



# Year Eight Project Report

<b>Project ID: R1-A3</b>					
<b>Title: Dual-Wave Methods for Biomedical Imaging</b>					
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## **I. Brief Overview of the Project and Its Significance**

Optical techniques for imaging in turbid media, such as biological tissues, have received considerable attention in recent years [1]. This is due to both the non-invasive and non-ionizing properties of these methods, as well as the ability of these techniques to provide functional information based on the absorption and scattering properties of various tissue constituents. High-resolution optical imaging of biological media is complicated by optical scattering, which typically results in a tradeoff between image resolution and imaging depth. Acousto-optic imaging (AOI) [2-4] is a dual-wave imaging technique that holds promise for improving image resolution at greater depth by making use of a combination of diffuse laser light and focused ultrasound (US) and by taking advantage of the fact that ultrasound is much less readily scattered in biological tissues than is light. In this technique, a focused ultrasound beam is used to modulate or “tag” diffuse light through the displacement of optical scatterers and ultrasound-induced changes in refractive index [5]. The detection of this modulated light yields spatially resolved opto-mechanical information. The advantage of this hybrid technique is that it can reveal optically relevant physiological information while maintaining ultrasonic spatial resolution. The biggest technical barrier to AOI has been low sensitivity, due primarily to the low flux of modulated photons and the spatial incoherence of the modulated signal. The flux of phase-modulated photons in biological tissue is small due to both the high effective attenuation coefficient of biological tissue ( $\sim 2 \text{ cm}^{-1}$ ) and the fact that the light is only modulated in the light/sound interaction region. The last point is especially important when one considers using high-frequency, tightly focused, short-pulse ultrasound for AOI. Moreover, a spatial incoherence of the modulated signal results from the fact that photons, after traveling through turbid media, form speckles, whose individual grains are phase-modulated (and amplitude-modulated due to interference with the background optical field) at the ultrasonic frequency. In highly diffuse media, photons travel over multiple paths from the optical source to the detection system, and the modulation of these individual grains induced by the ultrasound depends on the path that a given photon takes, as well as the spatial position that the acousto-optic interaction takes place. The net result is that the modulation of individual speckle grains is not coherent, and therefore the modulation depth will be reduced when multiple speckle grains are incident on the aperture of the optical detector.

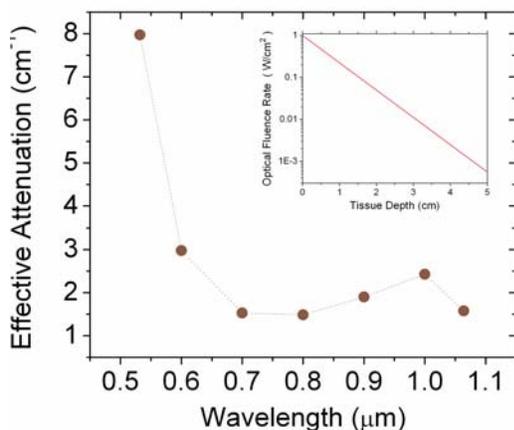
The Acousto-Optic Imaging Project has two interrelated goals. The first goal is the development of a dual-modality imaging device that combines conventional ultrasound imaging and AOI and

is suitable for *in vivo* imaging. We have made several significant breakthroughs in AOI over the past several years.

First, it was demonstrated that the novel photorefractive crystal-based interferometry system that has been developed has sufficient sensitivity to detect acousto-optic signals in highly scattering media using a *pulsed ultrasonic source* [6, 7]. The fact that the system has sufficient sensitivity to use pulsed ultrasound provides several important advantages over the AOI systems that use continuous-wave (CW) ultrasound: the use of short ultrasound pulse trains allows for spatial resolution along the ultrasound axis, and pulsed ultrasound minimizes deleterious thermal bio-effects that can result from high-intensity ultrasound exposure.

Second, we have combined the AOI system with a conventional ultrasound imaging system, using a commercially available ultrasound probe that was excited by the Analogic Engine (AN2300) [8]. The ultrasound emitted by the probe was used to generate both a conventional, B-mode or grayscale ultrasonic image and as the source for AOI imaging. In this system, B-mode and AO images are automatically co-registered. We have demonstrated that AOI has the potential to supplement ultrasound images with subsurface optical and opto-mechanical information. Subsurface inhomogeneities exhibiting similar mechanical contrast can be discriminated through variations in optical contrast, allowing for the possibility of functional imaging and tissue delineation. We have demonstrated 3-D imaging in *ex vivo* biological tissue using the combined US/AOI system. There are two major technical issues that must be overcome before the system is suitable for *in vivo* imaging. First, the detection system speed must be improved such that it is rendered insensitive to the speckle decorrelation associated with physiological motion. Next, the imaging acquisition time must be decreased.

