ABSTRACTS

1. Cardiac Imaging/ARFI

1.1 **Assessment of cardiac dysfunction in overweight adolescents using echocardiographic-based 'whole heart' global longitudinal strain analyses**, Mark R. Holland, Bernadette Vitola, Samuel Klein, Timothy J. Sekarski, James G. Miller and Gautam K. Singh, *Washington University in St. Louis, St. Louis, MO, james.g.miller@wustl.edu.*

Background: The prevalence of pediatric obesity has reached an alarming level in the U.S. In adults, obesity has been associated with cardiomyopathy due to cardiac steatosis from intramyocellular lipid accumulation, resulting in a higher incidence of cardiac dysfunction and mortality. It is not known if overweight adolescents exhibit an early onset of cardiac dysfunction.

Objective: The goal of this study was to assess the presence of early onset cardiac dysfunction in overweight adolescents through echocardiographic-based cardiac strain measurements.

Methods: Echocardiographic images of 37 adolescent subjects (age range 13 to 18 years; 20 male, 17 female) were acquired using a GE Vivid 7 echocardiographic imaging system. Measurements of global longitudinal strains and early-diastolic strain rates were obtained using the 2D speckle tracking capabilities of the GE EchoPAC image analysis system. For each subject, global peak longitudinal strain and strain rate measurements were obtained for the apical long-axis, four-chamber and two-chamber echocardiographic views and averaged together to give 'whole-heart' peak longitudinal strain and strain rate values, respectively. The subjects were segregated into two groups: an Overweight (Obese) Group (N = 24; BMI = 35.4 ± 5.0 kg/m^2; 15.0 ± 1.6 years; mean ± SD) and a Normal Weight (Lean) Group (N = 15; BMI = 19.8 ± 1.6 kg/m^2; 15.2 ± 1.3 years). The 'whole-heart' peak longitudinal strain and strain rate values for each group were compared.

Results: Results demonstrate a value of the mean magnitude of 'whole-heart' peak longitudinal strain for the Normal Weight Group (18.2 ± 2.7%; mean ± SD) that is significantly larger than the mean value for the Overweight Group (15.8 ± 3.0%; p = 0.02). The mean early-diastolic "whole-heart" peak longitudinal strain rate for the Normal Weight Group (1.59 ± 0.34%/sec) was significantly larger than that measured for the Overweight Group (1.30 ± 0.27%/sec; p = 0.01). The Overweight Group was further segregated into two subgroups: an Overweight Group with normal hepatic fat content and an Overweight Group with elevated hepatic fat content. Results demonstrated monotonically increasing values of the mean 'whole-heart' peak longitudinal strains and strain rates for the Overweight Group with elevated hepatic fat content, Overweight Group with normal hepatic fat content and Normal Weight Group, respectively.

Conclusion: Results of this study demonstrate significant differences in both systolic and diastolic cardiac function in overweight adolescents relative to that for adolescents of normal weight. These observations suggest measurements of echocardiographically-based 'whole-heart' peak longitudinal strain and strain rate may provide a noninvasive approach for assessing early subclinical alterations of cardiac function associated with obesity in adolescents.

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1.2. **A Bayesian parameter estimation approach for enhancement of the analysis of myocardial strain and strain rate data,** Christian C. Anderson, Christopher W. Lloyd, G.

Larry Bretthorst, Ravi Rasalingam, Gautam K. Singh, Mark R. Holland and James G. Miller, *Washington University in St. Louis, St. Louis, MO, james.g.miller@wustl.edu*.

Background: Global and segmental strain and strain rate measurements derived from echocardiographic data are increasingly used as indicators of impaired myocardial function. However, strain and (especially) strain rate data can often suffer from significant physiologically-meaningless variations that complicate the determination of parameters typically used to characterize the data. In practice, to obtain a full analysis of the data for each patient, physicians must manually examine strain and strain rate data from myocardial segments in the radial, circumferential and longitudinal directions for each of six different echocardiographic views. The time required to perform a full analysis is prohibitive for routine clinical implementation. Furthermore, the noisy variations complicate efforts to make an objective determination of key features in the data.

Objective: The goal of this study was to model strain and strain rate data with smoothly-varying functions to make data analysis less time-intensive and less susceptible to the effects of physiologically-meaningless variations.

Methods: Strain data were modeled using a piecewise model that incorporates cosinusoidal and linear segments. This model requires nine adjustable model parameters to characterize the strain data. To estimate these parameters, the strain data were used as input to a program that implements a Bayesian parameter estimation calculation. Marginal posterior probability distributions for each of the parameters in the model were obtained using Markov chain Monte Carlo with simulated annealing. The model function that maximized the joint posterior probability for the parameters was differentiated to obtain the strain rate for the input data.

Results: The model functions constructed using the Bayesian parameter estimation approach are in good agreement with the acquired strain data. The strain rates derived from the models for the strain data provide smoothly-varying curves that are easily interpreted and compare favorably to results anticipated based on physiologic considerations.

Conclusion: A model analysis of myocardial strain and strain rate data appears to show promise as a way to further automate and enhance current methods of analysis. Bayesian probability theory is a practical method for carrying out these model analyses because it not only determines parameter estimates for the model but is also capable of providing probability distributions for each model parameter, allowing measures of uncertainty in the model parameters to be quantified in a straightforward manner.

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1.3 **Backscatter from tissue-mimicking phantoms exhibiting a range of lipid concentrations comparable to that observed in the hearts of obese subjects**, Benjamin L. Johnson, Joseph J. Hoffman, Jean E. Schaffer, Linda R. Peterson, Gautam K. Singh, Mark R. Holland and James G. Miller, *Washington University in St. Louis, St. Louis, MO, james.g.miller @wustl.edu.*

Background: Obese individuals are at elevated risk for cardiac dysfunction. Studies have demonstrated cardiac steatosis from intramyocellular lipid accumulation in obese subjects and suggest that excess lipid accumulation in the heart may contribute to the pathogenesis of heart failure. Development of echocardiographic-based methods to assess the level of myocardial lipid content may provide a useful tool for physicians to utilize in the management of these patients.

Objective: The goal of this study was to develop a series of myocardial tissue-mimicking phantoms exhibiting a range of oil concentrations and distributions comparable to the lipid levels reported in the hearts of obese subjects and determine if these levels can be differentiated using ultrasonic backscatter measurements over clinically-relevant frequency ranges.

Methods: A series of gelatin-based ultrasonic tissue-mimicking phantoms was constructed containing 0% ($n = 8$), 0.5% ($n = 5$), 1.0% ($n = 1$) and 4.0% ($n = 6$) suspensions of olive oil by volume. Special care was taken to ensure that the size distribution of oil droplets within the phantoms was consistent with the size of myocardial lipid droplets reported in the literature. Ultrasonic measurements were performed at a temperature of 22.6 ± 0.3°C on the phantoms using a 5 MHz focused transducer over a bandwidth ranging from 3 to 9 MHz. The speed of sound, frequency dependence of the attenuation coefficient, apparent integrated backscatter and the level and frequency dependence of the backscatter coefficient were determined for each phantom.

Results: Measurements of apparent integrated backscatter over the frequency range from 3 to 5 MHz yielded values of –62.8 ± 0.5 dB (mean ± standard deviation), –59.6 ± 1.3 dB, -57.6 dB, and –55.9 ± 1.5 dB for the 0% ($n = 8$), 0.5% ($n = 5$), 1.0% ($n = 1$), and 4.0% ($n = 6$) oil phantoms, respectively. The fully reduced backscatter coefficient plotted as a function of frequency exhibited a frequency dependence, f^n, of $n = 3.5 \pm 0.1$ for all the phantoms irrespective of the lipid concentration. The values of the backscatter coefficient increased monotonically and systematically with lipid concentration over the full range studied.

Conclusion: Results of this study suggest that the increased lipid levels observed in the hearts of obese subjects may produce corresponding increases in measured ultrasonic backscatter levels over clinically-relevant frequency ranges. Hence, development of echocardiographic-based methods to assess myocardial lipid content and its change with therapeutic intervention may be feasible.

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1.4 **Rapid acquisition of cardiovascular elasticity and blood-flow information using a combined ARFI/ Doppler imaging system**, D.M. Dumont,[1] J. J. Dahl,[1] S. J. Hsu[1] and G.E. Trahey,[1, 2] *[1]Departments of [1]Biomedical Engineering and [2]Radiology, Duke University, Durham, NC, dmd@duke.edu.*

It is well known that mechanical changes often accompany pathological changes in tissue, especially in cardiovascular tissue. In our previous work, we have shown that acoustic radiation force impulse (ARFI) imaging can be used to visualize the mechanical properties of healthy and diseased vascular tissue *in vivo*[(1, 2)] and to evaluate myocardial function during the cardiac cycle.[(3)] However, changes in hemodynamics can precede or exacerbate pathological processes. For example, hemodynamics can play an important role in both atherogenesis and plaque remodeling.[(4)] Given that blood flow is routinely assessed clinically (for example, to assess degree of stenosis and to help delineate hypoechoic plaque), it could be useful to provide a spatially and temporally co-registered depiction of cardiovascular elasticity with blood flow.

In this work, we describe and evaluate new beam sequencing techniques that allow for the simultaneous acquisition of ARFI data with directional and power Doppler flow information. The proposed system uses a parallel-transmit, parallel-receive approach combined with interleaved Doppler pulses to reduce acquisition time without sacrificing spatial sampling or reducing the field-of-view. As cardiovascular ARFI imaging is typically performed with the transducer oriented perpendicular to the region-of-interest, the proposed system uses steered Doppler beams to improve flow performance. We discuss tradeoffs between acoustic exposure, frame rate and ARFI and Doppler imaging quality. Results are presented for phantom and clinical data. Our results suggest that significant improvements in frame rates are possible with only a marginal reduction in ARFI and Doppler imaging quality.

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1.5 **Elasticity measurements through the cardiac cycle using acoustic radiation force impulse imaging (ARFI) on an intracardiac echocardiography (ICE) transducer**, Peter J. Hollender, Stephen J. Hsu, Richard R. Bouchard, David P. Bradway, Patrick D. Wolf and Gregg E. Trahey, *Duke University, Durham, NC, peter.hollender@duke.edu.*

Acoustic Radiation Force Impulse (ARFI) imaging is a viable and noninvasive way to image tissue elastic properties. On- and off-axis ARFI imaging techniques (M-mode ARFI and Shear Wave Elasticity Imaging (SWEI), respectively) are used on an intracardiac echocardiography (ICE) catheter transducer to characterize the stiffness changes of cardiac tissue during systole and diastole. The temporal and spatial stability of these measurements throughout the cardiac cycle is assessed through serial data acquisitions and interrogations of independent tissue regions, respectively. Matched M-mode and SWEI results are compared for performance and repeatability. Cyclic stiffening and relaxation of the ventricular septum is shown through these metrics, utilizing *in vivo* canine studies. Feasibility of clinical applications and acoustic safety issues are discussed.

