AD_____
(Leave blank)

Award Number: W81XWH-07-1-0640

TITLE: Acoustic Inverse Scattering for Breast Cancer Microcalcification

PRINCIPAL INVESTIGATOR: Matthew A. Lewis, Ph.D

CONTRACTING ORGANIZATION:
University of Texas Southwestern Medical Center at Dallas
5323 Harry Hines Blvd
Dallas, TX 75390

REPORT DATE: September 2008

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE 16-09-2008	**2. REPORT TYPE** Annual	**3. DATES COVERED** *17 Aug 2007-16 Aug 2008*

4. TITLE AND SUBTITLE
Acoustic Inverse Scattering for Breast Cancer Microcalcification

5a. CONTRACT NUMBER
W81XWH-07-1-0640

5b. GRANT NUMBER
BC063989

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Matthew A. Lewis

Email: matthew.lewis@utsouthwestern.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Texas
Southwestern Medical Center
5323 Harry Hines Blvd
Dallas TX 75390-9105

The University of Texas at Arlington
202 E. Border Street
Arlington, TX 76019-0145

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland
21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
An advanced scalar inverse scattering theory developed by Colton, Kirsch, and others in the inverse scattering community can determine the shape of scatterers with size on the order of the wavelength. In addition to size and number, the morphology of breast microcalcifications is an important diagnostic indicator. Our hypothesis is that the linear sampling method (LS), when augmented with a method for estimating the inhomogeneous Green's function for wave propagation in the breast, can be translated to an acoustic imaging system to detect, localize, and characterize microcalcifications in breast phantoms using data from the far-field scattering measurements. To realize this goal, we have implemented a new data acquisition systen for water tank measurements, designed breast phantoms including appropriate hard scatterers of known shape, and developed numerical methods for both simulation and image reconstruction. Year 2 will focus on the evaluation of these methods.

15. SUBJECT TERMS
ultrasound, inverse scattering, optimum array processing, breast cancer screening, detection, estimation, linear sampling method

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			**19b. TELEPHONE NUMBER** *(include area code)*
U	U	U	UU	10	USAMRMC

Table of Contents

	Page
Introduction…….	**4**
Body……..	**4**
Key Research Accomplishments……..	**8**
Reportable Outcomes……	**9**
Conclusion……	**9**
References……	**10**
Appendices……	**N/A**

1 Introduction

Microcalcification detection is the hallmark of mammography as a breast cancer screening modality. For technical reasons, ultrasonic detection of all mammographically-visible microcalcifications has been problematic. In clinical ultrasound, high frequencies must be used to resolve microcalcifications below 200 micrometers. Unfortunately, ultrasonics above 10 MHz suffer from appreciable attenuation in soft tissues, and depth of penetration is limited. Transmission diffraction tomography, while well-suited for the geometry of the breast, is inherently insensitive to scattering caused by small, hard inhomogeneities. A more general form of acoustic inverse scattering is therefore needed for microcalcification detection and localization by ultrasound. We find rationale in the advanced scalar inverse scattering theory developed by Colton, Kirsch, and others in the RADAR community that can determine the shape of scatterers with size on the order of the wavelength. In addition to size and number, the morphology of breast microcalcifications is an important diagnostic indicator. Our hypothesis is that the linear sampling method (LS), when augmented with a method for estimating the inhomogeneous Green's function for wave propagation in the breast, can be translated to an acoustic imaging system to detect, localize, and characterize microcalcifications in breast phantoms using data from the scattering measurements in a tomographic geometry.

2 Body

The goal of this research endeavor is to develop a bistatic ultrasound imaging method that specifically targets breast microcalcifications. By bistatic imaging, we mean that receiver and transmitter can be separated in space. Since there are several commercial breast acoustic tomography systems currently undergoing FDA trials, we believe that it is the appropriate time to apply state-of-the-art methods from optimum array processing and inverse scattering to this important biomedical imaging problem.

As denoted in Tasks 8 and 9 of Year 1, we have have upgraded our water tank testing station to facilitate quicker data acquisition from custom ultrasound arrays with improved signal-to-noise ratio. As shown in Figure 1, this funding mechanism has replaced an obsolete, 40 MHz, 8 bit, 48 channel DAQ system with a compact, portable, 64 channel, 12-bit, 65 MHz, commercial DAQ system. This piece of major equipment is based on a National Instruments (Austin, Texas) Compact PCI chassis containing 8 PXI-5105 8 channel digitizer boards. Through the development of custom software in the LabVIEW programming environment, we can capture data simultaneously from all 64 array elements. We note that this DAQ system is a novel design that has attracted the attention of the manufacturer, and we anticipate that our research project will be highlighted by National Instruments in the future.

