-8 (a) and (b) present the contrast between healthy breast tissue with 5% or less adipose content (12 samples) and malignant breast tissue with 85% or more malignant tissue content (6 samples).

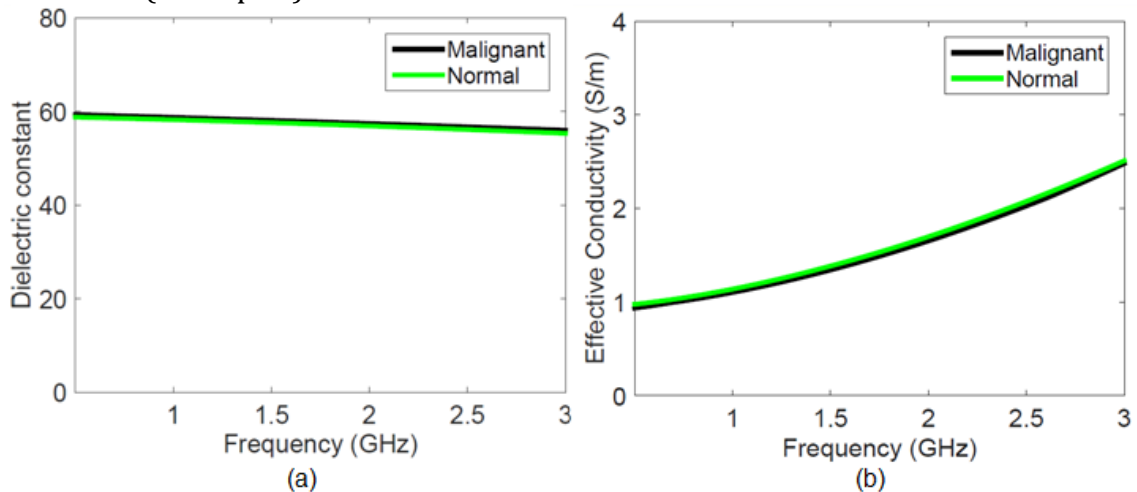


Figure-8: Contrast between healthy and malignant breast tissue: (a) Median dielectric constant and (b) effective conductivity; solid red line malignant tissue with 85% cancer content (6 samples), solid blue line healthy glandular tissue with 0% adipose content (12 samples).

These plots indicate that the microwave-frequency dielectric-properties contrast between malignant breast tissues and normal glandular breast tissue is considerably low and varies based on the tissue composition of the healthy glandular tissue and malignant glandular tissue. Our findings indicated a contrast under 10% in the three cases, but the contrast became nonexistent when twelve pure healthy glandular tissue samples were compared with the six malignant tissue samples containing 85% or more malignant content.

SECTION-3: Do *in vivo* properties differ from the reported data on *ex vivo* tissue?

3.1. Motivation and overview

Haemmerich et al measured swine liver resistivity *in vivo* in three animals. Measurements continued after excision of a tissue sample in one animal for 12 hours to examine the amount of resistivity change. Changes in low-frequency dielectric properties, specifically conductivity, have been observed with in situ physiological changes after excision. Figure 8(a) shows the time course of resistivity during the first 10 minutes after obstruction of blood vessels supplying the liver. Figure 8(b) shows the time course of resistivity of the extracted tissue sample for the first 12 hours after extraction (Haemmerich et al., Med. Biol. Eng. Comput., 2002). The initial value at $t=0$ is from an *in vivo* measurement at the location of tissue extraction. Resistivity increases for all frequencies from 0-2 hours after removal of the liver. The difference in change reduces as the frequency increases, reading the lowest difference at radio frequencies, such as 1MHz. Following the trend shown in figure 6(b), we expect the change in resistivity to be even less at microwave frequencies (0.5GHz-3GHz).