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1.6 **Acoustic radiation force-driven assessment of myocardial elasticity**, Richard Bouchard,[1] Stephen Hsu,[1] Mark Palmeri,[1] Ned Rouze[1] and Gregg Trahey,[1,2] [1]*Department of Biomedical Engineering, Duke University, Durham, NC and* [2]*Department of Radiology, Duke University Medical Center, Durham, NC, rrb@duke.edu.*

A noninvasive method of characterizing myocardial stiffness could have significant implications in diagnosing cardiac disease. Acoustic radiation force (ARF)-driven techniques have demonstrated their ability to discern elastic properties of soft tissue. For the purpose of myocardial elasticity imaging, a novel ARF-based imaging technique, the displacement ratio rate (DRR) method, was developed. The basis and performance of this technique was demonstrated through numerical and phantom imaging results. This new method requires a relatively small temporal (< 1 ms) and spatial (tenths of mm^2) sampling window and appears to be independent of ARF excitation intensity. The DRR method was implemented in an *in vivo* canine study, during which time data were acquired through the full cardiac cycle by imaging directly on the exposed epicardium. These data were then compared to results obtained by acoustic radiation force impulse (ARFI) imaging and shear wave elasticity imaging (SWEI), with the latter being used as the gold standard. Through the cardiac cycle, SWEI results predict a range of shear wave velocities from 0.76 to 2.09 m/s, with the highest velocities observed during systole and lowest observed during diastole. If a basic shear wave elasticity model is assumed, such a velocity result would suggest a period of increased stiffness during systole (when compared to diastole). Despite drawbacks of each (DRR method – sensitivity to noise; ARFI imaging – variable displacement ratio and dependence on ARF excitation intensity), the DRR method and ARFI imaging results, in general, predicted a similar cyclic stiffness variation to that offered by SWEI. Given the reduced temporal/spatial sampling requirements of either, both show promise in future myocardial elasticity investigations.

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1.7 ***In vivo* and *in vitro* investigation of shear wave velocity anisotropy in myocardial tissue**, Richard Bouchard,[1] Benjamin Maimon,[1] Daniel Haughton,[1] Yuan Long,[1] Stephen Hsu[1] and Gregg Trahey,[1,2] *[1]Department of Biomedical Engineering, Duke University, Durham, NC and [2]Department of Radiology, Duke University Medical Center, Durham, NC, rrb@duke.edu.*

Previous investigations of shear wave propagation in skeletal muscle have noted a wave velocity anisotropy through the tissue due to the transverse isotropy of its fibers.(1) Given myocardial tissue's inherent structural anisotropy, the existence of a similar shear wave velocity anisotropy is possible. In an effort to investigate such a phenomenon, shear waves were generated and tracked, with acoustic radiation force-based techniques, at different angles through the mid-myocardium of the left ventricular free wall (LVFW) of a canine heart *in vitro* and *in vivo*. For the *in vitro* study, the LVFW of freshly-excised canine hearts was placed on a rotating stage in a water tank. Shear wave speed acquisitions were then obtained with the ultrasound transducer face kept fixed and approximately parallel to the specimen surface; the sample was then rotated in 15° increments (through 180°) between successive acquisitions. For the *in vivo* study, the ultrasound transducer was secured directly on the exposed epicardium with the aid of a rotating vacuum-coupling device; the ultrasound transducer was then rotated in 45° increments (through 180°) between successive acquisitions (which were obtained during diastole). In both *in vitro* and *in vivo* data sets, as much as a two-fold increase in shear wave velocity was observed through 180° of sample (*in vitro*) or transducer (*in vivo*) rotation, with velocities ranging from approximately 0.8 to 1.6 m/s. The existence of such anisotropy suggests that shear wave velocity through the myocardium is not solely based on material parameters (e.g., stiffness) but is also dependent on sampling orientation.

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1.8 **Acoustic radiation force impulse imaging of acute myocardial ischemia and infarct**, David P. Bradway, Stephen J. Hsu, Patrick D. Wolf and Gregg E. Trahey, *Duke University, Durham, NC, david.bradway@duke.edu*

Acoustic radiation force impulse (ARFI) imaging has been used to characterize acute myocardial ischemia and infarct in canines. Three-line M-mode ARFI images of the LV myocardium were acquired epicardially before and during occlusion of the left anterior descending coronary artery of two canines. The M-mode lines spanned ischemic and intact regions of the myocardium. Compared with the pre-occlusion state and intact peripheral regions, ARFI-induced displacement and recovery curves along the central M-mode line exhibited progressive reductions in amplitude of cyclic displacements and the rate of change of those displacements. We discuss the clinical relevance of ARFI imaging of myocardial ischemia and infarct.

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1.9 **Integration of intracardiac acoustic radiation force impulse imaging with electro-anatomic mapping for *in vivo* visualization of radiofrequency ablation lesions**, Patrick D. Wolf, Tristram D. Bahnson, Stephanie A. Eyerly, Stephen J. Hsu, David P. Bradway and Gregg E. Trahey *Department of Biomedical Engineering, Duke University and Duke University Medical Center, Durham, NC, sae9@duke.edu*.

Radiofrequency ablation (RFA) lesion assessment is a critical missing component to interventional arrhythmia therapy. Acoustic radiation force impulse (ARFI) imaging can visualize RFA lesions by quantifying myocardial elasticity with local radiation-force induced tissue displacements. Locating lesions with a 2D image plane in a beating heart is difficult. Intracardiac ultrasound (ICE) ARFI imaging was integrated with electro-anatomic (EA) mapping to facilitate the location and assessment of RFA lesions *in vivo*.

An activation map of a canine right atrium was constructed using EA catheter-point mapping (Carto, CartoSound; Biosense Webster; Diamond Bar, CA). Endocardial atrial and ventricular target sites were tagged and then rf ablated. A modified S2000 Siemens Acuson scanner and Sound-Star ICE catheter (Biosense Webster) were used to obtain B-mode and ARFI images of target sites before and after RFA treatment. EA navigation was used to guide the ICE imaging plane to transect ablation sites. Pathologic examination confirmed RFA lesion presence.

EA guidance facilitated rapid intracardiac ARFI imaging of *in vivo* endocardial rf ablations. ARFI imaging correctly identified the presence or absence of RFA lesions in both atrial and ventricular myocardium. ARFI images also provided an assessment of lesion line discontinuities and myocardial transmurality. This integrated system will be useful for assessment of lesion transmurality or contiguity during focal or linear ablation to treat atrial and ventricular arrhythmias in humans.

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1.10 **Direct visualization of canine cardiac-ablation lesions — comparisons between ARFI, strain and strain-rate imaging**, Brett Byram,[1] Stephen Hsu,[1] Patrick Wolf[1] and Gregg E. Trahey,[1, 2] *Departments of [1]Biomedical Engineering and [2]Radiology, Duke University, Durham, NC, bcb16@duke.edu.*

Radiofrequency ablations are a common procedure for a number of electrophysiological complications in the heart. One of the challenges of these ablation procedures is that it is difficult to determine the actual size and location of the ablated region. This challenge is particularly problematic when trying to determine whether an aberrant region of electrical signal generation has been adequately isolated or destroyed. ARFI imaging has been previously validated against histology as a method for direct *in vivo* visualization of ablated tissue.

ARFI contrast of ablated tissue derives from the differences in stiffness between the actively-contracting tissue and 'passive' ablated tissue. The contrast between the two regions is dynamic and is a function of the time point within the cardiac cycle. Because the contrast of the ablation lesion derives from the active versus passive tissue, it is hypothesized that visualization of the lesion would also be possible with strain and strain-rate imaging. To this end, data were acquired that featured matched ARFI and 160 Hz B-Mode data sets of ablation lesions on canine right-ventricles ablation. Strain and strain-rate images were made using the B-Mode data sets and compared to the ARFI data. In this case, ARFI makes a reasonable gold-standard since it has been shown to correlate very well with histology.

The ARFI image of the ablation lesion had peak contrast near 0.75 and a peak contrast-to-noise ratio (CNR) of 3.6. Strain imaging produced a peak contrast of 1.6 and a peak CNR of 6. Strain rate contrast peaked near end-diastole and end-systole with contrasts around 3.5 but was consistently between 0.5 and 0.75. Strain-rate CNR peaked at 5.5 just after the onset of systole but had several other peaks that were all around 4. The initial validation of strain and strain-rate imaging to distinguish between healthy and ablated myocardium indicates that additional research is warranted.

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1.11 **Extrapolative and interpolative methods for modeling short-time cardiac motion estimated from ultrasonic data, with applications to cardiac ARFI**, Brett Byram,[1] Doug Giannantonio,[1] Douglas Dumont[1] and Gregg E. Trahey,[1, 2] *Departments of [1]Biomedical Engineering and [2]Radiology, Duke University, Durham, NC, bcb16@duke.edu.*

There are no medical imaging modalities that practically can sample cardiac motion at rates as high as those possible with medical ultrasound. Because such high temporal sampling rates are so easily realized with ultrasound, ultrasonic data sets can contain information and motion that is not often considered by researchers of other modalities, or even ultrasound researchers, since it is often the case that the temporal sampling of a single location is decreased in order to expand the field of view. The highest temporal sampling rates in cardiac imaging sequences occur with applications such as M-Mode, tissue Doppler imaging, SWEI and ARFI imaging.

In order to explore cardiac motion at high temporal sampling rates, M-Mode data of canine hearts were acquired both transthoracically and with direct fixed contact with the epicardial layer of the heart in an open-chest preparation. Baseband data were acquired with a line-to-line sampling rate of 10 kHz. The data were used to test several predictive models of cardiac motion. The effect of the amount and type of information supplied to the models and the subsequent impact on prediction accuracy were also tested.

The results of the study showed that the predictive accuracy of a given model was highly dependent on the proximity of the data to the location of motion prediction. To this end, extrapolative models proved to be extremely effective at producing accurate estimates of the motion within the first millisecond after the last motion estimate input into the model. Additionally, with extrapolative models there was not a significant improvement in predictive ability if more than 0.3-0.5 ms of motion data was input into the model. The best extrapolative models had prediction errors — as a mean absolute difference (MAD) — on the order of 1 μm or less for predictions within the first 0.5 ms after the last motion estimate.

To predict motion at time points more than 1 ms away from the last motion sample, interpolative models performed better. Interpolation models were those that had motion estimates located temporally both before and after the location where motion was to be predicted. For interpolation models, performance was improved by using more data points near the point of prediction rather than using the same number of motion estimates on either side of the point to be predicted. The best interpolation models had prediction errors — as a MAD — on the order of 1-2 μm up to 2 ms away from the closest motion data. The total displacement for some of the longest time spans tested for the interpolation models were on the order of 100 μm.

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2. Tissue Parameters/Contrast

2.1 **Ultrasonic backscatter coefficient quantitative estimates from chinese hamster ovary cell pellet biophantoms**, Aiguo Han,[1] Maxime Teisseire,[1, 2] Rami Abuhabsah,[1] James P. Blue Jr.,[1] Sandhya Sarwate[1] and William D. O'Brien, Jr.,[1] *[1]Bioacoustics Research Laboratory, Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, 405 N. Mathews, Urbana, IL 61801 and [2]École Centrale de Lille, Cité Scientifique, BP 48, 59650 Villeneuve d'Ascq, France, czaramahan51@illinois.edu.*

Objective: Previous work has demonstrated that backscatter coefficient (BSC) measurements made from physical phantoms show good agreement with the Faran or Anderson the-

oretical models. This work focused on BSC measurements made from biophantoms containing live Chinese Hamster Ovary (CHO) cells. The measured BSC was compared to a new concentric sphere scattering model as it is geometrically similar to cells.

Methodology: Live CHO cells (10-15 μm diameter) of known concentration are placed in a mixture of bovine plasma and thrombin to form a clot, what we call a cell pellet. BCS measurements of the cell pellet biophantoms were made with 40MHz and 65MHz focused transducers (overall bandwidth: 20-75 MHz). Cell pellets were then histologically processed (H&E) for viability assessment.

Results: Over 100 cell pellet samples with five different number densities (1.25, 5, 20, 80 and 320 million cells/mL) were evaluated. These echo data yielded consistent BSC results that were also correlated with cell concentrations. The BSC magnitude has a linear relationship with the number density except when the number density is high such that coherent scattering appears to play a significant role. Additionally, the BSC data were fitted to the new concentric sphere scattering model and yielded approximate quantitative acoustic impedance values for the outer sphere (cytoplasm) and inner sphere (nucleus) of 1.54 and 1.6 Mrayl, respectively.

