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ULTRASONIC ANALYSIS OF BREAST TISSUE FOR PATHOLOGY CLASSIFICATION

by

Kristina Marie Sorensen

**Thesis submitted in partial fulfillment
of the requirements for the degree**

of

**HONORS IN UNIVERSITY STUDIES
WITH DEPARTMENTAL HONORS**

in

**Applied Mathematics
in the Department of Mathematics and Statistics**

Approved:

Thesis/Project Advisor
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**UTAH STATE UNIVERSITY
Logan, UT**

Fall 2012

ABSTRACT

Ultrasonic Analysis of Breast Tissue for Pathology Classification

by

Kristina Marie Sorensen

Utah State University, Fall 2012

Thesis Advisor: Dr. Timothy E. Doyle
Department: Mathematics and Statistics

Real time measurements may assist surgeons in obtaining negative or cancer free margins during lumpectomy to eliminate invasive re-excision. Previous findings show that high-frequency ultrasound can differentiate between a range of breast pathologies in surgical specimens. Two parameters, peak density and second-order spectral slope, are sensitive to histopathology. Our objective was to determine the mechanism linking high-frequency ultrasound to histology. The hypothesis is that ultrasound sensitivity is a function of the microscopic heterogeneity (and thus histology) of the tissue. Ultrasonic results from breast specimens were used to construct a multivariate analysis of the parameters that permitted differentiation of normal, adipose, benign, and malignant breast pathologies.

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Kristina M. Sorensen

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BACKGROUND

Breast cancer impacts 12.2% of women in the United States, with a third of all patients dying from the disease. Approximately half of breast cancer patients choose a procedure known as lumpectomy for major part of their treatment to remove the malignant (cancerous) tissue. Surgeons strive to obtain negative margins (cancer-free tissues surrounding the tumor) in surgery to prevent further malignancy in the treated breast. Nevertheless, 30-50% of lumpectomy patients require additional surgery due to positive margins.

An interdisciplinary team of scientists and medical doctors from three Utah universities and the Huntsman Cancer Institute are developing advanced ultrasonic technology for surgical use that will assist surgeons in removing microscopic cancer from the breast during procedures such as lumpectomy. The new technique promises to reduce the high number of repeat surgeries after lumpectomy by detecting and identifying cancerous tissues along the margin edges, rapidly and in real-time. This will allow the surgeon to accurately remove enough tissue to ensure no cancer remains, while preserving as much unaffected tissue as possible.

The new method uses ultrasonic frequencies that are much higher than currently used in standard medical ultrasound to classify the pathology and identify breast tissue health. In addition to these higher frequencies, new state-of-the-art data analysis methods are being developed and tested. Sophisticated computer programs that simulate the interaction of ultrasound with breast tissue at the microscopic level are used to differentiate normal from cancerous cells. The synergy of these innovative techniques provides a powerful tool for surgeons to improve the care of breast cancer patients using a simple, portable, and cost-effective ultrasonic system.

A feasibility study funded by the National Cancer Institute of the National Institutes of Health was recently completed at the Huntsman Cancer Institute of the University of Utah. The study included 34 specimens from 17 patients, each of whom had been diagnosed with breast cancer. Each tissue specimen was ultrasonically tested immediately following removal in surgery and before pathology analysis. These tissue samples were classified into 15 pathology types. Each tissue was analyzed for specific ultrasonic signal correlations using medical statistical methods and computer simulation. The preliminary data shows promising correlations between a wide range of breast tissue pathologies. These include normal tissue, benign conditions (such as fat necrosis-fibroadenomas and fibrocystic changes), and malignant disease (such as invasive ductal carcinoma or IDC). Initial sensitivities and specificities are comparable to current methods in use or under development. However, the high-frequency ultrasonic method is faster and provides the surgeon information that can impact the immediate care of the patient in the operating room.

Figure 1. Portable ultrasonic system used in breast tissue analysis at the Huntsman Cancer Institute.

New ultrasonic parameters discovered in this study are sensitive to the microscopic structure of breast tissue glands. These parameters not only allow malignant pathologies to be distinguished from benign conditions, but may also permit different types of cancer to be identified based on their microscopic ultrasonic properties. As a result, this new ultrasonic technology has significant potential for differentiating between different types of cancer. Many other methods being researched are incapable of similar selectivity. Beyond the treatment of breast cancer patients, our technique can also be applied to Moh's surgery (the technique used to assure complete removal of skin cancers) and any other cancer or disease where obtaining tumor-free margins is an important part of the treatment.