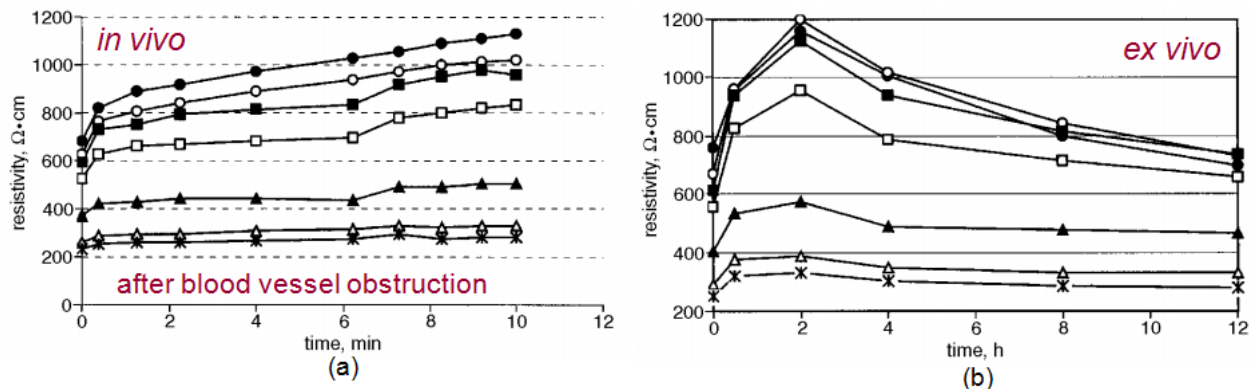


Figure-8: (a) Time course of resistivity during first 10 min after blood vessels supplying liver have been obstructed. Measured from 10Hz to 1MHz. (b) Time development of resistivity during first 12 h after excision of liver. Leftmost value is resistivity measured *in vivo* from 10Hz to 1MHz (Haemmerich et al., Med. Biol. Eng. Comput., 2002).

The Foster and Schwan study reviewed the electrical properties of tissues from DC to 20 GHz, with the emphasis on the underlying mechanisms responsible for the properties. The study showed the biophysical mechanisms at low frequencies differ from those at higher frequencies. The study also concluded that temperature decrease and desiccation, which affects extracellular water before intracellular water; have the most impact on microwave frequency dielectric properties after excision (Foster and Schwan, 1989).

The Wisconsin-Calgary study characterized the dielectric properties of freshly excised normal breast tissue obtained from breast reduction surgeries as well as malignant and normal breast tissue, obtained from cancer surgeries and biopsies. The time between excision and measurements varied between 5 and 80 min for tissue samples obtained at UW and between 5 and 320 min for samples obtained at UC (Lazebnik *et al* 2007).

The study reported a statistically significant trend between the dielectric properties and the time between excision and measurement for the adipose tissue type with 85–100% adipose content. Both the dielectric constant and effective conductivity decrease as the time between tissue excision and measurement increases. While this trend was statistically significant, the magnitude of the change is negligible compared to the much larger (by more than an order-of-magnitude) range of properties spanned by all tissue groups (0–100% adipose) in the breast. Consequently, this trend is not important from an engineering point of view. In addition, this trend was not observed for the other two adipose-defined tissue groups with higher water contents (Lazebnik *et al* 2007).

The Dartmouth study developed a protocol for spectroscopy measurements of the dielectric properties of breast tissue. The protocol involved measurement of *in vivo* tissue properties during mastectomy procedures, and location was marked with an embedded clip. This was followed by *ex vivo* tissue property recordings in the same locations in the excised tissue specimens in the pathology laboratory immediately after resection (Halter *et al.*, 2009).

The embedded clip was typically located and used to identify the region probed *in vivo*. Each probe was pressed against the surface of the tissue adjacent to this region and dielectric spectra were recorded. Two black ink coated pins were placed through the tissue on either side of the depression left by the probe tip. The tissue and pins were fixed in formalin for 24 hours prior to microscopic slide preparation. The pin holes remained in the tissue and provided microscopic landmarks used to precisely identify the region probed (Halter *et al.*, 2009).

The Dartmouth study recorded 25 dielectric spectra from six patients. The tissue types probed included intraductal carcinoma mixed with ductal carcinoma *in situ* (IDCa/DCIS). *In vivo* probes were used in a single patient with IDCa/DCIS. The comparison between the dielectric tissue measurements obtained *in vivo* and *ex vivo* is shown in Figure 9 (Haemmerich *et al.*, *Med. Biol. Eng. Comput.*, 2002). This data showed decreases as much as 20-35% in both the relative permittivity and conductivity of the *ex vivo* data with respect to the *in vivo* measurements. Since the study did not include an *in vivo* measurement of the healthy breast tissue, it is not possible to determine if the change observed on a malignant tissue sample would also be observed on healthy tissue to the same degree and if this would reveal any difference in contrast level between the dielectric properties of healthy and malignant breast tissues.