One unforeseen difficultly with the new DAQ system was the coupling of a pre-amplifier stage. Fortunately, one of the investigators (M. Lewis) has been involved in a separate research program using similar acoustic arrays to investigate bone properties. This system

Figure 1: Comparison of older, in-house data acquisition system (left) with commercial solution (right)

has also moved from 48 to 64 channels in the past year, with one by-product being an improved pre-amplifier board with minimal capacitive coupling. Efforts are in-progress to translate this technology to this project since the sensor technology is nearly identical.

Much of the research in this program deals with the Colton-Kirsch linear sampling (CK-LS) method. The CK-LS method is based on the mathematical analysis of a model of scattering called the far-field operator:

$$(Fg)(x) = \int_{\Omega} u^{\infty}(x,d)g(d)ds$$

Here, F is the far-field complex amplitude for a sensor in direction x. The scatterer g lies in the domain Ω, and a plane wave is used to insonify the object from direction d. An important result of analysis by David Colton is: *Assume that ∂D is analytic and let $z \in D$. Then for every $\epsilon > 0$ there exists a solution $g = g(\cdot, z) \in L^2(\Omega)$ of the inequality $\|Fg - \Phi^{\infty}(\cdot, z)\|_{L^2(\Omega)} < \epsilon$ such that*

$$\lim_{z \to \partial D} \|g(\cdot, z)\|_{L^2(\Omega)} = \infty$$

In layman's term, this means that the solution to this equation for the far-field data will *blow-up* if the test point z is on the boundary of a scatterer. This suggests our computational strategy for *imaging* the surface of object.

In the discrete version of this problem, Gaussian quadrature and linearization were used to reduce the problem to a matrix equation.

$$(Fg)(x) = \Phi^{\infty}(x,z)$$

Here, $\Phi^{\infty}(x,z)$ is the Green's function for a point scatterer at position z in the field-of-view. Even after linearization, this inverse problem is ill-posed, so some sort of regularization is

required. We have developed software routines in Matlab (Mathworks) for Task 1 that allow either Tikhonov regularization or singular value decomposition truncation, which is well-recognized as a simple form of regularization. This task is 90% complete. The choice of the Tikhonov regularization parameter is dependent upon measurement noise, which will become more clear in Year 2 experiments. For numerical experiments with noiseless data, the choice of the singular value cutoff is fairly arbitrary.

In the interim, we proposed in Task 2 to develop computation algorithms to generate synthetic data. Our existing finite element modelling codes in Comsol Multiphysics (COMSOL, Boston, MA) have been updated to include scatterers with penetrable boundary conditions. This is a more realistic model of hard scatterers than the Dirichlet and Neumann boundary conditions that were described in the original grant proposal. At present, our forward modelling code is linearized, and there is no interaction between the hard scatterers and secondary scattering by background heterogeneities. The scattered wave field from soft tissue heterogeneities is generated either by Fourier slice theorems or by the tomographic methods discussed below. It does not appear to be possible to simulate the full non-linear scattering process using FEM, so we are actively pursing existing solutions in the finite difference-time domain (FDTD) class.

Task 4, the migration of these computation tools to more powerful computer clusters, has been delayed by the introduction of multicore computers. We find that much of our code for 2D simulation and imaging reconstruction runs in a reasonable amount of time on the desktop. Likewise, the statistical characterization of speckle noise and its suppression (Task 7 - extends into Year 2) has been delayed by studies of novel image reconstruction models to be described below.

A significant portion of our collaborative efforts in Year 1 have dealt with Tasks 5 and 6, the development of methods for estimating the soft tissue heterogeneities that must be accounted for as a background scatterer in the CK-LS method [1]. An emerging model for time domain scattering in the bistatic ultrasound imaging geometry is the elliptical Radon transform (ERT). Small transducers can be modelled as having no directional sensitivity, and in this case the surface of constant time between a transmitter and receiver will be as follows.