Conclusion: The concentric sphere theory shows good quantitative agreement with the BSC measurements.

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2.2 **Ultrasonic backscatter coefficient measurement agreement across multiple imaging platforms**, Lauren A. Wirtzfeld,[1] Goutam Ghoshal,[1] Kibo Nam,[2] Yassin Labyed,[3] Janelle J. Anderson,[2] Alexander Haak,[1] Zhi He,[4] Rita J. Miller,[1] Sandhya Sarwate,[1] Douglas G. Simpson,[4] James A. Zagzebski,[2] Timothy A. Bigelow,[3] Michael L. Oelze,[1] Timothy J. Hall[2] and William D. O'Brien Jr.,[1] *[1]Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, Urbana, IL, [2]Department of Medical Physics, University of Wisconsin, Madison, WI, [3]Department of Electrical and Computer Engineering, Iowa State University, Ames, IA and [4]Department of Statistics, University of Illinois at Urbana-Champaign, Champaign, IL, lwirtz@uiuc.edu.*

The backscatter coefficient (BSC) as a function of frequency is a fundamental system and operator-independent parameter that forms the basis of some quantitative ultrasound (QUS) analysis. The ability to demonstrate agreement in BSC estimates across multiple imaging platforms in biological models is necessary for QUS techniques to be translated into a clinical setting. While studies in well characterized phantoms have been performed, there are few studies looking at biological tissue *in-vivo.* Two studies of spontaneous rat mammary tumors (primarily fibroadenomas) were performed. All tumors were imaged with three clinical systems and one single element laboratory system, for a total of nine different transducers. The three clinical systems were an Ultrasonix RP, a Zonare Z.one scan engine diagnostic system and a Siemens Acuson S2000.

The study was performed at UIUC to enable data collection from each system sequentially. Data were acquired from the same region of a tumor with each scanner. Reference scans were acquired from a reference phantom and a flat Plexiglas plate for the clinical systems and laboratory system, respectively. Data from each system were analyzed using methods developed by the respective research group. Attenuation values for data processing were determined individually for each animal due to the high level of variance in attenuation observed between tumors. For a particular tumor, good agreement was observed in the attenuation versus frequency data even when the analysis techniques varied. The BSC was observed to have good agreement versus frequency across most of the measurements. In many cases in regions of overlapping bandwidth, the BSC estimates overlapped each other,

showing no more variability than was observed between different images acquired from the same tumor with the same ultrasound system.

The results indicate that it is possible to obtain good agreement between BSC estimates from different ultrasound systems from a live animal, even when processing techniques vary. This type of agreement enables QUS results to be compared between laboratories and the potential to base diagnoses on QUS parameters.

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2.3 **A simulation study on spatial-distribution-dependent ultrasound backscattering of cell aggregates,** Ratan K. Saha and Michael C. Kolios, *Department of Physics, Ryerson University, 350 Victoria Street, Toronto, Ontario, M5B2K3, Canada, ratank.saha @ryerson.ca.*

Objective: We have previously shown that ultrasound backscatter from acute myeloid leukemia (AML) cells treated with chemotherapeutics increases when compared to untreated cells. The untreated AML cell aggregrates possess an inherent degree of organization while the treated cell aggreragates exhibit large structural changes leading to an increase in randomness of the spatial distribution of their nuclei. The present work aims to study systematically the effects of spatial organization of nuclei on ultrasound backscattering properties. Both frequency-dependent backscattering coefficients and signal statistics have been investigated for various tissue samples comprising of different proportions of regularly-aligned and randomly-located nuclei.

Method: The positions of regularly placed nuclei were generated by fixing the periodicity of particles. A Monte Carlo method known as random sequential adsorption (RSA) technique was implemented to assign coordinates of nonoverlapping randomly-distributed nuclei under periodic boundary conditions. These nuclei were treated as weak scatterers of ultrasound waves and the Anderson model was used to calculate backscattering amplitude for each nucleus. This work employs a modified version of a theoretical model, which has been extensively used to describe backscattering by red blood cells, to simulate ultrasound backscattering by a collection of AML cells. The ensemble average of backscattering coefficient was determined over a large number of simulated configurations whereas envelope histogram was generated for 100 A lines for each sample.

Results: We found that integrated backscattering coefficient (IBSC), computed between 10-30 MHz, increased nearly 26 dB for the tissue sample with completely random distribution of nuclei when compared to that of a regular distribution of nuclei. In this frequency band, the spectral slope decreased slightly from 4.36 to 4.17 (keeping the size of the cell constant). The signal envelope statistics in most cases followed the Rayleigh distribution for the scattering of an incident Gaussian pulse with 5 MHz as the center frequency. However, the Nakagami and generalized Gamma probability distribution functions provided better fit to the histogram when a particular sample was insonified by the 25 MHz pulse.

Conclusion: To the best of our knowledge, the approach described in this work has never been applied in the investigation of the backscattering properties of cell aggregates. Our simulation results show that IBSC increased up to 26 dB as the sample contained more randomly-spaced nuclei. It can be noted that a change in randomization has a small effect on spectral slope for fixed scatterer size. Further, for samples with partially-ordered cells, if the irradiating pulse contained a frequency for which the corresponding wavelength approached the periodicity in the spatial disitrubtion of the nuclei, then the histograms were best fitted by the Nakagami and generalized Gamma distribution functions. The simulation tool developed for this work can be used in future to examine backscattering behaviors of different cell lines under other relevant physical conditions.

2.4 **Effective scattering diameter estimates of rabbit liver via three-dimensional impedance map and quantitative ultrasound,** Alexander J. Dapore,[1] Lauren A. Wirtzfeld,[1] Sandhya Sarwate,[1] Michael L. Oelze,[1] Minh N. Do,[1] Timothy J. Hall[2] and William D. O'Brien, Jr.,[1] *[1]Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, 405 N Mathews, Urbana, IL 61801 and [2]Department of Medical Physics, University of Wisconsin-Madison, Madison, WI 53706, adapore2@illinois.edu.*

Three-dimensional impedance maps (3DZMs) are virtual volumes of acoustic impedance values constructed from histology to represent tissue microstructure acoustically. 3DZMs are potentially a valuable tool for quantitative ultrasound (QUS), as an estimation of ultrasonic backscatter and scatterer properties, such as effective scatterer diameter (ESD), can be made. Ultimately the 3DZM can be used to develop a more robust and effective acoustic scattering model to better represent the ultrasonic interaction with underlying tissue microstructure.

In this study, a sample of rabbit liver was chemically fixed and ultrasonically scanned *ex vivo*. The sample was scanned after fixation in order to produce a stronger link between ultrasonically- acquired ESD estimates and 3DZM ESD estimates. The sample was then sent to histology for the creation of 3DZMs. In total, 24 3DZMs of size 300x300x300 μm^3 were created from the rabbit-liver sample. ESD estimates were made using both 3DZM and QUS techniques using the fluid-filled sphere form factor model. For the collection of 24 3DZMs, two optimization techniques, at different acoustic scattering scales, were used to estimate ESD. The ESDs estimated from the two 3DZM techniques were 7.8 ± 0.8 μm and 59.7 ± 44.7 μm. Although there is no definitive link between individual ESD estimates and anatomical structures, the first estimate corresponded visually to the size of individual nuclei contained within the 3DZM, while the second estimate was visually on the order of the size of hepatocytes. QUS ESD estimations at 7.5, 13, 20, 40 and 65 MHz were 109.2 ± 30.5, 63.3 ± 12.2, 23.6 ± 26.2, 19.8 ± 1.1, and 2.8 ± 6.4 μm respectively.

The 3DZM ESD estimates were within the range of QUS ESD estimates from 7.5 to 65 MHz. The normalized backscattered power spectra from the samples using both the 3DZM and QUS techniques were also compared. This study gave new insight into the relationship between 3DZM and QUS parameter estimation. Additionally, the visualization of the 3DZM when compared to the ESD estimates from both modalities produced the identification of possible ultrasonic scattering sources in the rabbit liver.

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2.5 **Analysis of human fibroadenoma using three-dimensional impedance maps,** Alexander J. Dapore,[1] Michael R. King,[1] Sandhya Sarwate,[1] Josephine Harter,[2] Michael L. Oelze,[1] Minh N. Do,[1] Timothy J. Hall[2] and William D. O'Brien, Jr.[1], *[1]Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, 405 N Mathews, Urbana, IL 61801 and [2]Department of Medical Physics, University of Wisconsin-Madison, Madison, WI 53706, adapore2@illinois.edu.*

Three-dimensional impedance maps (3DZMs) are virtual volumes of acoustic impedance values constructed from histology to represent tissue microstructure acoustically. From the 3DZM, the ultrasonic backscattered power spectrum can be predicted and scatterer properties, such as effective scatterer diameter (ESD), can be estimated. Additionally, the 3DZM can be exploited to visualize and identify possible scattering sites, which may aid in the development of more effective scattering models to better represent the ultrasonic interaction with underlying tissue microstructure.

In this study, 33 3DZMs were created from human fibroadenoma samples. ESD estimates were made assuming a fluid-filled sphere form factor model from 3DZMs of volume 300 300 300 μm^3 and 150 150 150 μm^3. For a collection of 33 independent tissue samples,

the ESD was estimated to be 23.2 ± 11.2 μm with the large 3DZMs and 19.1 ± 11.5 μm when using the small 3DZMs.

The 3DZMs were then investigated visually to identify possible scattering sources which conformed to the estimated characteristic scatterer dimensions. This estimation technique allowed a better understanding of the spatial distribution and variability of ESD estimates for the human fibroadenoma samples of this study.

This work was supported by NIH Grant CA111289.

2.6 **Quantitative-ultrasound detection of metastases in dissected lymph nodes of cancer patients at 25 MHz**, Ernest J. Feleppa,[1] Jonathan Mamou,[1] Junji Machi,[2] Masaki Hata,[2] Emi Saegusa-Beecroft,[2] Alain Coron,[3] Eugene Yanagihara,[2] Pascal Laugier[3] and Michael L. Oelze,[4] *[1]Lizzi Center for Biomedical Engineering, Riverside Research Institute, New York, NY, [2]J. A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, HI, [3]Université Pierre et Marie Curie-Paris6, and CNRS, Paris, F-75005 France and [4]University of Illinois at Urbana-Champaign, Urbana, IL, efeleppa@rri-usa.org.* final as of 3/8

A reliable means of detecting metastases in regional lymph nodes is essential for accurate staging and prognoses of cancer and effective planning of therapy. Current standard histopathology methods appear to have high false-negative rates for metastases that are 2 mm or smaller. High-frequency (HF) quantitative ultrasound (QUS) methods are proving to be capable of providing a reliable method of detecting metastases in dissected nodes based on differences in ultrasound-scattering properties at the level of tissue microstructure. Equivalent methods may be useful for detecting metastases *in situ*.

We acquired ultrasound and histological data from 837 lymph nodes dissected from 281 patients with colorectal, breast, gastric and other cancers. Freshly-dissected nodes were scanned to acquire 3-D rf echo-signal data using a 2-D raster scan in a saline water bath. Scans were performed with a broadband, F-2, 25.6-MHz, single-element transducer with scan vectors separated by 25 μm in both cross-range directions. Scanned nodes were color inked to provide references for subsequent orientation, then fixed and serially-sectioned in their entire volume at 50-μm intervals. The presence of metastatic foci was determined histologically in every section, including the center section for comparison with conventional methods.