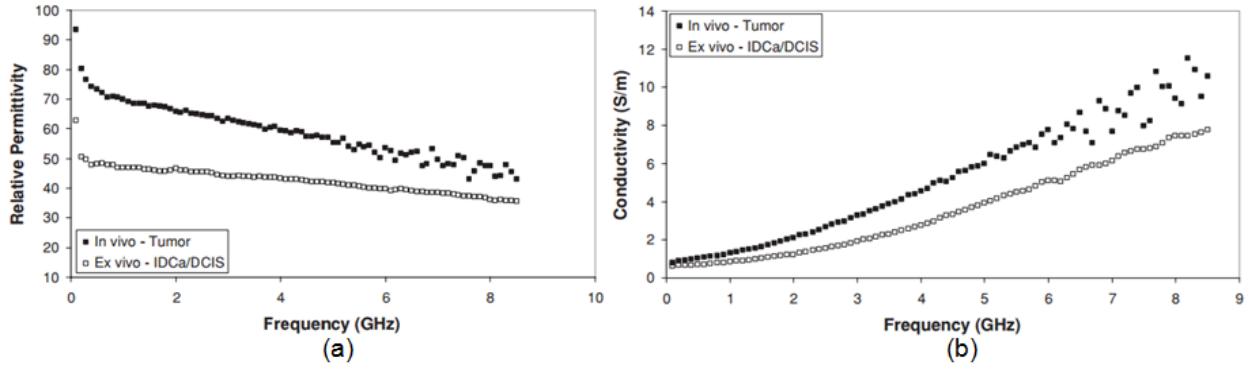


Figure-9: In vivo versus ex vivo dielectric spectra for (a) relative permittivity and (b) conductivity (S/m) using a single patient with IDCa/DCIS (Haemmerich et al., Med. Biol. Eng. Comput., 2002).

As seen in the Wisconsin-Calgary study and the Dartmouth study, there are inherent challenges in comparing *in/ex vivo* data. One of the challenges results from the limited number of available *in vivo* dielectric spectroscopy measurements of the healthy and malignant breast tissue specimens. Given the limitations of standard hospital procedures and protocols, the available number of *in vivo* versus *ex vivo* datasets in the literature fails to form a sample pool that is statistically large enough. Furthermore, measurement repeatability of dielectric spectra strongly depends on the consistent positioning of the probe when multiple measurements are taken from the same spot of a given tissue sample. When the high level heterogeneity of breast tissue on the microscopic (sub-mm) scale is considered, repeatability of *in/ex vivo* data measurement becomes an even bigger challenge. In this study we created a test case in a very controlled environment and measured dielectric properties of homogeneous and heterogeneous tissue mimicking material to show the variability in data.

3.2. Materials and Measurement Methods

Lazebnik et al, characterized oil-in-gelatin dispersions that approximate the dispersive dielectric properties of a variety of human soft tissues over the microwave frequency range from 500MHz to 20GHz. Different tissues can be mimicked by selection of an appropriate concentration of oil. These gelatin-based materials contain varying percentages of a solution of 50% kerosene and 50% safflower oil, which allows materials with a wide range of dielectric properties to be constructed (Lazebnik et al., 2005).

We apply the techniques reported by Lazebnik et al to produce a cylinder (dubbed the 'hockey-puck' sample). Within this cylinder, one half was occupied by a material containing 80% oil and the other half was occupied by a material containing 10% oil to characterize dielectric properties of heterogeneous samples. The material containing 80% oil represents adipose breast tissue and the material containing 10% oil represents glandular breast tissue with 10% percent adipose content. Figure 10 is a diagram of the 'hockey-puck' sample, used to test stability of the dielectric properties when two different samples are placed next to each other (Lazebnik et al., 2005).