Over the past year, we have completed and fully characterized a new AOI system that operates in the near-IR (1064nm) region of the spectrum. The system has been used to image tissue phantoms having inclusions with absorption contrast with the background media. This system offers two advantages over the previous system, which operated at 532nm. First, the effective



**Figure 1. Effective attenuation coefficient in breast tissue as a function of wavelength [9]. The inset shows the optical fluence rate as a function of depth.**

attenuation coefficient ( $\mu_{eff}$ ) in tissue is substantially reduced in the near-IR. In breast tissue, for example,  $\mu_{eff}$  is reduced from  $7.9\text{cm}^{-1}$  at a wavelength of 532nm to  $1.6\text{cm}^{-1}$  at a wavelength of 1064nm (see Figure 1). Next, the new system uses a GaAs photorefractive crystal with a response time of approximately 1ms under moderate illumination levels. This is expected to be sufficient to overcome speckle decorrelation and the system is potentially suitable for *in vivo* measurements.

In addition to completing the near-IR system, we have also obtained promising preliminary results in a new type of AOI based on the change in the AO response of a sample as a function of acoustic pressure. This imaging approach is referred to as pressure contrast AOI. In pressure contrast AOI, the

AO response is measured as a function of acoustic pressure, and this response is used to extract a parameter ( $\beta$ ) that is related to the mean phase shift imparted on the light. This parameter is independent of the background light level and the amount of light in the light-sound interaction region. Preliminary measurements suggest that pressure contrast imaging may be more sensitive

to local changes in optical properties than conventional AOI in some cases. In particular, we have observed inclusions exhibiting scattering contrast using pressure contrast imaging that were *not detectable using conventional AOI*.

The second goal of the AOI project is to obtain quantitative understanding of the mixing of diffusive optical waves with relatively high-intensity focused pulsed ultrasound. Two modeling approaches have been pursued. In the first, the light/sound interaction has been modeled combining a finite-difference time-domain (FDTD) model for acoustic wave propagation with a Monte-Carlo simulation for the light field [10]. This model has been used to track photons as they propagate through the ultrasound field in diffuse media and to calculate the accumulated phase shifts, taking into account both the ultrasound modulation of scatterers and the acoustically induced change in refractive index of the target. The results agree well with our experimental observations, and have helped us to better understand the physics of the photorefractive-crystal (PRC) detection approach. In the second, more recent, modeling approach, the diffusion approximation is used to model the optical field. The AOI signal received from a given subsurface region depends on the ultrasound field, the local optical intensity, the position of the region with respect to the excitation and detection points, and the characteristics of the source and receiver systems. We are working to model the optical field that develops in inhomogeneous media, and to evaluate the probability of detecting a phase-modulated photon from a given region within the sample. The goal is to obtain quantitative subsurface properties, such as the effective absorption coefficient, through a model-based inversion approach using 3-D AOI data obtained experimentally.

## **II. State of the Art, Major Contributions and Technical Approach**

### **A. AOI Background/ State of the Art**

Dolfi and Micheron first discussed the idea of imaging using tagged photons in 1989 [11]. The first demonstration of the modulation of diffuse laser light with pulsed, focused ultrasound in a homogeneous scattering media was presented in 1993 [2]. This was closely followed by the work of Wang *et al* [3] and Kempe *et al* [12], who demonstrated the utility of using the “ultrasound tagging” of diffuse photons for imaging purposes. In order to enhance the signal-to-noise ratio (SNR), Wang *et al* employed a CW ultrasound source, and the modulated signals were detected using a photomultiplier tube (PMT). Conventional single-detector techniques result in extremely low light levels when the detection aperture is limited to single-speckle detection, and reduced modulation depth when the detection aperture is increased to receive multiple speckles. To overcome the limitations of single-detector techniques, Leveque *et al* [4] employed a multiple-detector system based on a charge-coupled device (CCD) array. By adding up the individual modulation amplitudes from all of the pixels, they improved the SNR by a factor of  $\sim N^{1/2}$ , where  $N$  is the number of coherence areas detected, corresponding to the number of pixels on the CCD. The CCD approach that has been employed is not suitable for pulsed ultrasound measurements due to the relatively long time required for image acquisition; the system is sensitive to speckle decorrelation during the measurement time. More recently, Gross *et al* [13] improved the sensitivity of this parallel detection scheme by using a heterodyne technique, and proposed to filter out the speckle decorrelation noise using a spatial filter.

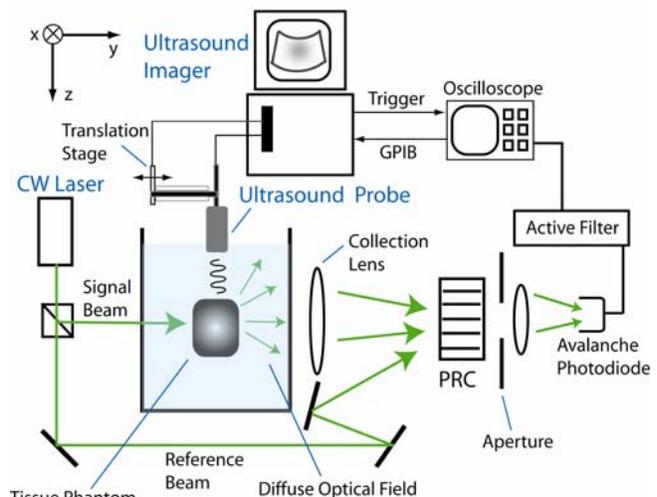
In the majority of AOI systems, CW ultrasound sources are employed, which allows for greatly enhanced sensitivity and noise immunity through a reduction in detection bandwidth. However, the use of broadband acoustic pulses provides two important advantages over CW ultrasound: enhanced spatial resolution is easily achieved along the ultrasonic axis, and the deleterious bio-