To date, we have analyzed the echo signals of 112 nodes of colorectal and gastric cancer patients; 92 nodes were entirely cancer free and 20 nodes were entirely or predominantly cancerous. 3-D images generated from rf data were segmented semi-automatically to distinguish nodal tissue from the immersion bath and periprostatic fibroadipose tissue. Echo signals from nodal tissue were processed to yield spectral-parameter estimates (slope intercept and midband), scatterer-property estimates associated with tissue microstructure (size and acoustic concentration) and statistical features of the backscattered envelope. Linear discriminant analysis and ROC-curve methods were applied to assess the ability of spectral parameters, scatterer-property estimates and statistical features to distinguish cancerous from noncancerous nodes for individual estimates and for various linear combinations of estimates.

ROC results showed outstanding classification for scatterer size alone or for scatterer size combined with one or two other estimates. For example, the area under the ROC curve for scatterer size alone was 0.986 ± 0.009; for scatterer size combined with one statistical feature, the area was 0.996 ± 0.003. These results promise an excellent ability to depict small metastatic foci in nodes, which we currently are assessing.

The potential clinical importance of these methods is indicated by the fact that 17 (37%) of the 46 histologically evaluated nodes that contained metastases smaller than 2 mm would have been missed by conventional single-section pathology methods.

These extremely encouraging initial results suggest that HF QUS methods may provide a clinically important and practical means of identifying small metastatic foci that might not be detected using standard pathology procedures. The benefit of this ability to reveal otherwise missed foci will enable pathologists to focus histological effort on cancer-containing regions of nodes. Future studies will investigate the applicability of these methods to detection of nodal metastases *in situ*.

This research is supported in part by NIH/NCI grant 5R01CA100183-04.

2.7 **Specular echo detection using generalized spectrum parameters**, Adam Luchies and Michael L. Oelze, *Bioacoustics Research Laboratory, Department of Electrical and Computer Engineering, The University of Illinois at Urbana-Champaign, Urbana, IL, 61801, luchies1@illinois.edu.*

Quantitative ultrasound (QUS) imaging methods are being developed to classify breast tumors. QUS estimates (e.g., scatterer size, acoustic concentration) are used to characterize the tissue microstructure of a region of interest (e.g., the inside of a tumor) having some degree of homogeneity. However, specular scatterers (e.g., blood vessels, calcifications, etc.) can exist within these regions that appear as isolated bright spots in a B-mode ultrasound scan. The existence of these specular scatterers can increase the variance of QUS imaging estimates.

The goal of this work was to use generalized spectrum (GS) parameters to detect echoes from specular or periodic scatterers in the underlying rf data of a B-mode image and to use this knowledge to reduce the variance of QUS estimates. Simulations and rodent tumor models were analyzed by measuring the GS collapsed average (GS-CA) intercept value for regions of interest (ROIs) used in the QUS estimation process. When an ROI contained a specular scatterer, the GS-CA intercept was observed to increase. Revised QUS parametric images were formed by discarding QUS estimates from ROIs whose GS-CA intercept values were above a certain threshold.

When using the GS-CA intercept threshold method, a significant reduction in variance was observed in QUS estimates for both simulated and experimental backscatter data containing specular scatterers. For example, a 73% reduction was observed in the variance of effective scatterer diameter (ESD) estimates from a simulated backscatter image containing four specular scatterers (with size twice that of the background scatterers). As another example, a 65% reduction was observed in the variance of ESD estimates measured from the inside of a rodent tumor containing a single large specular scatterer. A GS-CA intercept threshold value of 0.5 was used in both of these examples. The largest GS-CA intercepts were observed in ROIs containing a single specular scatterer (one specular echo per scan line). The smallest GS-CA intercepts were observed in ROIs containing only diffuse scattering (zero specular echoes per scan line). ROIs containing pairs of specular scatterers (two specular echoes per scan line where the spacing between scatterers is the same in each scan line) often produced a mid-valued GS-CA intercept. The GS-CA intercept method was observed to reduce the variance of QUS estimates and could improve diagnostics using QUS imaging.

This work was supported by NIH Grant CA111289.

2.8 **Phantom tests of attenuation and backscatter determinations in a preclinical tumor model**, Kibo Nam,[1] Lauren A. Wirtzfeld,[2] Alexander Haak,[2] Alexander D. Pawlicki,[2] Goutam Ghoshal,[2] Yassin Labyed,[3] Timothy A. Bigelow,[3] Michael L. Oelze,[2] Ernest L. Madsen,[1] James A. Zagzebski,[1] William D. O'Brien Jr.[2] and Timothy J. Hall,[1] *[1]Department of Medical Physics, University of Wisconsin-Madison, Madison, WI, [2]Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, Urbana, IL*

and [3]Department of Electrical and Computer Engineering, Iowa State University, Ames, IA, kibonam@wisc.edu.

The application of quantitative ultrasound (QUS) techniques to aid in the diagnosis of breast tumors is of interest because current procedures rely on needle biopsies to differentiate benign from malignant masses. Biopsies are invasive procedures with associated risks, and in the case of breast cancer, the majority return a benign diagnosis. An intercomparison of QUS measurements with clinical systems has been conducted with a rat-tumor model of benign fibroadenomas and the results demonstrated high values of attenuation, exceeding 13 dB/cm at 8 MHz. As there has been limited results for QUS estimates in a tissue with such high attenuation values and with this particular geometry (tumor extended above the surrounding tissue), this paper reports results from a phantom designed to mimic some of the complexities observed in the *in-vivo* rat tumor model.

The phantom consists of two 15 mm diameter simulated tumors protruding from an 8 8 8 cm tissue-mimicking (TM) background and immersed in a water-alcohol mixture. The speed of sound (SOS), attenuation coefficient and backscatter coefficients were measured for each of the three materials at the time of construction from test samples at frequencies from 2.5M Hz to 12 MHz. The TM background has an attenuation coefficient of 0.51dB/cm-MHz, a SOS of 1540 ± 4 m/s (lab results from the test sample), and contains 45-53 m diameter glass- bead scatterers distributed throughout the volume. The first simulated tumor has an attenuation coefficient of 1.00 dB/cm-MHz, a SOS of 1540 ± 4 m/s and contains 25-32 m diameter scatterers. The second simulated tumor has an attenuation coefficient of 1.58 dB/cm-MHz, a SOS of 1530 ± 3 m/s and contains 75-90 m diameter scatterers.

The phantom was initially scanned using a Siemens S2000 system equipped with a research interface. Radiofrequency echo data in the frequency range of 2-15 MHz were obtained with an 18L6 linear-array transducer. The attenuation and backscatter coefficients for the TM spheres were estimated using the TM background as a reference. Attenuation in the spheres was estimated by a reference phantom method.(1) Results were 1.02dB/cm-MHz and 1.71dB/cm-MHz, respectively, in excellent agreement with lab results. Backscatter coefficients estimated using the clinical system were in agreement with both lab results and theoretical backscatter coefficient determinations applying a formula derived by Faran.

This study suggests that attenuation and backscatter coefficients can be estimated accurately for the preclinical tumor models with our clinical-imaging system, even with the unusual geometry presented by the model and the unusually high attenuation coefficients. The phantom will be distributed to researchers at the Universities of Iowa and Illinois for QUS scans with a Zonare Z.One and an Ultrasonix RP system. Independently-derived results will be compared.

This work was supported by NIH Grant CA111289.

(1) *Ultrasonic Imaging 25*, 245-261 (2003)

2.9 **Comparison of attenuation measurements for live rat tumors using three clinical imaging systems**, Kibo Nam,[1] Lauren A. Wirtzfeld,[2] Alexander Haak,[2] Alexander D. Pawlicki,[2] Goutam Ghoshal,[2] Yassin Labyed,[3] Timothy A. Bigelow,[3] Michael L. Oelze,[2] James A. Zagzebski,[1] William D. O'Brien Jr[2] and Timothy J. Hall,[1] *[1]Department of Medical Physics, University of Wisconsin-Madison, Madison, WI, [2]Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, Urbana, IL and [3]Department of Electrical and Computer Engineering, Iowa State University, Ames, IA, kibonam@wisc.edu.*

Accurate measurements of attenuation in tissue are needed for estimating scattering properties and also would likely be a valuable diagnostic aid. Laboratory measurements of atten-

uation in phantoms with simple geometry have yielded accurate and reproducible results but adoption of attenuation estimation in a clinical setting will require that accurate estimates can be made regardless of the clinical system used. In this study, we compare the attenuation estimates of *in vivo* spontaneous rat mammary tumors made by three different research groups each using a different clinical imaging system.

Six live Sprague Dawley rats with spontaneous mammary tumors were scanned using an Ultrasonix RP (Ultrasonix Medical Corporation, Richmond, BC), a Zonare Z.one system (Zonare Medical Systems, inc., Mountain View, ca) and a Siemens Acuson S2000 (Siemens Medical Solutions USA, Inc., Malvern, PA). Radiofrequency echo data were acquired from five to nine parallel planes (depending on the tumor size) using each scanner in the frequency range of 1-14 MHz. A well-characterized reference phantom was also scanned with each system using the same transducers and system settings. The attenuation values within tumors were estimated by each group using their own implementation of a reference phantom method.(1)

The attenuation comparison showed good agreement among systems for most rat tumors. Where there was disagreement in values between groups, this likely was caused by tumor heterogeneity or high spatial variation noise due to the small size of some tumors. The combined results for all systems were fit by a power law function for each tumor. The results revealed a higher attenuation (mean attenuation of 13.7 dB/cm at 8MHz) than typically found for human breast fibroadenoma. Variations in attenuation were noted among tumors, a finding that correlated with subjective observations of B-mode images derived from rf data.

Very good agreement of attenuation values can be achieved from *in vivo* echo measurements using different clinical systems. These results demonstrate the possibility of performing quantitative ultrasound techniques in a clinical site independent of the imaging system used. This work was supported by NIH Grant CA111289.

(1) *Ultrasonic Imaging 25*, 245-261 (2003).

2.10 **Limitation of attenuation slope estimation using spectral shift**, Alexander Haak,[1] Alexander D. Pawlicki,[1] Ernest L. Madsen,[2] Timothy J. Hall[2] and William D. O'Brien Jr[1], *[1]Bioacoustics Research Laboratory, Department of Electrical and Computer Engineering, University of Illinois, Urbana, IL and [2]Department of Medical Physics, University of Wisconsin-Madison, 1300 University Avenue, Madison, WI, wdo@uiuc.edu.*

Introduction: The estimation of the acoustic attenuation in *vivo* is a challenging problem. The backscattered signal from tissue can be utilized to estimate the attenuation. One approach to estimate the attenuation is to utilize the spectral power difference vs. depth. This technique has good sensitivity and accuracy in homogenous media but the estimates can suffer from reflections at boundaries. The spectral shift method utilizes the down shift of the center frequency of an ultrasonic pulse vs. depth. The estimation becomes quite simple if a Gaussian shaped pulse is used and the medium has a linear frequency dependency. However, for low attenuating materials and shallow depths the spectral shift becomes small and will therefore be harder to detect.

In this work the accuracy and sensitivity of the spectral shift method was investigated. Computer simulations were used to determine the performance of this method for a wide variety of attenuation and total transducer bandwidths. Preliminary results were obtained experimentally on two tissue mimicking phantoms.

Methodology: Computational phantoms with linear frequency dependency of attenuation were created. The attenuation slope (AS) ranged from 0.5 to 1.5 dB/cm-MHz. Scatterers were uniformly distributed with a density of 15 scatterers per resolution cell within the phantom. The scattering function was constant with frequency and the source had no diffraction. Gaussian pulses with center frequencies ranging from 4 to 22 MHz and fractional bandwidths

from 20 to 65 percent were used to generate rf data from the virtual phantoms. The spectral shift as a function of depth was obtained by fitting a Gaussian function to the power spectra which was calculated from blocks of rf data obtained at different depths. The estimated spectral shifts and attenuation slopes were compared to the theoretical values.