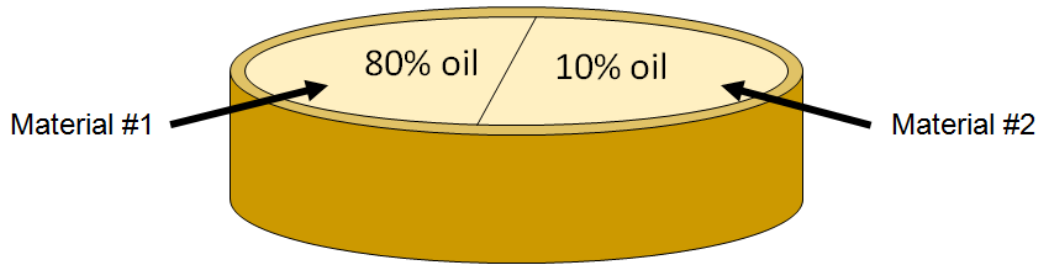


Figure-10: Diagram of the 'hockey-puck' sample, used to test the stability of the dielectric properties when two different samples are placed next to each other. Material #1 is adipose tissue mimicking material, containing 80% oil, and material #2 is glandular tissue mimicking material, containing 10% oil (Lazebnik et al., *Phys. Med. Bio.*, 2005).

We measured the dielectric properties of phantom materials using an Agilent slim-form probe (diameter: 2.2 mm) in conjunction with a vector network analyzer (VNA). The probe-VNA system was calibrated at the connector plane of the probe. During post-processing, a de-embedding model that takes into account the internal probe structure was used to translate the calibration plane to the aperture of the probe. Subsequently, a rational function model was used to extract the dielectric properties from the measured reflection coefficient.

We performed the measurements at room temperature (approximately 22 degrees Celsius). We placed the tip of the probe on the flat bare surface of the phantom sample, taking care not to puncture the surface or compress the gel excessively. We took four measurements on each sample with fixed location. Between measurements, the 'hockey-puck' sample was lowered using a fixture and raised back up to place the tip of the probe on the flat bare surface of the phantom sample again. These eight measurements demonstrate the measurement repeatability in homogeneous environment. Subsequently we took four measurements on the border between two phantom materials with fixed location and a second set of five measurements in a less controlled experimental protocol, intentionally varying the probe's contact location; -2mm, -1mm, 0mm, 1mm and 2mm across the border. Between measurements, the 'hockey-puck' sample was lowered and raised back up to place the tip of the probe on the flat bare surface of the phantom sample again. These nine measurements demonstrate the measurement repeatability in heterogeneous environment. Figure 11 shows the setup for these measurements.