Consider an ellipse with foci at $\vec{x}_e$ and $\vec{x}_r$. The family of ellipses at these foci have semi-major axis a, semi-minor axis b, and a foci separation of $2c = |\vec{x}_e - \vec{x}_r|$. The vector form of the ellipse can be written:

$$|\vec{x} - \vec{x}_e| + |\vec{x} - \vec{x}_r| = 2a$$

Next, we make use of an identity linking the a and c with the *eccentricity* e of the ellipse.

$$a = \frac{c}{e}$$

$$|\vec{x} - \vec{x}_e| + |\vec{x} - \vec{x}_r| = \frac{1}{e}|\vec{x}_e - \vec{x}_r|$$

e is defined in the domain $0 \leq e < 1$.

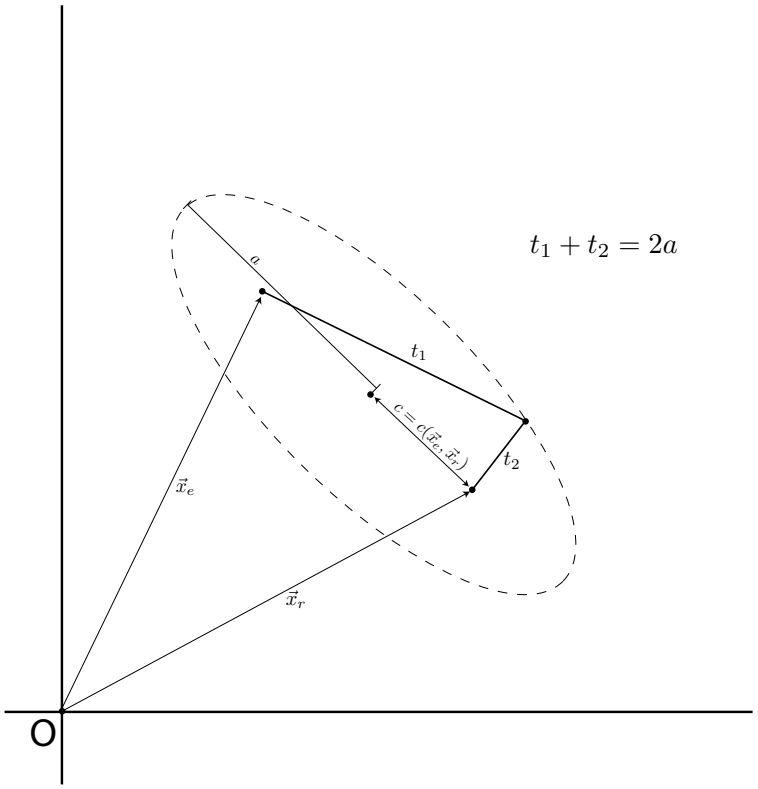

Figure 2: Geometry for elliptical Radon transform - a model for bistatic ultrasound array imaging in the breast

One possible definition for the elliptical Radon transform would therefore be:

$$R^{\mathcal{O}}_{\vec{x}_e,\vec{x}_r}(e) = \int_{|\vec{x}-\vec{x}_e|+|\vec{x}-\vec{x}_r|=\frac{1}{e}|\vec{x}_e-\vec{x}_r|} f(\vec{x})ds$$

There are 5 parameters in this expression. If we additionally require that the semi-major axis be orthogonal to a line from the origin to the center of the ellipse, then the number of parameters can be reduced to 4. Based on the principle of dimensionality, the system is still over-determined. Thus, a shot record for a circular aperture could be modelled as these integrals over ellipses, and some sort of inversion/image reconstruction should be possible in at least the least squares sense.

Recently, there appeared in the literature a backprojection-type algorithm for bistatic imaging according to the the ERT model [2]. Initially, we thought this algorithm might accelerate our development of the Green's function estimator in Task 6. However, one of the co-investigators (G. Ambartsoumian) is an expert in the area of image reconstruction for photoacoustic tomography (PAT), another imaging method that has shown much promise for breast cancer imaging. PAT uses a spherical Radon transform, and it was only in 2007 that a filtered backprojection algorithm appeared in the literature for the 2D problem [3].

In operator form, the proposed filtered backprojection algorithm for the elliptical model

was

$$f = B \circ F^{-1} \circ Abs \circ F \circ R_E \circ f$$

where F is a Fourier transform pair and Abs is the familiar ramp filter from classical tomography. In the case that the transmitter and received are brought together, then this inversion formula should reproduce the exact reconstruction algorithm found in [3]. Unfortunately, this is not the case. The filter found in [3] is logarithmic in the radius, and so the results in [2] are not correct.