Figure 2. Peak densities measured at frequencies of 20 to 80 MHZ for tissue classifications employed in differentiating between cancer pathologies. [FN-FA-TA: fat necrosis–fibroadenoma–tubular adenoma; DC: ductal carcinomas (DCIS & IDC); LC: lobular carcinomas (LCIS & ILC)]

New data analysis methods supply greater detail that can be utilized in distinguishing between many breast pathologies, thus providing surgeons with new information to operate with greater accuracy. For example, preliminary results visibly display the potential of the ultrasonic method to ascertain the presence of lobular carcinoma (LC). As shown in Figure 2, the peak density of LC (an ultrasonic parameter derived from data analysis and computer simulation) is

greater than that of other pathologies. The sensitivity of the high-frequency ultrasonic data to LC (particularly invasive lobular carcinoma or ILC) has immense surgical implications since LC is one of the most difficult cancers to fully remove in a lumpectomy.

Part of the continuing research includes improving the data analysis methods by looking at various combinations of data sets. One example includes comparing the calculated attenuation (decrease in amplitude) and peak density (concentration of “waves”) of an unknown specimen against a specific pathology. High-frequency array methods are also being explored to improve the imaging capabilities of this technique. Further testing of surgical specimens will likewise help to increase the accuracy and reliability of the method.

Figure 3. A three-dimensional rendition of simulated breast tissue that was used in the sophisticated computer modeling of ultrasonic waves.

In response to this critical medical concern, collaborative research is ongoing to develop this advanced ultrasonic technology. By implementing a real-time technique to determine the pathology of surgical margins during breast cancer surgery, the Utah team seeks to alleviate unnecessary patient suffering and reduce health care costs for those who are diagnosed with breast cancer.

Animation 1. Computer simulation of scattered ultrasonic waves. The elliptical structures model cross-sections through simulated breast gland ducts. Simulated adipocytes (fat cells) are represented by the larger orange cells.

Animation 2. Total ultrasonic wave field, showing the incident wave plus the scattered wave.

Figure 4. Diagram of breast tissue structure, depicting intraductal spread of carcinoma (Doyle T.E., et. al., 2011. BMC Cancer 11:444).

Figure 5. Image of breast tissue ducts (Keymeulen V., et al., 2011. Nature 479: 189-193).

METHODOLOGY

The surgical specimens tested were classified as either benign or malignant. Benign tissues were classified as either lymph nodes, normal breast tissue, or atypical, or fat tissue. Atypical specimens included benign with calcifications, atypical ductal hyperplasia, and fibrocystic change. Fat, or adipose, tissues included fat necrosis, fibroadenoma, or tubular adenoma. Malignant tissues were distinguished as either ductal carcinomas (DC) or lobular carcinomas (LC). Further subgroups of the ductal carcinomas (DC) include ductal carcinoma in situ (DCIS), DCIS—solid & cribriform, invasive ductal carcinoma (IDC), and DCIS plus IDC. Subgroups of the lobular carcinomas (LC) include lobular carcinoma in situ (LCIS) and invasive lobular carcinoma (ILC).

Benign	Malignant
Lymph nodes	Ductal Carcinomas (DC): <ul style="list-style-type: none"> ● Ductal carcinoma in situ (DCIS) ● DCIS, solid & cribriform ● Invasive ductal carcinoma (IDC) ● DCIS + IDC
Normal breast	
Atypical: <ul style="list-style-type: none"> ● Benign with calcifications ● Atypical ductal hyperplasia ● Fibrocystic change ● Papilloma 	
FN-FA-TA: <ul style="list-style-type: none"> ● Fat necrosis ● Fibroadenoma ● Tubular adenoma 	Lobular Carcinomas (LC): <ul style="list-style-type: none"> ● Lobular carcinoma in situ (LCIS) ● Invasive lobular carcinoma (ILC)
Total measurement positions = 29	Total measurement positions = 26

Figure 6. Table of breast tissue pathologies.

Equipment

Through-transmission (also known as pitch-catch) and pulse-echo waveforms were collected for each of the surgical specimens. The Utah State University Ultrasonics Laboratory includes a state-of-the-art, high-frequency, ultrasonic experimental system assembled for pulse-echo and through-transmission measurements, specifically designed to pick up and amplify (63 dB max) ultrasonic signals from 7-150 MHz. The system includes a UTEX UT340 high-frequency ultrasonic pulser-receiver (3 ns pulse of up to 250 V), three digital storage oscilloscopes (Hewlett-Packard HP54522A: 500 MHz, 2 Gs/s/channel, 2 channels; LeCroy 9350AM: 500 MHz, 1 Gs/s/channel, 2 channels; Textronix TDS 2014: 100 MHz, 1 Gs/s/channel, 4 channels), a variety of ultrasonic transducers in the 7-50 MHz range, and a notebook PC with LabVIEW programs for data acquisition. The system is portable and reconfigurable into a variety of modes of operation, particularly for a variety of medical ultrasonic tests.

Figure 7. (a) Test set-up. (b) Through-transmission methodology. (c) Pulse-echo methodology.

Figure 8. Equipment diagram for data acquisition.

Figure 9. Ultrasonic system.

