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The correlation of *in vivo* and *ex vivo* tissue dielectric properties to validate electromagnetic breast imaging: initial clinical experience

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Abstract

Electromagnetic (EM) breast imaging provides low-cost, safe and potentially a more specific modality for cancer detection than conventional imaging systems. A primary difficulty in validating these EM imaging modalities is that the true dielectric property values of the particular breast being imaged are not readily available on an individual subject basis. Here, we describe our initial experience in seeking to correlate tomographic EM imaging studies with discrete point spectroscopy measurements of the dielectric properties of breast tissue. The protocol we have developed involves measurement of *in vivo* tissue properties during partial and full mastectomy procedures in the operating room (OR) followed by *ex vivo* tissue property recordings in the same locations in the excised tissue specimens in the pathology laboratory immediately after resection. We have successfully applied all of the elements of this validation protocol in a series of six women with cancer diagnoses. Conductivity and permittivity gauged from *ex vivo* samples over the frequency range 100 Hz–8.5 GHz are found to be similar to those reported in the literature. A decrease in both conductivity and permittivity is observed when these properties are gauged from *ex vivo* samples instead of *in vivo*. We present these results in addition to a case study demonstrating how discrete point spectroscopy measurements of the tissue can be correlated and used to validate EM imaging studies.

Keywords

electromagnetic imaging; breast cancer; electrical impedance tomography; microwave impedance spectroscopy; tissue dielectric properties

1. Introduction

Breast cancer is expected to be diagnosed in more than 180 000 women and nearly 41 000 are expected to die from the disease in 2008 (Jemal *et al* 2008). Imaging studies based on conventional technologies such as x-ray mammography, computed tomography (CT), and magnetic resonance imaging (MRI), provide clinicians with critical screening, diagnostic and staging information; however, these imaging methods make use of ionizing radiation (mammography, CT), are relatively expensive (CT, MRI), and are often limited in the specificity with which they identify disease. The dielectric properties of breast tissue,

namely its electrical conductivity and relative permittivity, offer alternative contrast mechanisms to those of conventional imaging modalities.

We have developed two distinct breast imaging technologies to map these dielectric properties over a substantial portion of the electromagnetic spectrum. An electrical impedance tomography (EIT) system is used to image over frequencies spanning from 10 kHz to 10 MHz (Halter *et al* 2008a), while a microwave tomography (MT) system operates over a band from 0.6 GHz to 1.7 GHz (Li *et al* 2004). One difficulty in validating these electromagnetic imaging modalities is that the true dielectric property values of the particular breast being imaged are not readily available on an individual subject basis. A number of investigators have reported on the average dielectric properties of the breast (Surowiec *et al* 1988, Campbell and Land 1992, Morimoto *et al* 1993, Jossinet 1998, da Silva *et al* 2000, Lazebnik *et al* 2007a, 2007b) and have found that the values can be widely distributed depending on the underlying tissue composition. With the exception of the Morimoto *et al* efforts, the majority of these studies are based on measurements in *ex vivo* tissue samples. It is well known that the electrical properties of *ex vivo* tissues differ from their *in vivo* counterparts (Haemmerich *et al* 2002, Casas *et al* 1999). Because emerging EM imaging systems offer the opportunity to noninvasively quantify tissue dielectric properties *in vivo*, methods to validate that the property values reported in imaging studies are comparable to the underlying tissue properties and not just to average values reported in the literature from *ex vivo* studies is of considerable interest.

Here, we describe our initial experience in seeking to correlate tomographic EM imaging studies with discrete point spectroscopy measurements of the dielectric properties of breast tissue. The protocol we have developed involves measurement of *in vivo* tissue properties during partial and full mastectomy procedures in the operating room (OR) followed by *ex vivo* tissue property recordings in the same locations in the excised tissue specimens in the pathology laboratory immediately after resection. We detail our current procedures and report a number of results collected during protocol development. Specifically, we present data on the spectroscopy probe systems used during different stages of the validation procedure and illustrate cumulative, as well as individual, case study results obtained from a series of women who have participated in the protocol to date.