We have dedicated a focused effort on developing a proper method for estimating the soft tissue background in this ERT model. One of use (M. Lewis) has developed Matlab codes for forward projection and for estimating a discrete transfer matrix A so that iterative reconstruction methods such as Karmacz can be applied. In addition, a graduate student supported by this award has been studying the empirical behavior of the spherical filtered backprojection algorithm applied naively in the case of ERT. For geometries that described moving transducers, the spherical filtered backprojection algorithm appears to work reasonably well with the elliptical geometry. As noted in the original statement of work, this task was slated to run into the 1 quarter of the second year, so research will continue on these promising methods.

Phantoms for algorithm testing and characterization have been finalized. They are based on existing soft tissue phantoms for low-contrast diffraction tomography. 10 grams of agarose is dissolved in 75 ml heat water and poured into a mold to congeal. Acrylic inserts can be used to create voids that are filled in a second pass with a different density agarose. Modification of this phantom includes the addition of hexagonal Allen wrenches and square and round steel rod to simulate extended scatterers of known shape. Efforts are ongoing to identity a rod with concave edges. Despite the ready supply of convex scatterers, the CK-LS should also work with concave scatterers, and we note that many of the most troubling breast microcalcification morphologies are non-convex.

The commencement of experiments with phantoms (Task 11) was scheduled to begin in the summer of 2008. Due to increased focus on Task 6, a more realistic initiation time for Task 11 will be November 2008.

3 Key Research Accomplishments

- Upgrade of water tank data acquisition system for acquiring real scattering data in Year 2.
- Design of 2D ultrasound phantoms with soft tissue heterogeneities and hard scatterers of extended shape.
- Development of software tools for forward modelling of the low frequency scattering process and the ill-posed algorithm for reconstructing the shape of scatterers.
- Identification of fundamentals shortcoming in the breast ultrasound tomography literature as it relates to bistatic imaging, and the development of an iterative approach

for estimating the inhomogeneous background in the inverse scattering problem.

4 Reportable Outcomes

- Two publications are under preparation, as originally denoted in Task 13 of our statement of work. One publication describes our research efforts in the area of the elliptical Radon transform model for reconstructing the soft tissue background, and the second paper highlights our computational implementations for forward modelling and the CK-LS regularization problem.

- An abstract and poster were presented at the 2008 Era of Hope conference in Baltimore, Maryland: Acoustic Inverse Scattering for Task-Specific Breast Sonography - Development of Non-Ionizing Methods for Microcalcification Detection in High-Risk Populations.

- An abstract and poster were presented at the 2008 SIAM Imaging Science meeting in San Diego: Estimating Tumor Bounds in Bioluminescence Tomography. Here, methods related to CK-LS were applied to a problem in optical imaging for breast cancer research.

- A graduate student supported by this grant has submitted an abstract based on his work with the elliptical model to 2009 SPIE Medical Imaging conference. In addition, he has applied for a DoD Prostate Cancer Predoctoral Training Award (PC081528 - Advanced Array Imaging in Prostate Sonography) where he will utilize many of the methods in this study for prostate cancer ultrasound.

5 Conclusion

Despite the ambitious nature of this research project, we have maintained a reasonable focus with our original Statement of Work. Our translation from experimental preparation and computational modelling has been slightly delayed by interesting work related to the task of estimating the soft tissue background in the breast. In retrospect, we did not think that this area would be as fruitful, since there is a solid 25 years of literature on acoustic tomography. However, there is an obvious shortcoming in our understanding, and we have adopted a novel but promising approach for generating a piecewise constant background model for integration in our CK-LS scheme. Two outstanding issues will remain at the successful completion of this project: First, will the methods developed here be translatable to the breast ultrasound tomography systems that are now in clinical trials? And second, will the methods need to be converted to fully 3D methods for success *in vivo*?

References

[1] David Colton and Peter Monk. A linear sampling method for the detection of leukemia using microwaves. *SIAM J. Appl. Math.*, 58(3):926–941, 1998.

[2] Serge Mensah and Emile Franceschini. Near-field ultrasound tomography. *JASA*, 121(3):1423, 2007.

[3] David Finch, Markus Haltmeier, and Rakesh. Inversion of spherical means and the wave equation in even dimensions. *SIAM J Appl Math*, 68(2):392, 2007.