Two tissue mimicking phantoms (phantoms A and B) with attenuation slopes of 0.42 and 0.67 dB/cm-MHz respectively were scanned with two single element transducers. The actual attenuation slopes were obtained using an insertion loss measurement. The measured center frequencies were 4.0 and 8.8 MHz and the 3 dB fractional band widths were 32 and 40 percent respectively. Diffraction was accounted for by taking a reference scan from a planar reflector. The AS was then obtained from the diffraction corrected spectra in a similar fashion as it was for the virtual phantoms.

Results: The spectral shifts obtained from the virtual phantoms agreed well with the theoretical trends. The estimated spectral shifts vs. depth and ASs from the simulated data agreed within three percent to the theoretical values for low spatial variation noise. The experimentally-obtained AS for the 8.8 MHz transducer differed from the actual value by less than 15 percent when 10 rf lines were used to calculate the average power spectrum, decreasing to 5 percent when 400 rF lines were averaged. This work was supported by NIH Grant R01CA111289.

2.11 **Novel low-frequency ultrasound detection of apoptosis *in vitro* and *in vivo*,**
Gregory J. Czarnota,[1,2] Anoja Giles,[1,2] Ervis Sofroni,[1,2] Naum Papanicolau,[1,2] Sara Iraji,[1,2] Rebecca Dent,[3] Jacqueline Spayne[2] and Michael C. Kolios,[4] *[1]Radiation Oncology and Imaging Research, Sunnybrook Health Sciences Centre and Department of Radiation Oncology, University of Toronto, [2]Department of Radiation Oncology and Medical Biophysics, University of Toronto, [3]Department of Medical Oncology, Sunnybrook Health Sciences Centre and University of Toronto and [4]Department of Physics, Ryerson University, gregory.czarnota@gmail.com.*

The aim of many cancer therapies is to induce apoptotic cell death. We demonstrate here for the first time that diagnostic-range conventional-frequency ultrasound imaging may be used to detect apoptotic cell death *in vitro*, *in vivo* using animal models and in patients receiving neoadjuvant chemotherapy for breast cancer.

In vitro experiments employed a leukemia cell model (AML-3). Apoptosis was induced in cells by exposure to 10 g/ml cisplatinum for various times (0, 6, 12, 24, 48 and 72 hours). Concentration dependence was also evaluated by preparing samples of 0, 10, 20, 40, 60, 80 and 100% apoptotic cells. Samples were examined by a 10 MHz, 3.8 cm conventional transducer using an Ultrasonix-RP ultrasound device and results compared with data collected by a 30 MHz f2 high-frequency transducer coupled to a VisualSonics VS40B or VEVO-770 ultrasound device. For *in vivo* experiments, solid tumors were grown in SCID ($n = 32$) mice using a human prostate cell line (PC-3) and breast tumours (MDA MB-231). Mice were treated with radiation alone (0, 2, 8 Gy) in a single fraction, novel chemical and biophysical anti-angiogenics or the therapies combined.

Human data was collected from 20 women with large (7-10 cm) locally-advanced breast cancers receiving combined anthracycline-taxane based chemotherapy using an Ultrasonix-RP system as above. Data was collected before chemotherapy, at weeks 1, 4, and 8 after commencing chemotherapy and preoperatively 1-2 months later.

Ultrasound analyses of *in vitro*, animal and patient data were carried out examining spectral parameters and statistical methods. Cell and animal samples were processed for histopathologic analysis using both hematoxylin and eosin and TUNEL staining for apoptosis. Patient mastectomy specimens were processed as whole mount sections and hematoxylin and eosin stained to determine pathological response.

For experiments conducted with *in vitro* samples, analyses indicated an up to 8-fold increase in ultrasound backscatter intensity (6.2 dB) coinciding with maximal apoptosis (48 hours). Detection-limit experiments indicated a statistically-significant difference between viable cells and the 10% apoptotic sample. Results also correlated well with high-frequency ultrasound data with the exception that increases in backscatter at 30 MHz were larger 0.8 dB). Increases in spectral slope with cell death were suggestive of a decrease in mean scatterer size, consistent with our working model that nuclear compaction and degradation during apoptosis influences ultrasound backscatter.

Experiments *in vivo* indicated spectral changes that were correlated with increases in measured cell death. Treatments with anti-angiogenics alone gave rise to an increase of mid-band fit of 5.0 2.9 dB, radiation alone up to5.1 2.0 dB, whereas combined treatments yielded increases of up to 8.0 4.2 dB. High-frequency ultrasound changes indicated increases in backscatter of similar magnitude. Changes in spectral slope and 0-MHz intercept parameters were also consistent in trend with data acquired at high frequency. Ultrasound parameters could be correlated with increases in cell death although slope measurements at the lower frequency were less pronounced.

Data from patients indicated comparable changes in responsive patients at week 4 after commencing chemotherapy whereas nonresponding women demonstrated no significant change in ultrasound parameters at that time.

In summary, ultrasound analyses using conventional frequency ultrasound with correlational immunohistochemistry and histology indicated that conventional frequency ultrasound could detect apoptosis *in vitro* and *in vivo* in preclinical prostate and breast cancer models. This opens the avenue for this type of modality to be used to monitor the efficacy of cancer treatments leading to customization and optimization of treatments. Preliminary patient data indicates the ability of such spectral measures to monitor early changes in clinical response and predict pathological outcomes in response to neoadjuvant chemotherapy.

2.12 **High-frequency characterization of atherosclerotic arteries with targeted contrast agents**, Pavlos Anastasiadis and John S. Allen, *University of Hawaii at Manoa, Mechanical Engineering, 2540 Dole St., Holmes Hall 302, Honolulu, HI 96822, pavlos@hawaii.edu.*

Atherosclerotic cardiovascular disease is the leading cause of morbidity and mortality in the industrialized world. Atherosclerotic lesions (atheromata), occur when monocytes migrate from the bloodstream into the innermost layer of the artery wall and form asymmetric focal thickenings. Atheromata consist of connective-tissue elements, lipids, and debris. Atherosclerotic plaques, especially those in coronary and carotid arteries, may rupture without prior exhibition of markers or symptoms, leading to acute coronary syndromes, peripheral vascular disease, myocardial infarctions and stroke.

The current conventional imaging methods used for the detection of atherosclerotic lesions are intravascular ultrasound (IVUS), magnetic resonance imaging (MRI) and computed tomography (CT). Although these techniques have proven useful in the clinical practice, significant limitations exist. IVUS has the potential to characterize atheromata in the vicinity of the ultrasound catheter but is unable to detect vulnerable plaques. Although MRI is noninvasive, its long image-acquisition time hinders the consistent imaging of structures such as coronary vessels. Imaging CT angiographic methods provide adequate resolution but lack the ability to visualize rupture-prone, nonstenotic, lipid-rich lesions. Moreover, this type of lesions has been attributed to more than half of all acute myocardial infarction incidents.

Novel techniques need to be developed for *in vivo* and *in situ* applications. In this study, the feasibility of applying targeted ultrasound contrast agents (UCAs) for the detection of

rupture-risk atherosclerotic lesion sites is investigated with respect to high-frequency ultrasound as IVUS probes operate in the range of approximately 20-50 MHz.

Targeted UCAs were used for binding to atherosclerotic sides of excised human arteries. The artery samples were embedded in cryomolds containing OCT compound without previous fixation and sections with a thickness of 60 μm were obtained using a Leica CM3050S cryostat (Leica, Bannockburn, IL). Subsequently, targeted UCAs were bound onto the sections and examined with a scanning acoustic microscope at center frequencies of 50 MHz and 100 MHz (Fraunhofer IBMT, St. Ingbert, Germany). The coordinates of several regions of interest (ROIs) were saved using a motorized measuring stage with micrometer-precision (Märzhäuser Wetzlar GmbH, Wetzlar, Germany).

Following the ultrasonic imaging, the samples were removed from the microscope stage for fixation and staining. The stained artery sections were placed back onto the measuring stage and *epifluorescence* images for the saved ROIs were acquired with a digital Lumenera Infinity 3-1 cooled monochrome camera (Lumenera, Ottawa, Ontario, Canada) mounted on a Zeiss Axiovert 200M inverted microscope (Carl Zeiss, Oberkochen, Germany). The obtained acoustic and *epifluorescence*d data were postprocessed and the images overlapped for comparison of the respective acoustic and molecular information. Novel insights are obtained in regard to the mechanical properties of diseased sites in atherosclerotic lesions and the binding efficacy of targeted UCAs.

2.13 **Ultrasound microbubbles-mediated gene transfer into the ocular ciliary muscle**, Michèle Boudinet,[1] Laura Kowalczuk,[2] Amena Saïed,[1] Francine Behar-Cohen[2] and Pascal Laugier,[1] *[1]Laboratoire d'Imagerie Paramétrique UMR CNRS 7623, 15 rue de l'Ecole de médecine, 75006 Paris France and [2]Centre de Recherche des Cordeliers UMRS872 Equipe17 Physiopathologie des maladies oculaires:Innovations Thérapeutiques, 15 rue de l'école de médecine, 75006 Paris France laugier@lip.bhdc.jussieu.fr.*

Purpose: Sonoporation by ultrasound–activated microbubble contrast agents is a noninvasive approach of delivering genes at the cellular level that is becoming more widely used for nonviral gene transfer. The aim of this *in vivo* study was to assess the feasibility of using low-intensity ultrasound combined with commercially-available echo-contrast agent microbubbles to specifically transfect the ocular ciliary muscle, which is used as a possible secreting tissue for therapeutic proteins into the ocular sphere.

Materials and methods: A reporter plasmid DNAencoding Renilla luciferase (pCMV-Gluc-1) and -galactosidase (pVAX1-LacZ) alone or mixed with 50% echo-contrast microbubbles (Artison) were injected into rat eye ciliary muscles with or without ultrasound exposure (1 MHz, 2W/cm^2 *I*sata for 2 minutes, 50% duty cycle). Animals were sacrified 7 and 30 days later for the measurement of luciferase gene expression in the ocular fluids by luminometry**.** Localization of gene expression was investigated by -galactosidase histochemistry in the ciliary muscles of both eyes 7 days after transfection. Finally, tissue damage was assessed on histological sections through the eyes. Statistical significance was determined using Kruskal-Wallis/Dunn's nonparametric tests.

Results: Seven days after transfection, luciferase activity was more increased in ciliary muscle transfected with microbubbles (MB) and ultrasound than with ultrasound alone or plasmid alone. Ultrasound plus microbubbles showed a 2.6-fold increase in gene expression (p<0.023) compared with the control non-ultrasound exposed muscle. Thirty days after transfection, a significant decrease in luciferase gene expression was observed in each experimental group. Histochemical staining demonstrated -galactosidase expression localized in the ciliary region to the injection site. No apparent toxicity could be detected histologically in muscle tissue transfected with plasmid DNA with ultrasound and Artison bubbles.

Conclusion: We demonstrate for the first time the feasibility of a nonviral gene transfer method targeted to the ciliary muscle cells, mediated by ultrasound and microbubbles, allowing muscle cells to produce intraocular proteins in ocular medias without apparent toxicity. These results indicate that targeting intraocular ciliary muscle is a potentially useful delivery method for the therapy of ocular diseases.

3. IVUS

3.1 **Clinical perspective on the role of intravascular ultrasound (IVUS) imaging and tissue characterization in the coronary arteries**, Itsik Ben-Dor, *Cardiac Catheterization Laboratories, Washington Hospital Center, Washington, DC, itsik.ben-dor@medstar.net* (invited overview).

3.2 **Challenges in atherosclerotic plaque characterization using intravascular ultrasound**, Shashidhar Sathyanarayana, Wenguang Li and Lewis Thomas, *Boston Scientific Corp., 47900 Bayside Parkway, Fremont, CA 94538-6515, sathyans@bsci.com* (invited).