2. Dielectric probe systems

Four different dielectric probes were employed during the validation protocol—(1) an *in vivo* electrical impedance spectroscopy (EIS) probe, (2) an *ex vivo* EIS probe, (3) an *in vivo* microwave impedance spectroscopy (MIS) probe and (4) *ex vivo* MIS probe—because of the distinctly different design demands in the OR relative to pathology. The *in vivo* probes were used during the intraoperative resection procedure, while the *ex vivo* probes were used to measure the electrical properties of the excised tissue specimens. Minimally invasive technique is needed in the OR to minimize perturbation induced by probe invasion whereas once the tissue specimen has been removed, access to the points of interest is readily achieved and is amenable to probe designs with more robust measurement characteristics.

2.1. Electrical impedance spectroscopy probes

The *in vivo* EIS probe consists of three cylindrical stainless-steel needles (15 gauge, 19 gauge, and 24 gauge) arranged coaxially around a 125 μm diameter central conductor (see figure 1). A 100–200 μm layer of Epoxylite 6000m deposited between the individual elements provides four electrically isolated electrodes. The assembly tip is beveled to a 30° angle so the tissue conforms around the sensing electrodes. The four electrodes are interfaced through four shielded cables to an HP4284A impedance analyzer (Agilent Technologies, Santa Clara, CA) and a custom built analog front-end module which allows

tetrapolar impedance measurements. This probe underwent multiple design iterations before these specifications were finalized and is currently being manufactured by FHC Inc (Bowdoin, ME). The impedances gauged with the early iterations of the probe design were inaccurate because of inappropriate electrode layout, mechanical failure occurring during intraoperative use, and material degradation resulting from probe sterilization. These problems arose in the early designs which were based on more fragile, higher gauge needle electrodes, insufficient stress relief for the probe cable, and tip geometries limiting the tissue–probe interface (i.e. a more blunt 60° bevel).

The *ex vivo* EIS probe consists of a 4 cm (in length) stub of rigid coaxial cable configured to collect bipolar impedance measurements between the 3.5 mm outer conductor and a 1 mm central conductor (see figure 1). While tetrapolar probe configurations are more immune to contact impedance artifacts especially at lower frequencies and could be employed in the *ex vivo* setting in the future, we have previously characterized and deployed this bipolar probe successfully to interrogate accurately the electrical properties of excised (prostate) tissue (Halter *et al* 2007,2008b). Experience from these studies has shown that the design minimizes parasitic impedance effects and has a signal-to-noise ratio greater than 85 dB making it ideal for rapid but accurate tissue specimen measurements (however, its diameter is too large for intraoperative use).

Both probes are computer controlled through a custom software interface. The *in vivo* probe is programmed to sample the tissue at 31 logarithmically spaced frequencies ranging from 100 Hz to 100 kHz, while the *ex vivo* probe records 41 logarithmically spaced frequencies ranging from 100 Hz to 1 MHz. The higher frequencies (>100 kHz) are not collected with the *in vivo* probe due to large parasitic impedances associated with the long cables (~2 m) necessary for use in a surgical environment and the electrode capacitance associated with the long axial geometry of the probe.

2.2. Microwave impedance spectroscopy probes

For the *in vivo* MIS probe measurements, an Agilent slim form dielectric probe was connected to an Agilent E5071B network analyzer and controlled through the 85070E dielectric probe kit software in the OR (see figure 2). The probe is a semi-rigid coaxial transmission line, with a small 2.2 mm outer diameter making it convenient for minimally invasive use in the surgical setting. The last, short section of the coaxial insulator has been replaced with glass instead of the standard teflon in the majority of the probe length. This is essential for preventing cold flow and mechanical distortion of the dielectric during steam sterilization of the sensor. An all-teflon insulated probe was initially employed during validation protocol development but has been replaced with the glass insulated design which was introduced to ensure more reliable dielectric property assessments.

For *ex vivo* measurements, the set-up was the same except that an Agilent 85070E high temperature probe was used (see figure 2). This probe has a wide 19 mm flange which ensures high quality contact between the probe and the flat *ex vivo* tissue sections interrogated. A single shielded coaxial cable interfaces the probe with the network analyzer, which is computer controlled and programmed to record dielectric properties over the frequency range 0.1–8.5 GHz in 100 MHz increments.