effects that can result from the high-intensity ultrasound exposure can be minimized. To achieve axial resolution for CW exposures, Wang and Ku [14] introduced a technique in which a single optical detector is used and the CW ultrasound source is chirped, thereby assigning a particular frequency to each location along the ultrasonic axis. A 1-D axial scan could then be produced from the time-dependent frequency-domain information of the ultrasound-modulated signals. Yao *et al* [15] and Forget *et al* [16] also combined this technique with the parallel detection system to achieve the axial resolution with enhanced sensitivity. Alternatively, in time domain, Lev and Sfez [17] used ultrasonic pulses to construct CW signals by devising a reshaping algorithm to synchronize the ultrasonic pulses.

We have designed and developed a PRC-based interferometry system for the detection of ultrasound-modulated light in diffuse media, which was shown to have sufficient sensitivity to detect the *transiently modulated optical signals generated using a pulsed ultrasound source operating at medically relevant output levels* [6]. By using short pulses of focused ultrasound, a 1-D image of an absorbing target buried in a tissue mimicking phantom was obtained from a single (averaged) time domain waveform. The transverse resolution of the measurement was determined by the width of the ultrasonic beam, while the axial resolution was controlled by the spatial length of the ultrasound pulse. In addition, two-dimensional imaging of optical inhomogeneities buried in turbid media was demonstrated through scanning of the ultrasound transducer in one dimension. Finally, we have successfully integrated this AO sensing approach with a commercial ultrasound-imaging machine (Analogic Corp., AN2300) in which the same scan head is used to both produce the ultrasound image and excite the AO response. The result is a system for producing automatically co-registered ultrasound and AO images. Resulting images display contrast in both the acoustical and optical properties of the propagation medium (tissue phantoms and excised chicken breast) [6-8]. Ramaz *et al* have worked in parallel with our group and have also recently developed a PRC-based demodulator for AO signals. Their system is designed to operate with a CW ultrasound source [18].

## B. Technical Approach

Here we first present previous work illustrating the operation of pulsed ultrasound AOI and multimode US/AO imaging, and then go on to describe the near-IR AOI system and present imaging results and a description of the new pressure contrast imaging approach. The experimental setup is given in Figure 2. It combines the PRC-based optical detection system with a commercially available, PC-based, diagnostic ultrasound scanner (Analogic Corp., AN2300). An 80 mW frequency-doubled Nd:YAG laser source is sent to a variable beam splitter where it is split into signal and reference beams. The reference beam is directed around the test tank and sent to the PRC-based interferometer. The signal beam is sent through a 10x beam expander along the Y-axis to the submerged tissue-mimicking phantom. Light scattered from the phantom is collected by a lens and directed into the



**Figure 2. Experimental setup combining a PRC-based interferometer with the commercial pulsed ultrasound scanner.**

PRC, where it interferes with the reference beam. The PRC-interferometer employs a Bismuth Silicon Oxide (BSO) crystal with dimensions  $5 \times 5 \times 7 \text{ mm}^3$  (X, Z, Y). A 4 kHz high-voltage field ( $10^6 \text{ V/m}$ ) is applied to the crystal to enhance the two-wave mixing process. The signal beam and diffracted reference beam exiting the crystal are collected by an avalanche photodiode (APD) with a 10mm diameter active aperture. The signal from the APD is sent to the preamplifier (x10), low-pass filtered ( $<500 \text{ kHz}$ ), and digitized by the oscilloscope. Both single shot and time-averaged waveforms can be displayed directly on the scope or transferred to the ultrasound scanner via a general purpose interface bus (GPIB) interface.

A commercially-available ultrasound probe with 5 MHz center frequency and a 192-element linear array (model 8802, B&K Medical, Herlev, Denmark) is excited by the AN2300 and projects ultrasonic pulses along the Z-axis to generate both ultrasound and AO images in the ZX-plane. The diffusive tissue phantoms consist of a transparent polyacrylamide gel seeded with  $0.4\text{-}\mu\text{m}$  diameter polystyrene microspheres to obtain a reduced scattering coefficient  $\mu_s' \approx 10 \text{ cm}^{-1}$ . The phantom's dimensions are  $40 \times 40 \times 27 \text{ mm}^3$  (X,Z,Y). During the manufacturing process, targets ( $2 \times 2 \times 8 \text{ mm}^3$  or  $3 \times 3 \times 8 \text{ mm}^3$ , along directions X, Z and Y) were embedded in the phantoms using dedicated molds. The targets are made of polyacrylamide gel with India ink added to increase the optical absorption coefficient while minimally altering the acoustical properties. In short, this target possesses minimal acoustical contrast and significant optical contrast.