3.3 **VH™ intravascular ultrasound: limitations, validation and clinical data**, Anuja Nair, Russell J. Fedewa, M. Pauliina Margolis and D. Geoffrey Vince, *Volcano Corporation, 3661 Valley Centre Drive Suite 200, San Diego, CA 92130, anair@volcanocorp.com* (invited).

3.4 **Effect of angle of insonification on apparent backscatter from human coronary arteries**, Joseph J. Hoffman,[1] Benjamin L. Johnson,[1] Mark R. Holland,[1] Russell J. Fedewa,[2] Anuja Nair[2] and James G. Miller,[1] [1]*Washington University in St. Louis, St. Louis, MO and* [2]*Volcano Corporation, 3661 Valley Centre Drive Suite 200, San Diego, CA 92130, james.g.miller@wustl.edu.*

Clinical imaging of the coronary arteries in the cardiac catheterization laboratory using Intravascular Ultrasound (IVUS) provides data acquired with the ultrasonic beam approximately perpendicular to the arterial wall. In this 'side-looking' (or radial) configuration, an image formed from the backscattered signal typically has a three-layered appearance, corresponding to the intima/plaque, media and adventitia. By insonifying a transverse slice of a vessel, measurements of the backscatter can be made from a forward-looking (or axial) direction. The axial orientation is closer to proposed forward-looking intravascular ultrasound than standard IVUS. The current study was carried out *in vitro* with both radial and axial imaging of fresh human coronary arteries. Twenty-six sites from twelve excised arteries were first imaged with a side-looking intravascular imaging system and subsequently with an acoustic microscope in both the radial and the axial directions. Data from the acoustic microscope were processed to yield values of apparent integrated backscatter. In the radial orientation, apparent integrated backscatter images exhibited the same 'bright-dark-bright' three-layer appearance as observed in the preceding side-looking IVUS scans. However, apparent integrated backscatter images obtained in the axial orientation exhibit a markedly different pattern, with the relative brightness of the media significantly larger than that of the intima/plaque. Apparent integrated backscatter from the adventitia was not significantly different in the two orientations.

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4. HIFU

4.1 **Temperature-dependent ultrasonic characterization of biological media**, Goutam Ghoshal and Michael L. Oelze, *Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, gghoshal@illinois.edu*.

High intensity focused ultrasound (HIFU) is a noninvasive technique that has great potential for improving targeted thermal therapies. To target specified regions accurately for treatment, a robust imaging technique is required to monitor HIFU application. Therefore, the development of an ultrasonic imaging technique for monitoring HIFU treatment is highly medically significant. Quantitative ultrasound (QUS) is a novel imaging technique that has the potential to improve monitoring of HIFU treatment by quantifying tissue changes.

Ultrasonic backscatter experiments were performed on tissue-mimicking phantoms, fresh rabbit liver and beef liver samples. The phantoms were made of agar and contained either mouse mammary carcinoma cells or Chinese hamster ovary cells as scatterers. All scatterers were uniformly distributed spatially at random throughout the phantoms. QUS parameters were estimated from the samples versus increases in temperature from 37 to 50 C in 1 C increments. All the samples were scanned using a 20-MHz single-element f/3 transducer. Sound speed and attenuation were estimated versus temperature using insertion loss methods. Two parameters were estimated from the backscatter coefficient (effective scatterer diameter (ESD) and effective acoustic concentration (EAC)) and two parameters were estimated from the envelope statistics (*k* parameter and parameter) of the backscattered echoes versus temperature.

The estimates of sound speed increased monotonically in all the samples with increases in temperature except for the rabbit liver samples. The rabbit liver samples contained higher levels of fat content compared to normal liver. A decrease of 10-20% in attenuation slope was observed in all the samples with increasing temperature. No significant changes in the ESD were observed for the biophantoms but the ESD increased with increasing temperature in the liver samples. Significant decreases in EAC of 20-40% were observed in all the samples. No significant trends in the envelope statistics parameters with increasing temperature were observed.

From the results it was observed that some parameters were more sensitive to temperature changes than the others for a particular type of sample. The results of this study suggest that QUS has the potential to be used for noninvasive monitoring of temperature changes in tissues. The work was supported by NIH Grant R01-EB008992.

4.2 **Temperature imaging during nonuniform tissue heating with ultrasonic backscatter energy using self-calibration**, R. M. Arthur,[1] D. Basu,[1] Y. Guo,[1] J.W. Trobaugh,[1] W. L. Straube[2] and E. G. Moros,[3] *[1]Electrical & System Engineering, [2]Radiation Oncology, Washington University in St. Louis, St. Louis, MO 63130 and [3]Radiation Oncology, University of Arkansas, Little Rock, AK, rma@ese.wustl.edu.*

Background: Hyperthermia alone or in conjunction with chemotherapy and radiation is used for cancer treatment. One of its limitations is lack of detailed temperature monitoring. Ultrasound is an inexpensive, nonionizing and readily-available method with potential for noninvasive temperature imaging. Previously, we predicted monotonic changes in backscattered energy (CBE) of ultrasound with temperature. Measured CBE values from bovine liver, turkey breast and pork muscle in 1D and 2D matched our prediction. In this study, the volumetric (3D) change in ultrasonic backscattered energy (CBE) was calibrated and used to estimate temperature during nonuniform heating.(1)

Methods: For accurate temperature validation, a grid of thermocouples was calibrated using a NIST- traceable thermometer. 3D ultrasonic data sets were obtained by moving a 7.5 MHz linear, phased-array transducer in 0.6 mm steps in elevation. CBE was computed from a ratio of motion-compensated, envelope-detected images and a reference ultrasonic image, typically taken at 37°C. CBE curves obtained from turkey breast muscle were well matched by a linear regression that had a slope of 0.3dB/°C. To evaluate the effects of noise, scatterer distribution, and spatial resolution on estimation errors, thermal modeling was performed for nonuniform heating using finite element methods. Specimens of turkey breast muscle were heated nonuniformly from a central 65°C source so that the spatial temperature pattern decreased radially. Temperature images were computed from CBE maps using a fixed CBE sensitivity of 0.3dB/°C, as well as from self-calibration from one indwelling thermocouple.

Results: Estimated temperature maps with a spatial resolution of 0.5 cm^2 were validated using thermocouple readings at locations distributed throughout the specimens. Estimation errors during nonuniform heating with 0.3dB/°C sensitivity were 0.3 ± 1.9°C. Even though the CBE temperature images were qualitatively similar with self calibration, error was reduced to 0.07± 1.0°C.

Conclusion: This work, which validated the use of CBE as a noninvasive thermometer during nonuniform heating, was the first of its kind. It also helped clarify sources of estimation errors, such as the size of the temperature image pixel. Validation of CBE thermometry *in vitro* during nonuniform heating is an important step in making the transition from the laboratory to the clinical application of CBE temperature imaging for hyperthermia and other thermal therapies.

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(1) Basu D, *Doctoral dissertation* (Washington University in St. Louis, May 2010).

4.3 **Optoacoustic characterization of HIFU-induced thermal lesions in live and excised tissues**, Parag V. Chitnis,[1] Peter Brecht,[2] Richard Su[2] and Alexander Oraevsky,[2] *[1]F. L. Lizzi Center for Biomedical Engineering, Riverside Research Institute, 156 William Street, 9th Floor, New York, NY 10038 and [2]Fairway Medical Technologies, 710 N. Post Oak Road, Suite 204, Houston, TX 77024, pchitnis@rri-usa.org.*

Although high-intensity focused ultrasound (HIFU) has exciting potential for noninvasively treating tumors and cardiac diseases, its clinical acceptance is hindered by the lack of a reliable and cost-effective method of noninvasively guiding and monitoring the treatment. The present study investigated the feasibility of employing optoacoustic imaging (OAI) for detecting the thermally necrosed tissue. OAI combines molecular specificity provided by optical imaging and the resolution provided by diagnostic ultrasound. A 3-D optoacoustic imaging system was used to visualize thermal lesions produced in excised tissue specimens and *in vivo* mice using high intensity focused ultrasound (HIFU). A 7.5-MHz surgical, focused transducer with a radius of curvature of 35 mm and an aperture of 23 mm generated HIFU. A pulsed laser, which could operate at 755 nm and 1064 nm, illuminated excised tissue and mice using a bifurcated fiber bundle resulting in two wide beams of light. Tomographic images were obtained while the specimens were rotated within a sphere outlined by a concave arc-shaped array of 64 piezo-composite transducers. Images were acquired before and after HIFU exposure. The images were then combined to reconstruct 3-D volume images (voxel resolution 0.5 mm). Optoacoustic images using 1064-nm illumination provided excellent visualization of HIFU lesions. The lesion in excised tissue was indicated by an increase in the optoacoustic signal; the *in vivo* lesion was indicated by a decrease in the optoacoustic signal. The location and the extent of the lesions were confirmed upon dissection. The discrepancy between the *ex vivo* and the *in vivo* results might be attributed to

the different effective thermal deposition in the two cases. These preliminary results demonstrate the potential of optoacoustic imaging to assess and monitor HIFU therapy.

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4.4 **Quantitative ultrasound assessment of HIFU-induced lesions in liver**. Jeremy Kemmerer and Michael Oelze, *Bioacoustics Research Laboratory, Department of Electrical and Computer Engineering, The University of Illinois at Urbana-Champaign, Urbana, IL, 61801, jeremy.kemmerer@gmail.com.*

High-Intensity Focused Ultrasound (HIFU) is a promising modality for noninvasive therapy but challenges remain for monitoring and assessment of treatment. Quantitative Ultrasound (QUS) characterization is a potential approach for assessing the treatment of tissue with HIFU because tissue properties change with both temperature elevation and due to HIFU-induced changes in tissue structure. As part of an ongoing effort to develop these techniques, rabbit, bovine and rat liver samples were obtained and exposed to HIFU. The HIFU was produced by a 1-MHz single-element transducer (f/1.2) with intensities measured at the focus of 1600 W/cm^2. Fresh liver samples were exposed to cw ultrasound for 5-10 seconds, resulting in visible lesions. The exposure locations were guided by a clinical ultrasound scanner system.

After exposing the livers with HIFU, the liver samples were imaged with a 10-MHz single-element transducer (f/3). The resulting data were processed to obtain parametric images of attenuation, effective scatterer diameter (ESD) and effective acoustic concentration (EAC). Estimates from the treated liver samples were correlated with the visible lesion locations and surrounding tissue. Both ESD and attenuation were observed to increase in tissue slices containing lesions as compared to the surrounding tissue, with attenuation changing the most dramatically. In the rabbit liver, attenuation was observed to increase by up to 100% in treated liver regions while ESD estimates increased by up to 30%. Results were similar for rat liver and bovine liver, where ESD estimates increased up to 20% and 12% in lesion regions, respectively. EAC results were inconsistent and no trends were observed. The results of this study suggest that QUS may be useful in the noninvasive assessment of HIFU therapy.