2.3. Probe calibration

All probes were calibrated using short, open and standard load configurations as is customarily performed. Saline solutions of different conductivities were used as the standard loads for calibrating both EIS probes, while deionized water was used as the MIS standard load. The *in vivo* probes were calibrated prior to sterilization and placed in sterile packaging

for clinical use. EIS calibration parameters were stored locally within the impedance analyzer and loaded automatically upon powering the system, whereas the network analyzer required the calibration parameters be loaded from a file stored in the interfacing computer. An additional water refresh calibration step was performed for the microwave probes in the sterile OR environment prior to each measurement session to minimize calibration errors associated with the bending of the signal transmission cable attached to the network analyzer during the surgical procedures.

3. Clinical EM imaging validation procedure

Women diagnosed with breast cancer and scheduled for surgical resection were referred to our clinical coordinator for possible inclusion in this study. The study protocol involved recording dielectric properties of breast tissue through three procedures, (1) *in vivo* EM imaging, (2) *in vivo* point dielectric spectroscopic probing and (3) *ex vivo* point dielectric spectroscopic probing. The protocol has institutional review board approval and all women enrolled into the study provided informed consent.

3.1. Imaging procedure

Each patient was examined with our EM imaging modalities, approximately 1 week prior to surgery. This imaging session involved a prone, pendant breast exam where the tissue is accessed through an opening in the exam table (see figure 3). In the case of EIT, a set of up to 64 8 mm diameter Ag/AgCl electrodes were brought into contact with the breast. Electrodes are distributed on four circular planes of 16 elements each; the individual planes are actuated into contact with the breast under push-button computer control and monitored by the exam attendant. Voltages were simultaneously applied to each of the electrodes to induce a current field within the breast. Both the voltage and current were recorded at each electrode and the data was supplied to a computational finite-element-method (FEM) algorithm to estimate the internal electrical properties of the breast (Halter *et al* 2008a). This algorithm employs a three-dimensional FEM forward model coupled with an iterative regularized Newton–Raphson inversion routine to estimate these dielectric properties (Dehghani *et al* 2005). A fine volumetric mesh, approximating the anatomic geometry, is used for the forward problem and a coarser mesh, constructed from a linear pixel basis of dimensions $20 \times 20 \times 10$, is used for the parameter estimation.

In the case of MT, the breast was pendant in a tank filled with a glycerine/water mixture that provided electromagnetic signal coupling. Sixteen antennas were automatically placed around the breast in a circular array which does not contact the tissue. Each antenna acts to broadcast a microwave signal that is recorded by the remaining antennas. The source location rotates to every antenna member of the array during a data acquisition procedure which is repeated for seven frequencies from 500 MHz to 1700 MHz. In addition, the antenna array is moved vertically to facilitate collection of measurement data at multiple planes along the length of the breast beginning closest to the chestwall and extending distally toward the nipple (Li *et al* 2004). Similarly to EIT imaging, a FEM algorithm was employed to estimate the high frequency dielectric properties of the tissue over the full extent of the breast based on measurements of the sourced and received EM radiation.

3.2. Surgical procedure

Prior to surgery, both the EIS and MIS *in vivo* probes were calibrated. The probes and cables were then disconnected from their respective analyzers and submitted for sterilization. Sterilization consisted of subjecting the probes to a 6 min steam bath at 135 °C followed by a drying period (>1 h), prior to bagging of the assemblies for transfer to the OR. On the day of surgery, the patient was brought into the OR and anesthetized following standard clinical

procedures. The probes were placed in the sterile field and a surgical assistant handed the connector end of each assembly to a member of the research team standing outside the sterile field in order to reconnect the probes to the analyzers at the bedside. The individual analyzers were powered and the pre-sterilization microwave calibration was recalled. The surgical assistant immersed the microwave probe tip into a bath of sterile water and a water refresh of the calibration was performed in order to minimize the effects of disconnecting and reconnecting the cables.