We now discuss how the ultrasound and AO images are constructed. To ultrasonically scan the XZ-plane, different groups of elements on the probe are successively activated and fired in concentric directions, with a fixed focal length (50 mm). This procedure yields a set of ultrasonic scan lines adjacent to each other. Along the direction of ultrasonic propagation, time is converted to space using an assumed sound speed ( $1.5 \text{ mm}/\mu\text{s}$  for our water-matched phantoms). To display grayscale images (B-mode images), the ultrasound scanner demodulates the received ultrasound echo train associated with a given scan line and converts the signal envelope function to grayscale. Because the envelope of an AO signal in the time-domain gives a measure of the photon distribution along the ultrasound path, AO images were built in the exact same manner, and superimposed on top of the B-mode images using a color-scale. As a consequence, B-mode and AO images were automatically co-registered. To generate the ultrasound images, short 5 MHz Gaussian pulses (about 1.5-cycles long) were used. A single ultrasonic shot can be used to build one "A line" and the 2-D B-mode image is constructed from 256 A lines, shifted laterally in space. However, the low SNR associated with AO sensing mandates longer duration pulses and time-averaging be used to pump the AO response. Four-cycle-long, 5 MHz sine bursts (corresponding to a spatial length of about 1.2 mm) were used to generate the AO signals. The spatial peak, temporal peak (SPTP) excursion of the sine bursts was typically 1 MPa peak negative and 6 MPa peak positive (measured in water). The pulse repetition frequency was about 3.3 kHz and each AO signal was coherently averaged 20,000 times, yielding a SNR of approximately 65:1.

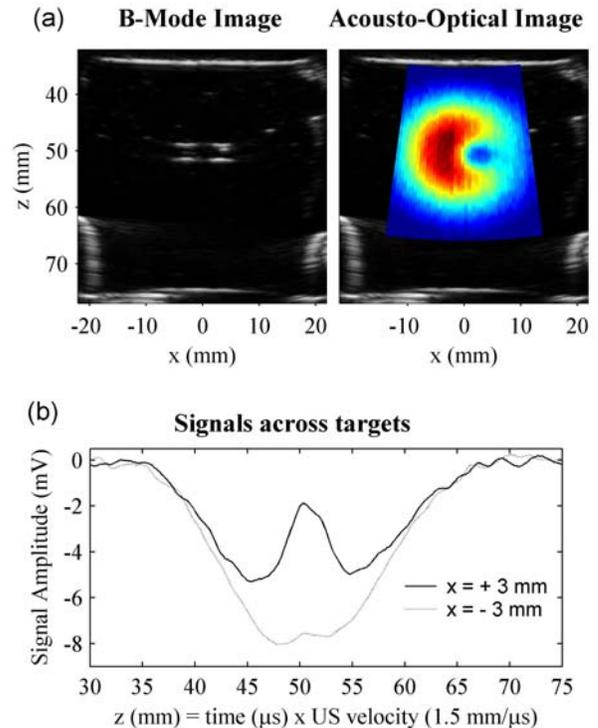
Figure 3a shows the B-Mode image (left) and superimposed AO image (right) obtained from a phantom made with two embedded targets ( $3 \times 3 \times 8 \text{ mm}^3$  each, separated by 3 mm), one with India ink and the other without. The two targets appear identical in the B-Mode image on the left. The parallel horizontal lines that demarcate the proximal and distal interfaces of the targets are due largely to imperfect bonding of the target and phantom materials during the manufacturing process and are not caused by an acoustic impedance mismatch between the target material and

the surrounding phantom material. On the other hand, the AO image on the right leaves no doubt as to the differing absorbing nature of each target.

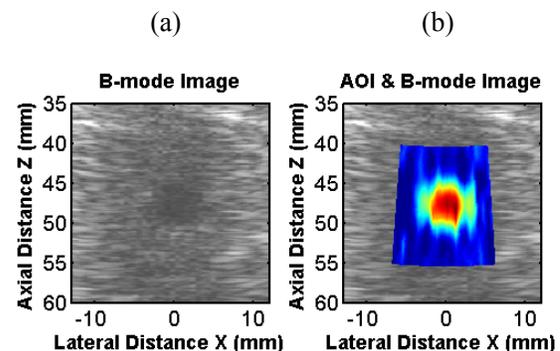
The AO image has a field of view given by the circular region seen in Figure 3a, typically 20 mm in diameter in these experiments. This distribution of detected modulated light is limited by the light distribution itself, but may also be limited by the aperture of the light-collecting system.

Note that the amplitude of the AO signal yields a measure of the strength of acousto-optic interaction at points along the acoustic propagation path. AO signals measured along scan lines traversing the two targets are shown in Figure 3b. The AO interaction is influenced by three factors: (1) the amplitude of the sound field, (2) the intensity of diffuse light, and (3) the optical characteristics of the medium. The acoustic pulse is a probe traveling down the acoustic axis, broadcasting information related to the acousto-optic interaction over that region of space for which the optical field possesses sufficient intensity to yield a detectable DC offset signal. For a focused ultrasound source, this region will likely be further restricted to the focal zone of the transducer. In the case of very short ultrasound pulses traversing optically uniform media, the duration of the AO signal simply defines the region of space where both the acoustical and optical fields have sufficient energy to produce a detectable signal. In the case of very long ultrasound pulses, the duration of the offset signal is essentially the duration of the acoustic pulse. The latter case is not particularly interesting from an imaging or tissue characterization perspective. The former allows for delineation of media variability along the ultrasound axis. For media with spatial optical variability, these changes will be manifested as changes in the AO signal, with respect to the background light distribution, as the ultrasound probe beam traverses these inhomogeneities.