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5. Bone

5.1 **Ultrasonic backscatter measurements of cancellous bone with and without an intervening layer of cortical bone**, Brent K. Hoffmeister,[1] Andrew P. Holt[1] and Sue C. Kaste,[2] *[1]Rhodes College, Department of Physics, Memphis, TN and [2]St. Jude Children's Research Hospital, Department of Radiological Sciences, Memphis, TN, hoffmeister@rhodes.edu.*

Ultrasonic backscatter techniques offer a potentially useful approach for detecting changes in bone tissue that occur as a result of osteoporosis. Backscatter measurements have been shown to correlate with the density, mechanical properties and microstructural characteristics of bone, depending on several factors. Most studies have been performed on excised specimens of cancellous bone with the outer layer of cortical bone removed. The goal of this study was to investigate how the presence of the cortical layer may impact ultrasonic backscatter measurements of the underlying cancellous bone tissue. Specimens of cancellous bone were prepared so that backscatter measurements could be performed in the same 1 cm 1 cm 1 cm region of interest along three different measurement directions. One direction presented an intervening layer of cortical bone to the incident ultrasonic wave

while the other two directions did not. Measurements were performed in a water bath using a 5 MHz broadband transducer. The backscatter signals were analyzed to measure the frequency averaged backscattered power returned from the region of interest. A total of 52 specimens were measured. A linear regression analysis was performed to determine the correlation between our backscatter measurements and bone mineral density as determined by x-ray CT. Measurements performed through the cortical layer yielded a correlation coefficient of 0.54. Measurements performed in the same region of interest along the other two directions that avoided the cortical layer yielded correlation coefficients of 0.51 and 0.53. We conclude that the cortical layer has a minimal effect on the correlation between backscatter measurements investigated in this study and specimen density.

5.2 **Multimode wave propagation in bovine cortical bone: parameter estimation using Bayesian probability theory**, Christian C. Anderson,[1] Takaaki Koizumi,[2] Tomohiro Nakatsuji,[2] Keisuke Yamashita,[2] Mami Matsukawa,[2] Mark R. Holland,[1] G. Larry Bretthorst[1] and James G. Miller,[1] *[1]Washington University in St. Louis, St. Louis, MO and [2]Doshisha University, Kyoto, Japan, james.g.miller@wustl.edu*.

Background: Studies have suggested that fast and slow wave propagation in cancellous bone may play a role in determining the source of the observed anomalous negative dispersion. Subsequent investigations have proposed ways to recover the ultrasonic properties of individual fast and slow waves from data acquired on cancellous bone to eliminate the artifacts that can occur when conventional analytic techniques are used to determine phase velocity and broadband ultrasound attenuation (BUA). A similar effect may occur in cortical bone. Fast and slow wave propagation in bovine cortical bone was first observed by Lakes, Yoon and Katz. More recent investigations on cortical bone have resulted in data exhibiting potential artifacts, such as negative dispersion, similar to those observed in cancellous bone.(1)

Objective: The goal of this study was to model data acquired on bovine cortical bone as the superposition of two overlapping compressional waves, a fast wave and a slow wave, and to recover the ultrasonic properties of the individual waves using Bayesian probability theory.

Methods: Data were acquired on bovine cortical bone using a pair of broadband transducers that were excited by single sinusoidal pulses at 5 and 10 MHz. When these data were analyzed using conventional phase spectroscopy and spectral subtraction techniques to obtain signal loss and phase velocity curves, negative dispersion and related apparent artifacts were observed. The data were then analyzed using Bayesian probability theory to estimate the ultrasonic properties of the individual overlapping waves. Markov chain Monte Carlo was used to construct marginal posterior probability density functions for the ultrasonic parameters and reconstruct the phase velocity and signal loss curves for the fast and slow waves.

Results: The Bayesian approach reconstructed phase velocity curves for the fast and slow waves that exhibited a positive dispersion and signal loss curves that had a linear dependence on frequency. The frequency-dependent behavior of these curves is free from the apparent artifacts exhibited by the data when analyzed conventionally.

Conclusion: This preliminary investigation of ultrasonic wave propagation suggests that for some sites in cortical bone, recovering the ultrasonic properties of individual fast and slow waves eliminates apparent artifacts that obscure the results obtained with single mode conventional analysis. These results demonstrate that Bayesian probability theory is a viable method for recovering artifact-free material properties in cortical bone as well as cancellous bone.

Supported in part by NIH R01AR057433.

(1) Koizumi T, et al. in *Proc 2009 IEEE Ultrason Symp* (abstract).

5.3 **Decomposition of two-component pulses: simulation and phantom experiment**, Keith A. Wear, *Food and Drug Administration, 10903 New Hampshire Blvd, Silver Spring, MD, 20993, keith.wear@fda.hhs.gov*.

Porous media often support the simultaneous propagation of two compressional waves (e.g., 'fast' and 'slow' waves). When cancellous bone samples are interrogated in through-transmission with broadband sources, these two waves often overlap in time. A method for measuring attenuation and velocity of the two component waves was developed. The method (1) assumes that the transfer function is the sum of two exponentially-modulated sinusoids and (2) minimizes the sum of the squared error between a model fit and the data. The method was tested for decomposing a 500 kHz-center-frequency signal containing two overlapping components: one passing through a polycarbonate plate ('fast' wave) and another passing through a cancellous-bone-mimicking phantom ('slow' wave). The method yielded estimates of attenuation slopes accurate to within 7% (polycarbonate plate) and 2% (cancellous bone phantom). The method yielded estimates of phase velocities accurate to within 1.5% (both media). The method was tested on simulated data generated using attenuation slopes and phase velocities corresponding to bovine cancellous bone. Throughout broad ranges of signal-to-noise ratio and fast-slow-wave-velocity differential, the method yielded estimates of attenuation slope that were accurate to within 10% and estimates of phase velocity that were accurate to within 5% (fast wave) and 2% (slow wave).

6. Review, Priorities and Funding of NIH Programs

6.1 **NIH/NCI,** Houston Baker, *Program Director, Imaging Technology Development Branch, Cancer Imaging Program, National Cancer Institute, NIH* (invited)

6.2 **NIH/NIBIB,** Hector Lopez, *Program Director, Division of Applied Science and Technology, National Institute for Biomedical Imaging and Bioengineering, NIH* (invited)

7. ARFI/Elasicity

7.1 **Acoustic radiation force assessment of muscular mechanical properties in a crossbred dystrophin-deficient, myostatin-null canine model,** Mallory R. Scola,[1] Joe N. Kornegay[2] and Caterina M. Gallippi,[1] [1]*Joint Department of Biomedical Engineering and* [2]*Department of Pathology and Laboratory Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27519, mrscola@unc.edu.*

*Back*ground: Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder caused by a mutation in the dystrophin gene leading to a loss of the dystrophin protein from the muscle cell membrane. Repeated cycles of muscle necrosis and regeneration result from the dystrophin deficiency, leading to severe and progressive loss of muscle mass and function. The golden retriever muscular dystrophy (GRMD) model also has a naturally-occurring dystrophin gene mutation and progressive phenotypic features analogous to those seen in DMD. Myostatin, a member of the TGF- family, is a negative regulator of muscle growth. It has been proposed that reduction or elimination of myostatin could promote muscle growth and indirectly compensate for muscle degradation in DMD. To further test the potential value of reducing myostatin, we cross bred a female GRMD carrier with semen from a whippet dog with a spontaneous myostatin gene mutation. We hypothesize that ARFI ultrasound is capable of differentiating mechanical properties of muscles caused by reduced myostatin in this crossbred canine model.

Methods: ARFI imaging was performed *in vivo* on the rectus femoris (RF) and cranial sartorius (CS) muscles of three golden retriever-whippet cross littermates with the following genotypes: (1) GRMD normal/myostatin normal, (2) GRMD/myostatin heterozygote null (Mstn+/-) and (3) GRMD/myostatin normal (Mstn+/+). Two ARFI excitation methods were employed: (1) a single 70 s ARFI excitation impulse (SP) and (2) a double excitation impulse (DP), with the two 70 s impulses administered in the same region of excitation 2 ms apart. ARFI imaging was implemented in planes transverse (Tr) and parallel (Par) to muscle fibers. Physiological motion was rejected and parametric images of peak displacement (SP) and difference in peak displacements (DP) were rendered.

Results: The GRMD/Mstn+/- RF underwent ARFI-induced displacements that were smaller (Tr:2.28 ± 1.02 m, Par:2.10 ± 1.61 m) than the control RF (Tr:3.60 ± 1.72 m, Par:2.46 ± 1.38 m; $p<0.02$, paired t-test) but larger than the GRMD/Mstn+/+RF (Tr:1.93 ± 1.19 m, Par:1.94 ± 1.41 m; $p<0.02$), suggesting an intermediate degree of stiffness in the GRMD/Mstn+/- RF. Similarly, differences in peaks in the GRMD/Mstn+/- RF were smaller (Tr:1.01 ± 0.48 m, Par:2.04 ± 1.33 m) than in the control RF (Tr:2.51 ± 1.40 mm, Par:3.30 ± 2.63 m; $p<0.02$) but larger than in the GRMD/Mstn+/+RF (Tr:0.73 ± 0.91 m, Par:1.22 ± 0.74 m; $p<0.02$), suggesting an intermediate degree of elasticity in the GRMD/Mstn+/- RF. In contrast, ARFI-induced displacements were largest in the control CS muscle (Tr:2.80 ± 0.48 m, Par:2.91 ± 0.43 m; $p<0.02$), but no significant difference ($p>0.02$) in displacement was observed in either the GRMD/Mstn+/- (Tr:1.66 ± 0.35 m, Par:1.76 ± 0.39 m) or the GRMD/Mstn+/+ (Tr:1.68 ± 0.29 m, Par:1.75 ± 0.31 m) in either plane, indicating comparable stiffness in the CS of the two dogs. Differences in peaks in the CS muscle were largest in the control dog (Tr:1.92 ± 0.56 m, Par:2.20 ± 0.70 m; $p<0.02$), and smallest in the GRMD/Mstn+/+dog (Tr:1.05 ± 0.21 m, Par:1.11 ± 0.17 m; $p<0.02$), suggesting an intermediate degree of elasticity in the GRMD/Mstn+/- CS.

Conclusion: This work demonstrates the feasibility of noninvasive ARFI imaging for tracking phenotypic features of muscle stiffness and elasticity in response to therapy in individuals affected by DMD.

7.2 **ARFI discrimination of renal fibrosis**, Mallory R. Scola,[1] So Yoon Jang,[2] Randy K. Detwiler,[3] Timothy C. Nichols,[4] Wui K. Chong,[5] Lauren M. Brubaker,[5] Melissa C. Caughey,[2] Melrose W. Fisher,[2] Sonya Whitehead[6] and Caterina M. Gallippi,[1] *[1]Joint Department of Biomedical Engineering, [2]Department of Medicine, [3]Department of Nephrology, [4]Department of Pathology and Laboratory Medicine and [5]Department of Radiology, [6]UNC Hospitals, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27519, mrscola@unc.edu.*

Introduction: Renal transplantation is the treatment of choice for most patients with end-stage renal disease but allograft failure is a serious and frequent complication. Timely treatment administration relies on early and accurate diagnosis of the cause of failure, which is currently assessed by invasive allograft biopsy. A safer, noninvasive alternative to biopsy could improve the outcome of transplantation. ARFI imaging may be relevant to detecting mechanical property changes associated with renal transplant failure. Specifically, we hypothesize that ARFI-induced displacements are smaller in fibrotic kidneys than control.

Methods: Imaging was performed *ex vivo* on freshly excised normal ($n = 1$) and diseased ($n = 1$) porcine kidneys using a Siemens SONOLINE Antares™ imaging system specially equipped for research purposes and VF7-3 transducer (Siemens Medical Solutions USA). The diseased kidney was harvested from a pig with clinically-important albuminuria (>30 g albumin/mg creatinine). In our experience this has been accompanied by histolopathological changes in kidneys consisting of glomerulosclerosis, interstitial fibrosis, tubular atrophy and mesangial matrix expansion. The transducer was mounted to a translation

stage and digital-motion controller to capture ARFI and spatially-matched B-Mode data along the midsagittal plane of the kidney. The ARFI data was spatially registered and assembled to generate one long ARFI image. Imaging was also performed *in vivo* on human volunters undergoing clinically-indicated renal transplant ultrasound with ($n = 2$) and without ($n = 7$) renal transplant biopsy for detection of rejection. ARFI and spatially-matched B-Mode images were acquired in the upper or lower pole of the transplanted kidneys. All procedures were approved by the IACUC and IRB of UNC Chapel Hill.