For superficial, palpable lesions, the surgeon introduced a 13 gauge biopsy needle and trocar (Bard TruGuide, Covington, GA) into the center of the tumor (see figure 4). In cases when the lesion was deeper and not palpable, ultrasonic guidance was used to properly locate the tumor and guide trocar insertion. The surgeon then introduced the MIS probe through the trocar so that its tip contacted the tissue. The trocar was extracted a few mm to ensure good tissue–probe tip contact and a microwave dielectric spectrum was recorded. The MIS probe was removed and a similar procedure was followed with the EIS probe in order to record the low frequency dielectric spectrum. Typically, two spectra were recorded and averaged for each frequency range. Following tissue probing, a biopsy clip (UltraClip II US Tissue Marker, INRAD, Kentwood, MI) was deposited within the tumor at the end of the trocar. This clip is a coiled metallic wire that becomes embedded in the tissue precisely where deposited. Upon tissue extraction, the clip provided a landmark to accurately locate the tissue probed *in vivo* once the specimen was removed and taken to pathology.

3.3. Pathological procedures

The standard clinical procedure for lumpectomy cases at our institution requires an x-ray to be obtained of the tissue sample to ensure that tumor has been adequately removed and to confirm that no radiographically visible positive surgical margins are present. This x-ray also provided visual documentation of the embedded clip and was used to verify that the dielectric property values were recorded within the lesion (see figure 5). The tissue sample was then transferred to the pathology department where it was sectioned and processed for histological evaluation (see figure 5). Tissue sampling involved cutting the specimen into approximately 5 mm thick sections that were laid out on the bench top. During the sectioning process, we recorded dielectric properties of the tissue near the site of *in vivo* property assessment using the *ex vivo* EIS and MIS probes. The embedded clip was typically located and used to identify the region probed *in vivo*. This clip was located in one of three ways: (1) the clip was visible on one of the section faces, (2) the hemorrhagic track left by the introduction of the trocar pointed to where the clip is located or (3) the sections were x-rayed individually in pathology to identify the slice in which the clip was positioned. Once the clip location was identified, each probe was pressed against the surface of the tissue adjacent to this region and dielectric spectra were recorded (see figure 6). 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 h prior to microscopic slide preparation. The pin holes remained in the tissue and provided microscopic landmarks used to precisely identify the region probed (see figure 6). The same pathologist (WW) assessed the region between the visible pin holes and specified the tissue type(s) present in the sample (see figure 7).

Initially, we did not employ this pinning technique for marking the precise location of tissue probed but instead sampled a larger 1 cm × 1 cm square area around the measurement site. The pathologist analyzed multiple microscopic fields-of-view from this 1 cm² area of tissue and estimated the tissue type probed based on the average composition of the fields sampled. The pinning procedure provides a much more precise method for assigning tissue types to the dielectric spectra and will continue to be used in the future.

4. Results

4.1. Study population

We have successfully applied all of the elements of this validation protocol in a series of six women with cancer diagnoses. EM imaging with both the EIT and MT systems was performed for each case. The final designs of the *in vivo* probes described in section 2 have been used in only one of the reported cases; however, previous iterations of the probes were employed during the other five surgeries. *Ex vivo* data has been collected from all six cases.

The imaging sessions required approximately 30 min (15 min MT, 15 min EIT) and the point spectroscopy procedure added approximately ten additional minutes to the surgical procedure and approximately 15 min to the pathological sectioning process. We have been able to successfully locate the embedded biopsy clip through one of the localization methods in each of the cases which has provided a robust process for interrogating dielectric properties from the same tissue region in both *in vivo* and *ex vivo* settings. Pinning of the tissue during fixation provides critical visual landmarks to assist the examining pathologist in co-localizing histological assessment with the recorded dielectric spectra. This pinning procedure was used in only two of the six cases reported here, while our initial technique of assessing multiple microscopic field-of-views from the 1 cm² area of tissue encompassing the region probed was used in the other four cases.