Experiments on excised biological tissue were performed with a similar experimental setup to that shown in Figure 1, but with the 80 mW detection laser replaced with a 230 mW source. The sample is a slab of chicken breast squeezed between two transparent plastic plates, each of which has a thickness of 1.3 mm. A cut is made across the X-Z plane (roughly midway through the breast) and a small optical absorber is



**Figure 3.** (a) B-mode (left) and AO (right) images of two  $3 \times 3 \times 8 \text{ mm}^3$  ( $z, x, y$ ) targets separated by 3 mm along the  $x$  axis. The target at  $x = -3 \text{ mm}$  is identical to the background medium, whereas the target at  $x = +3 \text{ mm}$  is absorbing. (b) Typical time averaged AO signals as displayed on the oscilloscope for separate scan lines traversing across each target.

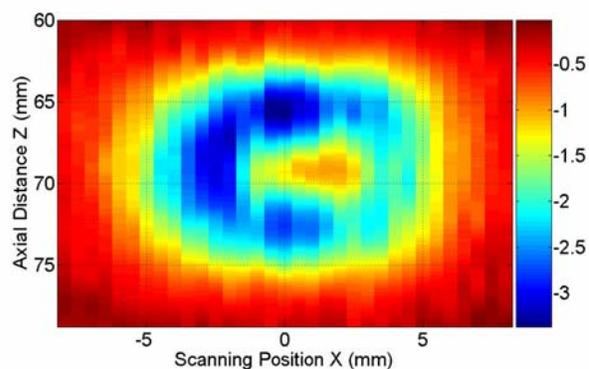


**Figure 4.** (a) X-Z plane B-mode and (b) AOI & B-mode images of a  $4 \text{ mm}^3$  ( $X, Y, Z$ ) optical absorber embedded at the center of a chicken breast with dimensions of  $4.5 \text{ cm} \times 2 \text{ cm} \times 4.5 \text{ cm}$  ( $X, Y, Z$ ).

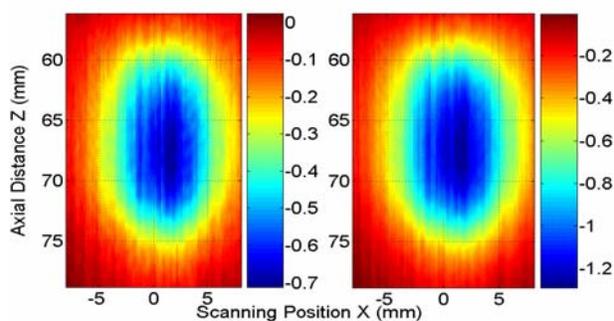
embedded roughly in the center. The embedded target consists of a cube (4 mm on a side) of polyacrylamide gel to which India ink has been added. Figure 4a shows a B-mode ultrasound image acquired in the X-Z plane at the center of the target. The acoustically homogeneous, optically absorbing target appears as a dark, uniform region in the middle of the sample; the image speckle surrounding the target is caused by acoustic scattering from the tissue microstructure. The AO image of the same target is given in Figure 4b, using a 3-cycle acoustical pulse at 5 MHz. The data in Figure 4b has been processed to remove the background (Gaussian) light distribution, which has been subtracted for display purposes. The ultrasound and AO images in Figure 4a and 4b are automatically co-registered.

Over the past year, we have completed the development of a new AOI system operating in the near-IR wavelength range. The basic experimental set-up is similar to that shown in Figure 1, with the 532nm laser replaced by a 400mW Nd:YAG laser operating at 1064nm and the BSO photorefractive crystal replaced by a GaAs crystal. The new system has two significant advantages over the previous system: the operating wavelength allows for substantially greater penetration in biological tissue (see Figure 1) and the response time of the PRC is greatly improved, thereby reducing the deleterious effects of speckle decorrelation noise. Figure 5 shows an AOI image obtained in a 2.5mm thick tissue phantom with a reduced scattering coefficient of  $4\text{cm}^{-1}$ , with a  $5\times 5\text{mm}$  inclusion embedded at the center of the phantom. The reduced AOI response (orange area at the center of the image) indicates the presence of the absorber. Over the past year, we have focused on quantifying the detection limits of the AOI system. The long-term goal is to use a combined theoretical and

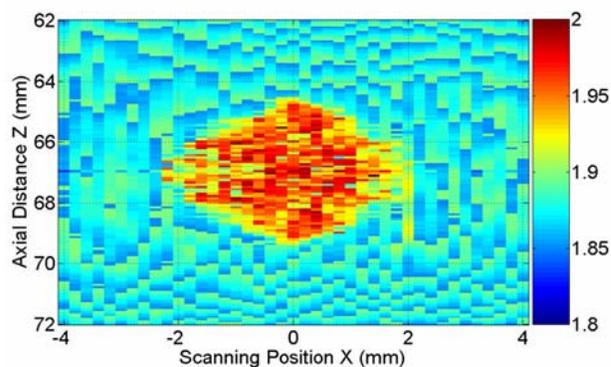
experimental approach to determine the maximum depth that an inhomogeneity with a given size and optical contrast can be detected. This, in turn, is a function of the experimental parameters and sensitivity or signal-to-noise ratio of the detection system. We have fully characterized the two-wave mixing gain of GaAs as a function of incident beam polarization, the angle between the signal and reference beams at the