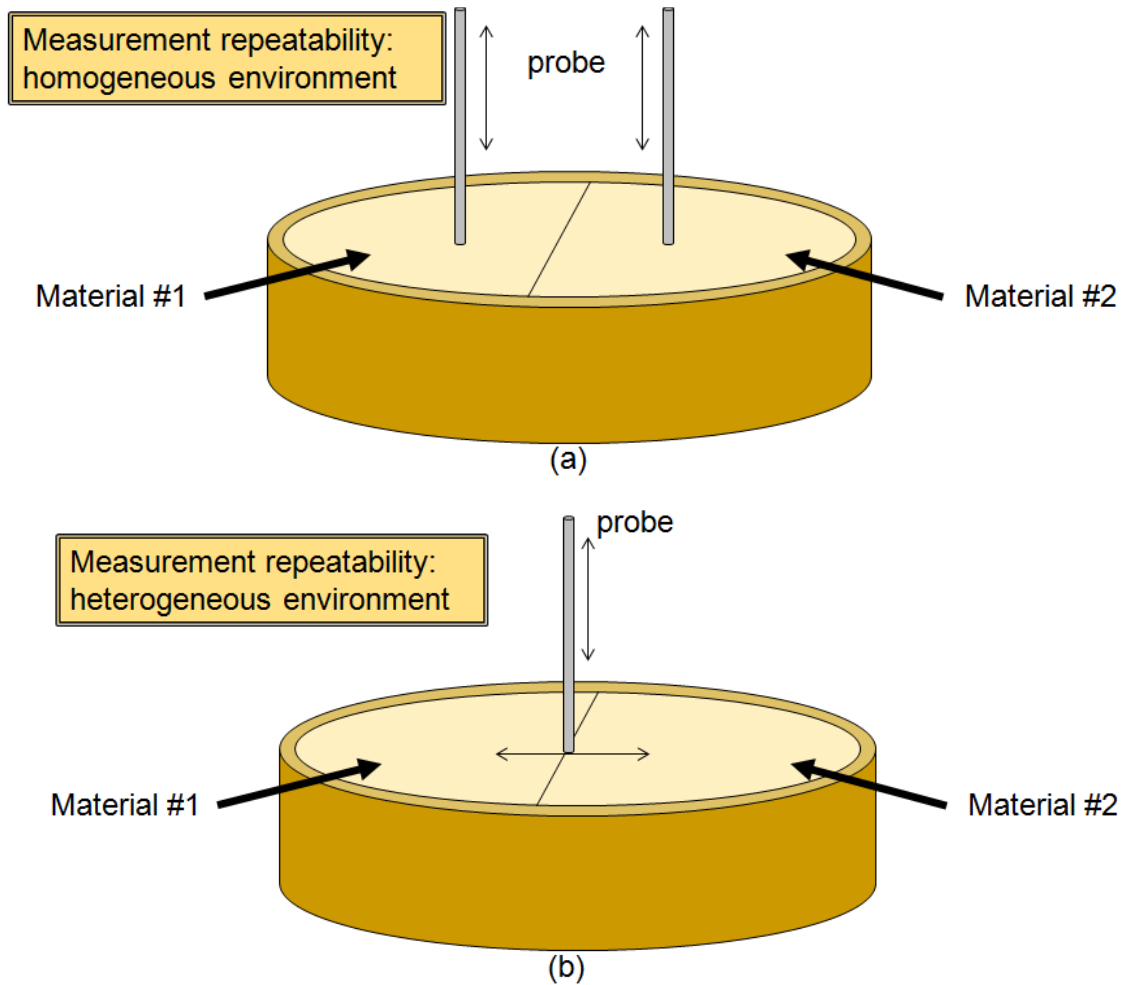


Figure-11: 'Hockey-puck' setup for measurement repeatability (a) in homogeneous and (b) in heterogeneous environments.

3.3. Results and discussion

Figures 12(a), (b), (c) and (d) show the relative permittivity and effective conductivity for phantom materials #1 and #2 respectively, over the frequency range of 500 MHz to 3 GHz. From these figures, it is clear the variability across measurements is negligible and measurement repeatability is very high in homogeneous samples with fixed location. Comparison between *in vivo* and *ex vivo* measurements of homogeneous tissue has the potential to be valid.