4.2. Cumulative point spectroscopy properties

From the six patients, we recorded 15 *ex vivo* dielectric spectra using the EIS probe and ten dielectric spectra with the MIS probe. The tissue types probed by EIS included ten intraductal carcinoma (IDCa) mixed with ductal carcinoma in situ (DCIS), one DCIS, one adipose and three fibrocystic disease (FCD), while those probed by MIS included six IDCa mixed with DCIS, one DCIS, one adipose, and two FCD. The individual EIS spectra are shown in figure 8 along with the mean IDCa/DCIS and mean fibrocystic tissues spectra. Paired testing revealed the mean conductivity of the IDCa/DCIS tissues to be significantly ($p < 0.05$) greater than the fibrocystic tissues over the frequency range of 5 kHz to 50 kHz. A significantly higher permittivity was also noted for the IDCa/DCIS tissues when compared to the fibrocystic specimens between 100 Hz and 1 kHz. The differences at the other frequencies were not significant. The electrical properties of the tumor tissues were less variable than that of the fibrocystic tissues (table 1). The conductivity at 10 kHz varied by 8.3% about the mean of the cancer tissue ($0.145 \pm 0.012 \text{ S m}^{-1}$) and by 34.8% about the mean for the fibrocystic samples ($0.068 \pm 0.024 \text{ S m}^{-1}$). Likewise, the relative permittivity at 500 Hz varied by 9% about the mean for tumor tissue ($1.46 \times 10^6 \pm 1.3 \times 10^5$) and 77% about the mean for fibrocystic tissues ($5.13 \times 10^5 \pm 3.95 \times 10^5$). Because of the smaller number of different tissues types sampled, the MIS data is not presented in figure 8. We did, however observe conductivities ranging from 20.8 mS cm⁻¹ to 30.7 mS cm⁻¹ and relative permittivities ranging from 44.1 to 58.5 for the IDCa/DCIS tissues at 3.2 GHz.

The finalized *in vivo* probes were used in a single patient with IDCa/DCIS and a comparison between the dielectric tissue measurements obtained *in vivo* and *ex vivo* is displayed in figure 9. A decrease in the low frequency (EIS) electrical properties was observed primarily above 1 kHz. Specifically, the conductivity decreased by 52% at 0.1 kHz and 70% at 100 kHz and the relative permittivity decreased by 31% at 0.1 kHz and by 97% at 100 kHz. The MIS data for the same patient showed similar decreases in both the permittivity and conductivity of the *ex vivo* data with respect to the *in vivo* measurements. The conductivity decreased by 36, 39 and 20% at 1, 4 and 8.5 GHz, respectively, while the relative permittivity decreased by 33, 27 and 21% at the same frequencies. These differences were more pronounced at the lower frequency range for the permittivity values and more

consistent over the full spectrum for the conductivity values (because of the large conductivity scale, it is difficult to see that the property differences at the lower frequencies are still quite substantial).

4.3. Example case study

A 59 year old woman presented with a new mammographic abnormality in her left breast. Mammographic findings included a 1.5 cm mass along with calcifications. She underwent a physical exam and MRI which revealed a 1.3 cm mass, 5 cm from the nipple located at 5:00 in the left breast. Histological analysis of a needle core biopsy confirmed an infiltrating ductal carcinoma. The patient was scheduled for a surgical lumpectomy. Prior to surgery this patient was contacted by our clinical coordinator and agreed to participate in the study.

EIT images were obtained of both the left and right breasts. Three levels of 16 circular electrodes were employed on both sides and patient-specific 3D meshes were constructed based on the opening diameters of the electrode arrays. The meshes were generated with Netgen (Schoberl 2004). The right breast mesh had 57 020 elements and 11 767 nodes while the left breast mesh contained 55 037 elements and 11 414 nodes. Conductivity and relative permittivity were computed at each of the 20 recorded frequencies using these meshes. Figure 10 shows the diagnostic MRI along with the reconstructed cross-sections of the conductivity distribution for both the left and right breast at 127 kHz. The MRI revealed extremely fatty breast composition. Similar findings were observed in the EIT images with 57% of all nodal conductivity values being less than 0.1 S m^{-1} in the left breast and 68% less than 0.1 S m^{-1} in the right breast at 127 kHz. The reconstructions displayed in figure 10 were windowed to a range of $0.1\text{--}0.7 \text{ S m}^{-1}$ to emphasize the non-adipose tissue structures. A threshold was applied to both right and left breasts ranging from 0.35 S m^{-1} to 0.7 S m^{-1} to denote the expected range of tumor conductivities. With this threshold, the reconstructed EIT images detected a region of higher conductivity at the 6:00 location, 4 cm from the nipple. No region of higher conductivity was observed in the right breast; the MRI similarly showed a uniformly fatty right breast. A 2 cm diameter spherical region of interest (ROI) was defined at the centroid of this elevated volume of conductivity on the left breast and a bilaterally symmetric ROI was established on the right side. The mean conductivity and permittivity were calculated over the whole breast volume and within these ROI's on both right and left reconstructions for each of the 20 system frequencies.