**Figure 5. X-Z AO images of a  $5\text{ mm}^3$  (X,Y,Z) optical absorber embedded at the center of a 2.5cm thick phantom with a reduced scattering coefficient of  $4\text{cm}^{-1}$ . The AO response was detected using the near-IR PRC system.**



**Figure 6. AOI Images taken at acoustic pressure levels of 1.0 MPa (left) and 1.5 MPa (right). A scattering inclusion has been embedded at the center of the phantom. The images show the background light distribution, but no sign of the inclusion.**



**Figure 7. The pressure contrast image, obtained by dividing the two images in Figure 6, shows contrast which appears to be the scattering inclusion at the center of the phantom.**

crystal face, and applied external field. The light collection efficiency, or *étendue*, of the detection system was measured and optimized. The noise in the detection system was measured and found to be dominated by thermal noise in the preamplifier used to amplify the photodetector output. Two low-noise pre-amplifiers were compared in terms of thermal noise output and a down-selection made based on performance. Finally, the AO response was characterized as a function of acoustic pressure and acoustic tone-burst length. We have thus completed an extensive evaluation of system performance and optimized the AO response within the experimental constraints of our setup. Over the next year, we will evaluate the detectability limits of the system and evaluate the feasibility of using the system for *in vivo* applications.

In addition to completing and evaluating the near-IR AOI system, we have also obtained promising preliminary results in a new type of AOI based on the change in the AO response of a sample as a function of acoustic pressure. This imaging approach is referred to as pressure contrast AOI. Previously, we have shown that in the AOI detection of acoustic transients, the AOI signal ( $S$ ) that is observed depends on one parameter ( $\alpha$ ) that is related to the total amount of modulated light collected by the detection system. This depends upon the amount of light in the light-sound interaction region, the light collection system, and the location of the interaction region within the phantom. The AOI signal also depends on a second parameter ( $\beta$ ), which depends on the mean phase shift imparted on the light by the ultrasound. A general relation between these parameters is:  $S \approx \alpha(1 - J_0(\beta))$ . An important point is that  $\beta$  is a function of the phase shift induced by the ultrasound and should be insensitive to the amount of light collected, non-uniformities in the optical field within the sample, or the propagation path between the light-sound interaction region and the detection point.  $\beta$  should thus be a direct measure of the light-sound interaction strength.  $\alpha$ , on the other hand, should be independent of the acoustic pressure. By taking the ratio of the AOI response at two different sound pressure levels, it is possible to create a *pressure contrast image* that is dependent on  $\beta$  alone. While this work is in the early stages, there is some indication that pressure contrast imaging may have advantages over AOI images in the detection of some types of tissue inhomogeneities. Figure 6 shows two AOI images taken on a sample with a reduced scattering coefficient of  $4\text{cm}^{-1}$ ; one with an acoustic pressure of 1.0 MPa and the other with 1.5 MPa. The phantom contains a  $5\times 5\times 8\text{mm}$  inclusion with a reduced scattering coefficient of  $18\text{cm}^{-1}$  and no absorption contrast. The images in Figure 6 show the background light distribution, but the position of the inclusion is not apparent. Figure 7 shows the pressure contrast image; obtained by dividing the two images in Figure 6. A distinct feature is observed at the center of the image. It is believed that this is the scattering inclusion. Our preliminary results in pressure contrast imaging have been promising, and we are currently working to better understand the contrast mechanism and to directly compare conventional AOI and pressure contrast imaging in a wide range of scattering and absorbing phantoms.

### C. Major Accomplishments of the Dual-Wave Imaging Project

- We have demonstrated multimode 3-D AOI/US imaging in *ex vivo* biological tissue.
- We have developed a PRC-based detection scheme that allows us to sense AOI signals excited by pulsed ultrasound with unprecedented sensitivity.
- We have developed a model for the detection of ultrasound-induced phase changes using the PRC-based detection system.

- We have studied the evolution of the AOI signal with increasing optical scattering and have found that the trends agree well, in terms of the modulated and DC offset component of the signal, with theory.
- We have developed a recipe for tissue phantoms with optical and acoustic properties mimicking that of tissue.
- We have developed an acoustical model that predicted acoustic particle displacements and velocities induced by the ultrasound beam. The model, an FDTD implementation, can handle nonlinear waves propagating through media with arbitrary variability.
- We have developed a Monte Carlo simulation of the interaction of near-infrared light and ultrasound in dense turbid media.
- We have demonstrated 1-D and 2-D AOI of optical inhomogeneities with a resolution on the order of the ultrasound focus (lateral) and pulse width (axial).
- We have integrated the AOI detector with the Analogic Ultrasound Engine to achieve multi-mode imaging capability.
- We have developed a Near-IR AOI system with a response time sufficient to overcome speckle decorrelation in living tissue.
- We have obtained 2-D AOI images of inclusions exhibiting absorption contrast using the Near-IR AOI system.
- We have fully characterized the Near-IR system and optimized the sensitivity of the detection approach.
- We have developed a new imaging technique called pressure contrast AOI. Preliminary results are promising.