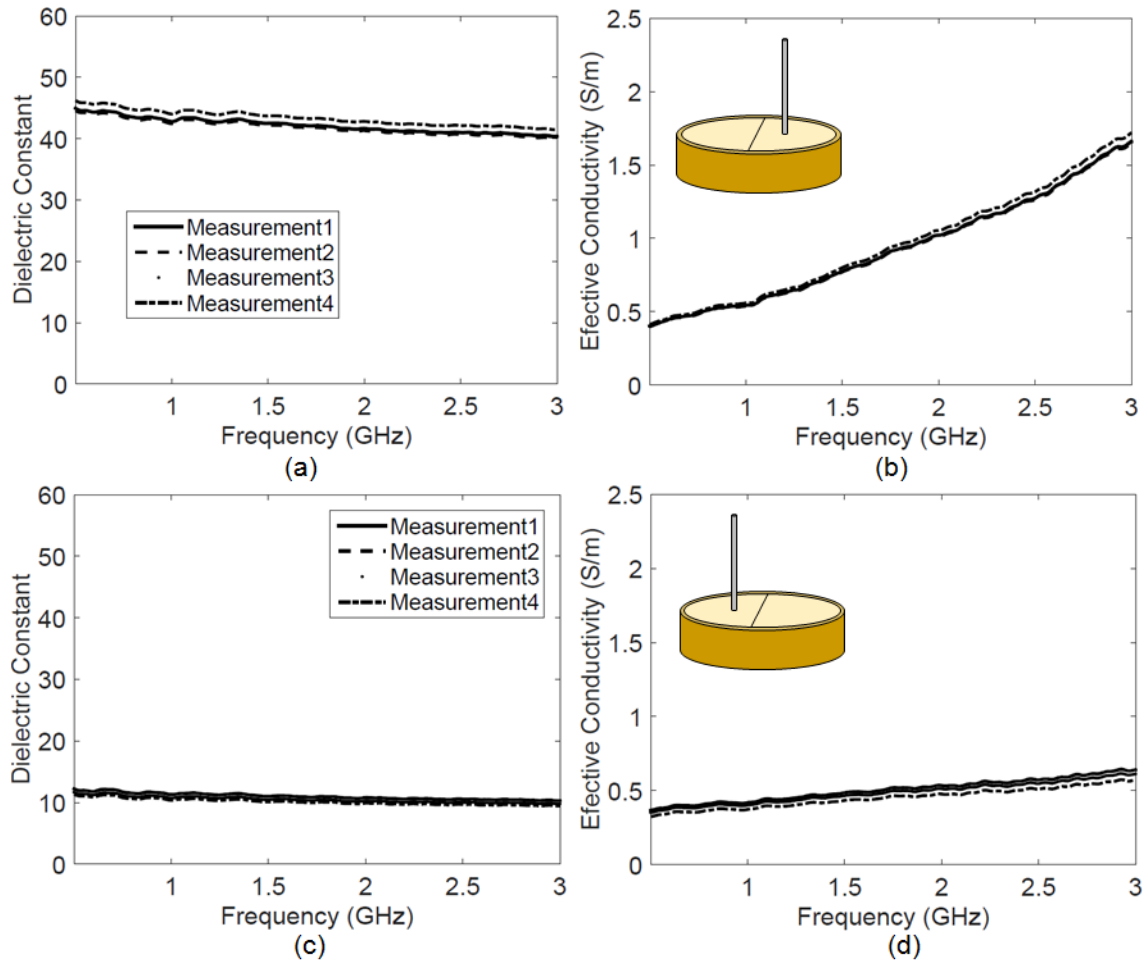


Figure-12: (a) Relative permittivity and (b) conductivity of the material #1 TM sample with fixed homogeneous location; (c) relative permittivity and (d) conductivity of material #2 TM sample with fixed homogeneous location.

Figures 13(a) and (b) show the relative permittivity and effective conductivity measured with fixed location on the border between material #1 and material #2, over the frequency range of 500 MHz to 3 GHz. These figures show that the variability across measurements is negligible and measurements are repeatable. Figures 13(c) and (d) show the relative permittivity and effective conductivity measured with ± 1 mm variation in location across the border between material #1 and material #2, over the same frequency range. Variability across measurements is very large and measurements are not repeatable. The validity of comparing *in vivo* and *ex vivo* measurements of heterogeneous tissue is highly questionable.