Three planes of the 1300 MHz permittivity and conductivity images of both breasts are also shown in figure 10. The images generally show the outline of the breast with respect to the surrounding bath (bath properties are higher than those of most of the breast) and decrease in diameter due to progression away from the chestwall (planes two toward four). Similar to the EIT images, 2 cm diameter ROI's were defined for the fibroglandular region in the right breast and the tumor site in the left breast. In addition, we selected representative regions of the more predominant adipose zones of each breast. In each case we analyzed the ratios between the ROI's and the background or adipose tissue. The right breast exhibits an elevated permittivity zone (4.01 times higher) just below the breast center with corresponding elevations (2.00 times higher) in the recovered breast conductivity regions. These features most likely correspond to normal fibroglandular tissue which we would expect to have higher dielectric properties (Lazebnik *et al* 2007a). For the left breast, the elevated permittivity areas appear elongated and extend from their central position to the breast perimeter (6:00) with slightly higher values (4.22 times higher) than for the right breast. Correspondingly elevated areas appear on the edges of the breast conductivity images but blur into the coupling medium portion of the image (5.29 times higher than the background) which also has higher conductivity than the breast parenchyma. These elevated permittivity and, more significantly, conductivity areas at 6:00 correspond nicely with the clinical interpretation of tumor location. This is also consistent with earlier reports (Poplack

et al 2007) where the conductivity images were more indicative of tumor presence than the associated permittivity levels.

Intraoperative EIS dielectric properties were recorded from this patient with an earlier iteration of the probe design and the data recorded was inaccurate (and therefore not included for this case). The clip deposited at the site of measurement during surgery was recovered during pathological sectioning allowing *ex vivo* properties to be recorded at the *in vivo* measurement site. The mean reconstruction properties of both the full volume and the ROI are shown in figure 11 along with the *ex vivo* point spectroscopy recordings. Similarly elevated conductivity and permittivity values are noted in the left ROI and *ex vivo* spectra.

5. Discussion

We have developed a successful procedural workflow capable of validating EM imaging systems. The protocol consists of patient diagnosis followed by (1) EM imaging, (2) intraoperative dielectric property measurement, (3) *ex vivo* dielectric property measurement, (4) histological confirmation of the precise tissue area probed as defined by pin holes and (5) final comparison of the dielectric properties estimated at different times by imaging and point spectroscopy.

The *ex vivo* conductivity and permittivity recorded here are similar to those values reported by others. For example, Surowiec *et al* (1988) showed that the 'low-frequency' tumor conductivity ranges from 2 mS cm^{-1} to 4 mS cm^{-1} and relative permittivities range from 2×10^3 to 6×10^3 at 100 kHz. We found conductivities ranging from 1.5 mS cm^{-1} to 2.1 mS cm^{-1} and relative permittivities ranging from 3.8×10^3 to 5.7×10^3 at 100 kHz. Similarly, Jossinet and Schmitt (1999) reported a low frequency conductivity of 2.8 mS cm^{-1} for breast cancer. Jossinet also noted that the variability in cancer permittivity is approximately six times lower than other tissues including fibroadenoma, mastopathy, mammary gland, adipose and connective tissues at 500 Hz (extracted from figure 3 Jossinet 1996). We similarly observed a large difference in the variability (9% versus 93%) of cancer versus non-cancer tissues. One reason for the variability is the vastly different morphologies making up the different tissue types. Because the pinning method was not used in all cases, some of the assigned tissue types represent an average assessment of a large area. Fibrocystic tissues, in particular, have considerable variation in morphology; these differences primarily resulted from cystic areas with large fluid collections and fibrous bands of tissue which have different electrical properties. We expect that incorporation of the pinning method will reduce the variability observed in the fibrocystic tissues because more specificity in the specimens probed will be available.