### **III. Gordon-CenSSIS Strategic Goals and Legacy**

The Dual-Wave Imaging Project is unique on several levels. First, it is a mixture of acoustic and optical technologies applied to difficult problems in biomedical imaging. This means that the descriptors being imaged are based on a complex combination of acoustical and optical contrast parameters. This could provide unique opportunities for imaging tissue structure and distinguishing tissue types. This joining of acoustics and optics is well aligned with the Center's goal for developing new sensing modalities that cut across different disciplines.

Another important facet of the project structure is that the AOI system is now capable of mapping the AOI response in three dimensions, and inversion methods will need to be applied to obtain quantitative property information from the measured signals. This is an ideal opportunity for establishing a collaborative effort across institutions and across thrusts. A third facet of the work that is particularly Center-relevant will become evident in the next year as we move towards *in vivo* tissue imaging. At that point, the project will dovetail with the system-level S3 project on 3-D multi-modal breast cancer imaging.

Finally, it is important to stress that the AOI project effort has led to a substantial enhancement in the state of the art (pulsed AOI) that likely would not have been possible had we not combined the efforts of opticians and acousticians in a collaborative effort. This efficacy of the Gordon-CenSSIS model of cross-disciplinary collaborative research has never been more evident. Although the future of AOI in clinical radiology is yet to be determined, the success of AOI

(particularly given the modest funds invested) serves as an excellent example of the power of the Gordon-CenSSIS concept for achieving innovative wave-based solutions to difficult problems in sensing and imaging.

#### **IV. Future Plans for AOI**

We have completed the development of a second-generation AOI system that uses a high-power laser in the near-IR wavelength range. This system allows for a substantial improvement in light throughput and thus allows for greater imaging depths and shorter acquisition times. We have optimized the system in terms of light collection and two-wave mixing gain, and worked to identify and remove sources of electronic noise in the system. Our next goal is to quantify the SNR for breast cancer applications. The critical questions that must be addressed in the coming year are: the size of the inhomogeneity (of a given optical contrast) that we can detect at a given depth, the required measurement time, and whether this can be improved or there is a fundamental physical limit. In addition, we plan to continue our study of pressure contrast imaging. The preliminary results have been promising and this approach may allow us to back out quantitative tissue optical parameters. Guided by these results, we hope to have a system suitable for *in vivo* testing by the end of 2008 and to begin *in vivo* testing in 2009-2010. This will be closely linked to the S-level project on biomedical imaging of breast tumors.

Specific research goals are:

- Continue to explore pressure contrast imaging and better understand the pros and cons of using this technique as compared to conventional AOI. (2008-2009)
- Understand the sensitivity limitations of AOI and quantify the SNR for breast cancer applications (2008-2009)
- Further model the details of the AOI interaction. Parameters of interest include the nature of the scattering particles (mainly size and shape) and the sensitivity of the AOI signal to optical scattering and mechanical contrast. (2008-2009)
- Development of an inversion algorithm to obtain quantitative optical property distributions from the measured 3-D AOI response. (2008-2010)

In addition to the work detailed above, we hope to initiate collaboration with the ultrasound imaging and therapy groups at the Institute for Cancer Research (ICR) at the Royal Marsden Hospital, Sutton UK. Gail ter Haar is a world authority in image-guided focused-ultrasound surgery, and Jeffrey Bamber is a leading researcher of novel methods of ultrasound imaging applied to tumor detection and characterization. Such collaborations should prove fruitful as the technology moves towards *in-vivo* applications.

#### **V. Broader Impact**

##### **A. Research**

The primary significance of this research is the development of a multimode imaging system, producing co-registered conventional ultrasound and acousto-optic images. The target application for this imaging technique is breast cancer, a disease that kills approximately 40,000 women, in the U.S. alone, each year [19]. The combination of mechanical (US) and optical (AOI) imaging has tremendous potential for increasing sensitivity and specificity over existing cancer screening techniques. Pulsed ultrasound is a well-established clinical imaging technique, and is now used extensively in the diagnosis of breast cancer. Ultrasound is used routinely, for

example, for the differentiation of cysts from solid lesions and for the characterization of masses that may be obscured on a conventional mammogram. Ultrasound examination alone, however, has thus far not been deemed suitable for breast cancer screening, and it serves mainly as a secondary, diagnostic test after routine mammography [20]. This is due in large part to possible limitations in specificity resulting from similarities in the mechanical properties of benign and malignant lesions. The motivation behind the development of a multi-mode US/AO imaging system is to supplement the well-established modality (US) with additional information. Finally, AOI imaging technology is expected to have broader impact in the area of biomedical imaging, with additional applications including, for example, image-guided therapy and the evaluation, and monitoring of the thermal lesions generated by high-intensity focused ultrasound (HIFU).