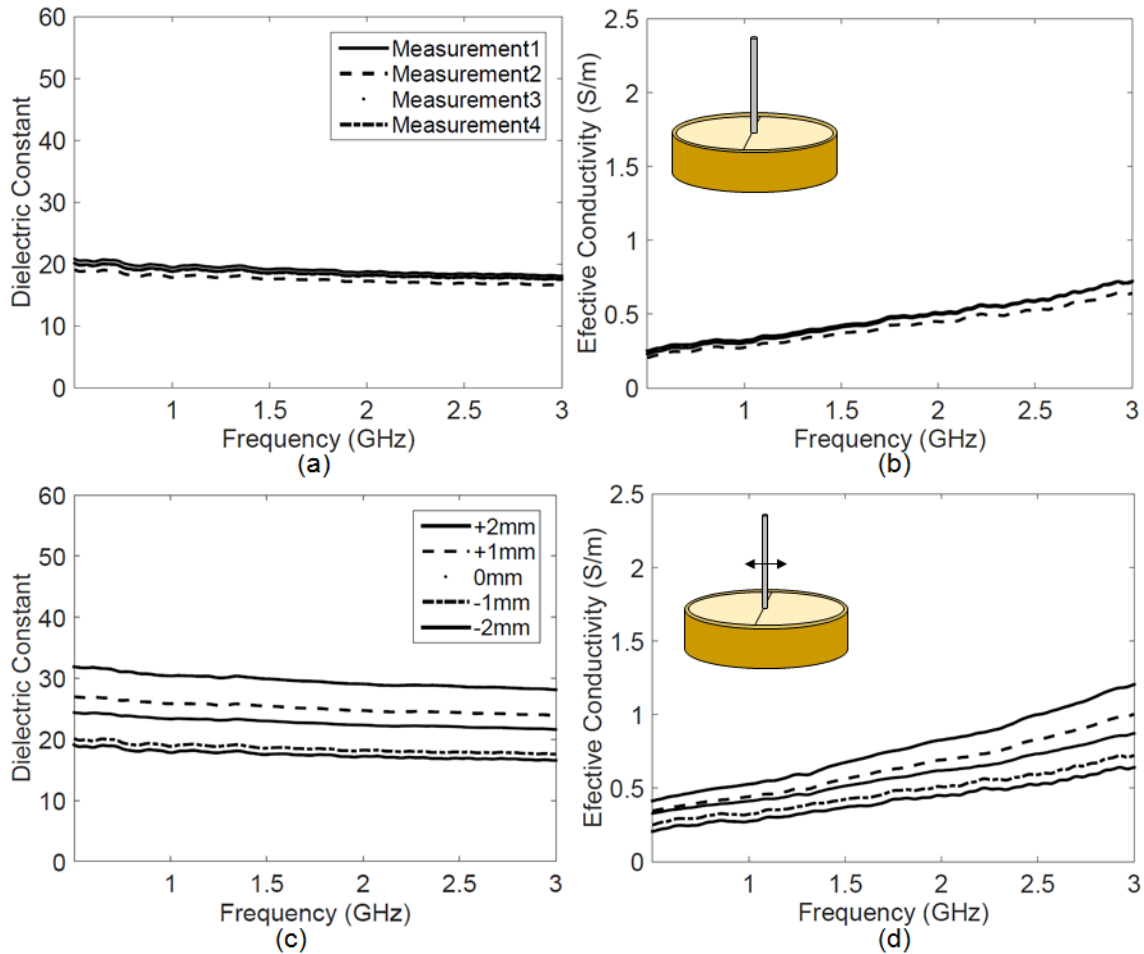


Figure-13: (a) Relative permittivity and (b) conductivity at the border between material #1 and material #2 TM samples with fixed heterogeneous location; (c) relative permittivity and (d) conductivity at the border with ± 1 mm variation in heterogeneous location

SECTION-4: Summary and Conclusions

In this study we revisited the Wisconsin-Calgary dielectric spectroscopy study to address the questions that have arisen since the publications of its findings. The first question is how well the published Cole-Cole models fit the data specifically in the UHF band, as opposed to ultrawideband frequency range. The second question is whether the in vivo properties differ from the reported data on ex vivo tissue.

In the first part, we applied the techniques reported by Lazebnik et al. to obtain one-pole Cole-Cole fits to the measured complex permittivity data for normal and malignant breast tissue, specifically over the 0.5–3 GHz frequency range. We compared the median curves obtained in the UHF band to the median curves obtained by the Wisconsin-Calgary study in the ultrawideband frequency range. We found no statistically significant differences between the median dielectric constant and effective conductivity dispersion curves. We showed that published Cole-Cole models by Lazebnik et al. (PMB 2007 a,b) are sufficiently accurate in fitting the measured data in the UHF band.

In the second part, we created a test case in a very controlled environment and measured dielectric properties of homogeneous and heterogeneous tissue mimicking material to show the variability in data. We showed that variability across measurements is negligible and measurement repeatability is very high in homogeneous samples. Comparison between *in vivo* and *ex vivo* measurements of homogeneous tissue has the potential to be valid. However the variability across measurements is not negligible and measurement repeatability is very poor in heterogeneous samples. The validity of comparing *in vivo* and *ex vivo* measurements of heterogeneous tissue is highly questionable. Considering the high level heterogeneity of breast tissue on the microscopic (sub-mm) scale, no practical method currently exists for rigorously comparing dielectric properties measurements of *in vivo* and *ex vivo* breast tissue.

Acknowledgments

I would like to express my sincere gratitude to my advisor Professor Susan C. Hagness for her assistance with and support of this project.

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