Similar electrical properties have been reported in the literature at higher frequencies. For example, Campbell and Land (1992) list conductivities and relative permittivities ranging from 2 to 34 mS cm^{-1} and 9 to 59, respectively, for cancer at 3.2 GHz. We found conductivities ranging from 20.8 mS cm^{-1} to 30.7 mS cm^{-1} and relative permittivities ranging from 44.1 to 58.5 at this frequency. Similarly, Lazebnik *et al* (2007b) reported conductivity and relative permittivity values of 26.6 mS cm^{-1} and 53.6, respectively, at 3.2 GHz.

Both conductivity and permittivity were observed to decrease for excised tissues. This trend is comparable with that observed previously and arises primarily from temperature changes, tissue dehydration and ischemic effects. It is well established that as a tissue or organ is devascularized, its electrical properties will change. Haemmerich *et al* (2002) report resistivity increases of greater than 32% at all frequencies ranging from 10 Hz to 1 MHz in liver at 2 h following removal from an animal subject. Tissue conductivity trends inversely

to resistivity and the conductivity decreases we observed in excised breast tissue are consistent with these findings in liver. These changes arise from the drop in temperature and from the metabolic breakdown of cellular regulation following tissue excision. Metabolic resources are depleted when the tissue is devascularized which leads to cellular swelling and a decreased volume of extracellular fluid available for current flow.

Over the microwave frequency range, we have also noted a fairly substantial decrease in both malignant tissue permittivity and conductivity from the *in vivo* to *ex vivo* states. To date, the most extensive study of microwave breast tissue properties has been conducted by teams from the University of Wisconsin and University of Calgary (Lazebnik *et al* 2007a, 2007b). While these studies showed that there can be considerable variation in the normal breast dielectric properties—largely depending on water content—and that there is some contrast between most normal and malignant tissues in the breast, the authors suggested that negligible property variation occurs between *in vivo* and *ex vivo* data for the majority of different adipose content tissues. However, they did note that a statistically significant difference resulted in the 85–100% adipose tissue conductivity as a function of time (typical values decreased about 30% when measured on the 0–50 min time frame relative to 250–300 min afterwards). If these changes were due to dehydration (loss of blood and other liquids during the measurement period), they are consistent with the related findings of Foster and Schepps (1981) based on mixture laws in which inherently low water content tissues (such as adipose) were more susceptible to property changes than their higher water-content counterparts.

Interestingly, the Lazebnik *et al* (2007a, 2007b) measurements were gauged from *ex vivo* specimens only between 5 min and 5 h after resection. Haemmerich *et al* (2002) report that the largest property changes occur immediately following tissue removal, with comparably small changes occurring during the period of 5 min to 5 h after removal where Lazebnik *et al* performed their measurements. This suggests that, perhaps, the Lazebnik report of modest property change with time to *ex vivo* measurement cannot be readily extrapolated to conclude that negligible property differences exist between *in vivo* and *ex vivo* breast tissues. In fact, careful scrutiny of the Haemmerich results shows that the predominant changes in their blood flow obstruction and tissue excision tests occurred on the order of seconds to minutes and stabilized over hours. While there may well be differences in the mechanisms of tissue dielectric property change between the lower and higher frequency ranges and tissue types in the Haemmerich data relative to ours, the apparent discrepancies in the degree and time course of property changes we observed in breast tissue when compared to the Lazebnik study warrants further investigation.

The case study demonstrates the potential of using this protocol to validate EM imaging *in vivo*. The primary limitation in our current protocol is the lack of registration between the pre-surgical diagnostic and EIT/MT images and the intraoperative probe placement. We are currently developing tools to capture the surface of the breast during EIT/MT image acquisition. The rendering of this surface can be elastically deformed to match the surface of an MR image. Imparting deformation to the reconstructed EIT/MT images will better colocalize lesions noted in diagnostic imaging and their subsequent location during surgery. Another technique to better coregister these images is to employ a multimodal imaging approach such as is being developed at RPI (Kao *et al* 2007). In that work, EIT images are obtained in a clinical mammographic system; the coregistration provided here would enable precise colocalization of lesions between the different imaging modalities.