## **B. Education**

This project provides an excellent opportunity for undergraduate and graduate students to receive truly interdisciplinary training in acoustics, optics, and biomedical imaging. In addition, the Gordon-CenSSIS partnership with Alabama A&M University (AAMU), developed through the AOI research effort, has provided research opportunities for AAMU students and spawned collaboration with two of the leading experts in the physics of photorefractive crystals: Nickolai and Tatiana Kukhtarev. The AAMU program sponsored five students from AAMU to work in research laboratories at Boston University each summer. In Year 7, three of these students, Gregory Stargell, Daryl Williams, and Eugene Harris, worked on AOI-related projects. Gregory worked on a project to evaluate a new phase demodulation technique for AOI based on the polarization self-modulation effect, Daryl worked on determining the physical properties of a PRCs through two-wave mixing experiments, and Eugene worked on developing a laser-based ultrasonic system for tissue evaluation. The Kukhtarevs have been working to develop more sensitive detection approaches for possible application in AOI, and operating in the so-called “therapeutic window” near-IR wavelength range. Finally, a BU undergraduate researcher, Howard Simpson, also worked in the AOI research lab on a new optoacoustic technique for tissue characterization during the summer of Year 7.

## **VI. Technology Transfer**

A patent is pending on the use of a PRC for the detection of acousto-optic signals in scattering media. This technology could have a broad impact in the detection of tissue abnormalities and diseases states, and can be readily combined with diagnostic ultrasound systems to provide enhanced diagnostic capabilities. Companies that could potentially benefit from this technology include: Analogic Corp., InSightec, China Medical Technologies, and Phillips Medical Systems.

**VIII. References Cited**

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## **IX. Documentation**

### **A. Technology Transfer**

1. DiMarzio, C.A., Roy, R.A., Murray, T.W., Blonigen, F., Nieva, A., Sui, L. and Maguluri, G., "Enhanced Detection of Acousto-photonic Emissions in Optically Turbid Media Using A Photorefractive Crystal-Based Detection System," PCT WO 2005/069997 (Patent Pending).

### **B. Publications Acknowledging NSF Support**

1. Murray, T.W. and Roy, R.A., "Illuminating sound: Imaging tissue optical properties with ultrasound," *Acoustics Today*, vol. 3, no. 3, pp. 17-23, Jul. 2007.
2. Murray, T.W., Roy, R.A., and Holt, R.G., "Laser-Ultrasonic Cavitation," in McGraw-Hill Yearbook of Science and Technology 2008. McGraw-Hill, 2007.
3. R.A. Roy, Wu, T., Farny, C.H., Murray, T.W., and Holt, R.G., "Nucleating Inertial Cavitation 'On Demand' using Laser-Illuminated Gold Nanoparticles, with applications to HIFU Therapy", *IEEE International Ultrasonics Symposium*, abstract 2A-5, New York, Oct. 2007.
4. Lai, P., Roy, R.A., and Murray, T.W., "Acousto-optic imaging in the near infrared using the photorefractive effect," *IEEE International Ultrasonics Symposium*, abstract 9E-4, New York, Oct. 2007.

### **C. List of Relevant RICC/Site Visit 2007 Posters**

1. Lai, P., Murray, T.W., and Roy, R.A., "Acousto-optic imaging in the near infrared using the photorefractive effect," poster presented at the *Gordon-CenSSIS Research and Industrial Collaboration Conference*, Boston MA, Oct. 2007.
2. Lai, P., Murray, T.W., and Roy, R.A., "Acousto-optic imaging in the near infrared: Optimization and quantitative characterization of the system," poster presented at the *Gordon-CenSSIS NSF Site Visit*, Boston MA, April, 2007.
3. Cleveland, R.O., Roy, R.A., Murray, T.W. and Barbone, P., "MedBED A: a testbed supporting research in biomedical ultrasonics and ultrasound imaging," poster presented at the *Gordon-CenSSIS NSF Site Visit*, Boston MA, April, 2007.
4. Lai, P., Roy, R.A., and Murray, T.W., "Acousto-optic imaging in the near infrared: Optimization and quantitative characterization of the system," poster presentation for *Boston University Science Day*, Boston MA, Apr. 2007.
5. Cleveland, R., Murray, T.W., Barbone, P., and Roy, R. A., "'MedBED-A: A TestBED Supporting Research in Biomedical Ultrasonics and Ultrasound Imaging'", poster

presented at the *Gordon-CenSSIS Research and Industrial Collaboration Conference*, Boston MA, Oct. 2007.

**D. Seminars, Workshops and Short Courses**

1. Roy, R.A., “Shedding Light on Sound: Multi-mode Biomedical Imaging Using Acousto-optic Sensing and B-Mode Ultrasound” *Medical Physics Colloquium*, Institute for Cancer Research, Sutton UK, Jan. 2007.
2. Roy. R.A., “Augmenting Biomedical Engineering and Therapy Using Light and Sound,” *Colloquium of the Departments of Mechanical Engineering and Medical Physics & Bioengineering*, University College London, London UK, January 2007.
3. Murray, T.W., "Laser based acoustic techniques for sensing and imaging: photoacoustic microscopy and acousto-optic imaging," *National Institute of Standards and Technology (NIST)*, Boulder, CO, April, 2007.