Procedure

The first-order spectra were obtained from through-transmission waveforms, whereas the second-order spectra were obtained from pulse-echo waveforms. This approach allowed clear differentiation between breast tissue pathologies.

Ultrasonic Analyses

Figure 10. (a) Through transmission waveforms (b) Pulse-echo waveforms (c) First-order spectra calculated from through-transmission waveforms (d) Second-order spectra calculated from pulse-echo waveforms.

PRELIMINARY RESULTS

Breast Histology Correlations

Previous pathologic data reveals that tissue heterogeneity increases from fibroadenoma (mostly stroma) to normal breast tissue to LCIS (tumor proliferation in lobules). Heterogeneity correlated directly with peak density and inversely with slope.

Figure 11. From left to right (a) Benign fibroadenoma (WebPathology.com). (b) Normal breast tissue (U. Mich.). (c) LCIS (WebPathology.com).

Surgical Margin Results

Figure 12. (a) Peak density, or number of peaks and valleys, from first-order spectra in the 20-80 MHz range. (b) Normalized slope from second-order spectra.

A Fast-Fourier-Transform (FFT) was performed on the both the raw waveforms as well as the first order spectra. The peak density, or number of peaks and valleys, from first-order spectra as well as the normalized slope from second-order spectra were calculated.

Application

Malignancies form either within the lining of milk ducts (ductal carcinoma) or the lobules of the breast that produce milk (lobular carcinoma). The cancer is defined as “in situ” if the malignancy has not invaded nearby tissue. Since lobular carcinoma (LC) is difficult to diagnosis in the preliminary invasive stages, our findings have vast implications for pathology classification. (Sakr RA, Poulet B, Kaufman GJ, Nos C, Clough KB: Clear margins for invasive lobular carcinoma: a surgical challenge. *Eur. J. Surg. Oncol.* 2011, 37:350-356.)

Statistical Significance

The *t*-test results for differentiation from normal tissue using a one-way ANOVA test demonstrated a 5% significance level for peak density and close to 1% significance level for normalized slope.

Pathology	Peak density	Slope
Lobular carcinomas	$p < 0.02$	$p > 0.20$
Ductal carcinomas	$p < 0.05$	$p < 0.20$
FN-FA-TA	$p < 0.05$	$p < 0.01$
Benign pathologies	$p < 0.10$	$p < 0.01$

Figure 13. The *t*-test results for differentiation from normal tissue using a one-way ANOVA test.

Simple Multivariate Analysis

Figure 14. (a) Attenuation vs. peak density. (b) Rotated and translated plot of attenuation vs. peak density, showing the use of parabolic and linear curves for the classification boundaries. F = fat necrosis - fibroadenoma - tubular adenoma. B = benign pathology. N = normal breast tissue. M = malignant breast tissue. (FN-FA-TA: fat necrosis–fibroadenoma–tubular adenoma; DC: ductal carcinomas (DCIS and IDC); LC: lobular carcinomas (LCIS and ILC)).

Classification Techniques

Additional classification procedures to be further explored include principle-component-analysis (PCA), minimization of the second vector norm, and logistic regression.

DISCUSSION

The data show repeatable correlations between tissue heterogeneity and peak density of first-order spectra corresponding to ductal and lobular carcinomas in human breast tissue. Furthermore, the standardized slopes of the second order spectra are the lowest for normal ductal structures, such as normal breast tissue and medullary collecting ducts. However, these correlations are less repeatable for slope of second-order spectra.

CONCLUSIONS

Tissues with greater peak densities in 1st-order spectra exhibit more complex (or less uniform) histology as well as larger or more widespread heterogeneities. Tissues with lower slopes in 2nd-order spectra exhibit normal microscopic ductal structures, such as shown between normal breast glands and renal medulla. The results support hypothesis that high-frequency ultrasound is sensitive to microscopic heterogeneity—and thus histology—in tissues. Further applications include intraoperative evaluation of margins during breast cancer surgery in addition to real-time pathology detection for other cancers and procedures.

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AUTHOR'S BIOGRAPHY

Kristina Marie Sorensen was born in Logan, UT and has since lived in five different states, soon to be seven, before coming full circle and returning to Logan during her undergraduate career. She graduated from Eden Prairie High School in June of 2009 and began studies at Utah State University the following fall.

She has performed research in Biomedical Ultrasonics with Dr. Timothy E. Doyle, Musical Acoustics with Dr. Timothy W. Leishman during a Physics REU at BYU during Summer 2011, and Pulse-Electro-Acoustics with Dr. Lee H. Pearson and Dr. JR Dennison. She has been a participant in the USU Flute Choir, Aggie Marching Band, and the USU Gymnastics Club as well as fulfilled her dream of running the Top of Utah marathon on 15 September 2012.

Following graduation, she will spend eighteen months in the California San Diego English-Speaking Mission for The Church of Jesus Christ of Latter Day Saints. Afterwards, she will attend graduate school and receive her PhD in acoustics.