6. Conclusions

We have successfully developed a protocol for assessing coregistered *in vivo* and *ex vivo* dielectric properties of breast tissue for comparison with EM imaging studies in order to validate the extent to which the properties recovered through imaging are quantitative. This validation is necessary for translating these alternative imaging modalities into a clinical environment where measures of property values are used as diagnostic indices. While this protocol has been employed in a small series of patients it has proved to be effective and offers the potential to provide a clear strategy for validating EM medical imaging modalities. Importantly, the protocol is both feasible and practical in terms of current clinical workflow and does not adversely affect or alter patient care.

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Figure 1. Point EIS probes. Bipolar *ex vivo* probe (left) and intraoperative probe (center) with an enlarged view of the tip (right).

Figure 2.
Point MIS probes. *Ex vivo* probe (left) and intraoperative probe (center) with an enlarged view of the tip (right).

Figure 3.

The EIT imaging system (left) interfaces to a stereotactic breast biopsy table retrofitted with slides (not shown) to accommodate the mechanical assembly. The MT imaging system is positioned beneath a custom examination table during patient exams (right). In both cases, the patient lies prone with her breast pendant through an opening in the exam table.

Figure 4.

Intraoperative probing procedure. Computer controlled analyzers housed on a portable cart at bedside (left). EIS/MIS probes and cables are sterilized prior to surgery. Probe cables bridge the sterile and non-sterile fields. Trocar is inserted into the tumor based on palpation or through US guidance and the probe tip is introduced through the trocar (center). Probe is inserted to the trocar tip and brought into contact with the tissue (right).

Figure 5. Pathological sectioning procedure. Mammogram of specimen (left) specifies the clip location. Also visible is a wire, locating a region of suspicious calcification. The specimen is sectioned in the pathology laboratory and laid out on the bench top (center). The clip is located in one of the specimens (right).

Figure 6. Pathological probing procedure. A specific region is probed (left), pins are inked and inserted into the tissue at the location probed (center), the tissue is stained and processed for microscopic review (right). The region within the circle is histologically assessed as in figure 7.

Figure 7. Pathological assessment. The tissue demarked by the pin holes defining the measurement region was denoted as mixed IDCa/DCIS. Note the variation in tissue morphology which influences the electrical properties.

Figure 8. Representative *ex vivo* dielectric spectra collected with the EIS probe during protocol development.

Figure 9. *In vivo* versus *ex vivo* dielectric spectra (EIS top and MIS bottom). Multiple spectra recorded for EIS are shown, while the average MIS spectrum is illustrated.

Figure 10.

Case study results showing clinical (MRI) and EM (EIT, MT) imaging results. For EIT (center), 3D image reconstructions of the left and right breast are presented. Focal enhancement of electrical conductivity in the left breast appears in the location defined to be tumor based on MR imaging. Anatomically coronal MT images (bottom) of relative permittivity and conductivity in three planes of the left and right breasts. Peripheral enhancement of electrical conductivity and permittivity in the left breast coincident with the MR location suggests the presence of tumor in the otherwise fatty breast.

Figure 11.

Case study results comparing EIT imaging with *ex vivo* point spectroscopy. ROI and whole breast average conductivity and permittivity values are presented as a function of frequency. ROI conductivity averages are greater in the left breast for all frequencies relative to the bilaterally symmetric position in the contralateral right breast as well as the whole breast averages in either the right or left breasts. The *ex vivo* point spectroscopy measurements in tumor mirror the *in vivo* imaged values being larger than the imaged normal tissue properties, but lower than the imaged tumor *in vivo* as expected.

Table 1

Statistics of low frequency dielectric properties of tissue gauged from six breast specimens with the *ex vivo* EIS probe. Conductivity and relative permittivity are reported at 10 kHz and 500 Hz, respectively; the properties at these frequencies exhibited significantly different values for tumor (IDCa/DCIS) and fibrocystic (FC) tissues. Conductivity is reported in units of S m^{-1} , while relative permittivity is unitless.

	σ (10 kHz)		ϵ_r (500 Hz)	
	IDCa/DCIS	FCD	IDCa/DCIS	FCD
Range stats				
Mean	0.145	0.068	1.46×10^6	5.13×10^5
SD	0.012	0.024	1.3×10^5	3.95×10^5
Minimum	0.127	0.036	1.6×10^6	9.3×10^5
Maximum	0.164	0.092	1.2×10^6	9.1×10^4