Results: In the normal porcine kidney, peak displacements were 5.51 ±1.2 mm, 14.36 ±8.81 mm and 60.95 ± 25.13 mm, in the renal cortex, medulla and calyces, respectively. In the diseased porcine kidney, displacements of 2.84 ± 1.20 mm, 8.11 ± 2.02 mm, and 13.62 ± 5.62 mm were measured. ARFI-induced displacements in the calyces of the normal porcine kidney were significantly larger than in either the medulla ($p<0.02$, paired t-test) or the cortex ($p<0.02$). Displacements in the calyces of the diseased kidney were larger than the displacements seen in the cortex ($p<0.02$) but not significantly different from displacements seen in the medulla ($p>0.02$). This porcine data suggests that the diseased kidney is stiffer than the normal kidney as well as more mechanically homogenous. In humans, we have preliminarily observed smaller displacements in the poles of transplanted kidneys undergoing biopsy for suspicion of rejection, but this study is ongoing.

Conclusion: ARFI-induced displacements are smaller in fibrotic porcine kidneys than controls. Significant differences in ARFI-induced peak displacement in the renal cortex, medulla and calyces were detected in the normal porcine kidney but not the medulla and calyces of the diseased porcine kidney. These results are consistent with interstitial fibrosis and suggest that ARFI could be relevant for diagnosing (fibrosis associated with) renal transplant failure.

7.3 **Comparison of beam sequence performance in an atherosclerosis-mimicking phantom**, Russell H. Behler,[1] Timothy C. Nichols,[2, 3] Elizabeth P. Merricks[2] and Caterina M. Gallippi,[1] *[1]Joint Department of Biomedical Engineering, [2]Department of Pathology and Laboratory Medicine and [3]Division of Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27519, russellbehler@unc.edu.*

Background: Acoustic radiation force impulse (ARFI) imaging has been shown for atherosclerosis characterization with a number of beam-sequencing methods. We hypothesize that beam-sequencing methods may be tailored to maximize contrast-to-noise ratios (CNRs) to highlight the composition and structure of atherosclerotic plaques. We test this hypothesis in a custom atherosclerosis-mimicking phantom.

Methods: ARFI imaging was performed in an agar-gelatin arterial mimicking phantom with two soft inclusions, 2 and 5 mm wide. ARFI imaging was performed using 300 cycle excitation pulses followed by 60 2-cycle tracking pulses. Three excitation methods were crossed with 3 tracking methods for a total of nine sequences. The three excitation methods were a single F/1.5 excitation (SP1.5), a single F/3 excitation (SP3) and two F/1.5 excitations separated by 0.8 ms (DP). The three tracking methods included single A-line receive (SRx) in the region of excitation (ROE), 4:1 parallel Rx in the ROE (ParRx) and 4:1 parallel Rx lateral to the ROE (SWEI). Contrast-to-noise ratios (CNR) were calculated for the peak displacement and recovery time images for SRx and ParRx methods and shear wave velocity images for SWEI methods. Shear-wave velocities were calculated using least squares for regions measuring 0.5 mm axially and 3 mm laterally.

Results: For the 2 mm inclusion, peak displacement CNRs were higher for the SP1.5 and SP3 excitations using SRx (4.63 and 5.26, respectively) versus ParRx tracking (2.99 and 4.02, respectively). Higher CNR associated with SRx appears due to lower axial variance in measured peak displacements. Recovery time CNRs were also higher for the SP1.5 and SP3

excitations using SRx (4.72 and 3.73, respectively) versus ParRx (1.55 and 1.31, respectively), consistent with recovery time distortion with shear wave propagation. Difference in peaks CNRs, measured using the DP excitation, were somewhat better for Srx (2.30) compared with ParRx (1.42) tracking methods. The inclusion width was overestimated more with ParRx (4.24 mm) versus SRx (3.18 mm), consistent with shear wave propagation. Shear-wave velocity CNRs were comparable for SP3 (1.94) and SP1.5 (2.27), as expected, but lower for the DP excitation (1.12), consistent with greater velocity variance. Similar results were observed for the 5 mm inclusion.

Conclusion: This work suggests that some beam sequences may be better suited to identifying certain plaque features than others and motivates further investigation on this topic.

7.4 **GPU-based real-time displacement estimation for acoustic radiation force impulse images,** Stephen J. Rosenzweig, Mark L. Palmeri and Kathryn R. Nightingale, *Duke University, Durham, NC, stephen.rosenzweig@duke.edu.*

Acoustic radiation force impulse (ARFI) images are often generated by acquiring quadrature demodulated data, which are later processed offline. The data are upsampled using cubic spline interpolation before the displacements are estimated using the Loupas phase shift algorithm and the magnitude of the complex correlation coefficient is computed. Using a Dell Precision M6400 with an Intel® Core™2 Extreme CPU Q9300 with 4 CPUs at 2.53GHz and 4GB of RAM, the Matlab implementation of the processing code requires 50 seconds for an example data set. For clinical applications, displaying the data in real-time is highly desired; thus, the adaptability of the processing code to the parallel architecture of graphics processing units (GPUs) was investigated. The above laptop has a CUDA-enabled NVIDIA Quadro FX 3700M graphics card with 1GB of memory and 128 processing cores with a clock rate of 1.40GHz. The processing code was rewritten using C for CUDA to upsample the data, perform displacement estimation and compute the magnitude of the complex correlation coefficients in a parallel environment. For the example data set, using the Matlab generated estimates as a gold standard, the CUDA processed displacement estimates had an RMS error of 0.003 μm. The total time required to process that data for displacement estimates and correlation coefficients was 0.55 seconds, a speed increase of 91x. Additionally, an image can be displayed to give immediate feedback to the user, which requires an additional 0.4 seconds, or the data can be saved for future processing in 0.55 seconds. Although the parallel GPU-based implementation can result in large speed increases compared to single-threaded CPU processing, to take full advantage of the card's architecture, it is necessary to parse the data set into 16 kB pieces that can be processed independently. Limitations of using GPU-based processing code as well as the relevance of using this processing code directly on modern ultrasound scanners, many of which include NVIDIA CUDA-enabled graphics cards, will be discussed.

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7.5 **Measurement of thermally-induced variation in liver shear modulus,** Etana Elegbe and Stephen McAleavey, *Department of Biomedical Engineering, University of Rochester, Rochester, NY 14627,elegbe@bme.rochester.edu.*

The process of tissue necrosis and coagulation as a result of thermal ablation is characterized by changes in the stiffness of the tissue. These changes are not discernible in a B-mode image, thus making standard ultrasound images inadequate in the monitoring of the ablation process. Spatially modulated ultrasound radiation force (SMURF) imaging is an elastographic

technique that determines the shear modulus of a material by using acoustic radiation force impulses to generate shear waves of a known distance apart and using motion-tracking techniques to measure the arrival time difference of the induced shear waves, allowing estimation of shear wave velocity. In this study, fresh porcine liver is submerged in 0.9% saline and thermally ablated in a water bath from 10°to 70°C while monitoring the progressive stiffening using SMURF. Thermal lesions were also induced in excised sample of porcine liver using a 2 cm Boston Scientific rf ablation electrode. The samples were ablated for 52 minutes with an average power of 5W while again, monitoring the changes in stiffness using SMURF. The results show that spatially modulated ultrasound radiation force imaging is effective in determining the shear modulus in liver tissue and thus monitoring the stiffness changes due to the thermal ablation process. Our study also indicates that between approximately 45° to 75°C, there is a rapid increase in the rate of stiffening as a function of temperature.

7.6 **Ultrasonic characterization of tissue properties and blood flow in myofascial pain syndromes**, Siddhartha Sikdar,[1] Jay P. Shah,[2] Tadesse Gebreab,[2] Robin Ortiz[2] and Lynn H. Gerber[1], *[1]George Mason University, Fairfax, VA and [2]National Institutes of Health, Bethesda, MD, ssikdar@gmu.edu*.

Chronic pain is a critical public health problem. Neck and back pain are the leading cause of job-related disability and the second leading cause of disability in the USA, costing Americans more than $50 billion each year. A vast number of patients in specialty pain management centers and 95% of people with chronic pain disorders suffer from myofascial pain syndrome (MPS). Despite its high prevalence, the underlying mechanisms are poorly undnful nodules in a taut band of skeletal muscle that are a characteristic finding in MPS. MTrPs are associated with spontaneous referred pain in symptomatic patients and are the target for current management strategies for MPS, such as dry needle therapy. Recently, our research group has developed new ultrasound imaging methods to visualize and characterize the physiology and physical properties of the MTrPs and their surrounding soft tissue.

In preliminary studies on nine subjects with acute neck pain, we utilized B-mode imaging, vibration sonoelastography (VSE) and Doppler imaging to study MTrPs and their neighborhood. Based on physical examination, four sites in each patient were labeled as either active MTrP (spontaneously-painful, A-MTrP), latent MTrP (non-painful, L-MTrP), or normal muscle. VSE was performed by color Doppler variance imaging while simultaneously inducing vibrations (~100Hz) with a handheld massage vibrator. Each site was assigned a tissue imaging score (TIS) as follows: 0 = uniform echogenicity and stiffness; 1 = focal hypoechoeic and/or stiff nodule; 2 = multiple hypoechoeic and stiff nodules. Blood flow in the neighborhood of MTrPs was assessed using Doppler imaging. Each site was assigned a blood flow waveform score (BFS) as follows: 0 = normal arterial flow in muscle with no diastolic flow; 1 = elevated diastolic flow; 2 = retrograde diastolic flow. MTrPs appeared as focal, hypoechoic regions, indicating local changes in tissue echogenicity, and as focal regions of reduced vibration amplitude on VSE, indicating a localized stiff nodule. Sites containing MTrPs were more likely to have higher TIS compared to normal muscle ($p<0.002$). Small arteries near A-MTrPs showed retrograde flow in diastole, indicating a highly resistive and compliant vascular bed, consistent with possible blood vessel compression. A-MTrP sites were more likely to have higher BFS compared to L-MTrPs ($p<0.021$).

Encouraged by these preliminary results, we have expanded our methods to include quantitative metrics for characterizing the soft tissue properties surrounding MTrPs based on the analysis of the backscattered rf ultrasound echoes and shear-wave propagation velocities. Further studies are currently underway for spectral analysis of ultrasonic echo signals for classification of MTrPs and surrounding tissue, quantification of elastic moduli and quanti-

tative analysis of Doppler spectral waveforms. We anticipate that these quantitative imaging methodologies will provide a unique opportunity to integrate physical and physiological findings to: achieve a more comprehensive understanding of the abnormalities associated with MTrPs (e.g., muscle, fascia, blood vessels); develop objective clinical outcome measures for evaluating natural history and treatment efficacy; and correlate these findings with clinical assessments to better understand the role of MTrPs in chronic pain.

7.7 **A finite-element modeling of prostate deformation for elastography**, S. Kaisar Alam,[1] Shaoting Zhang,[2] Dimitris Metaxas[2] and Ernest J. Feleppa,[1] *[1]Riverside Research Institute, New York, NY and [2]Rutgers University, New Brunswick, NJ, kalam@rri-usa.org*.

Treatments of elastography routinely have assumed a uniform planar compression applied to tissue surfaces and have used linear transducers with virtually flat surfaces. However, for prostate elastography, a cylindrical endocavity probe is used for scanning and compression. When the force is applied using a flat, relatively large surface, the stress distribution is relatively uniform close to the surface, but even in that case, the stress diverges with increasing tissue depth. This effect is exaggerated if the force is applied over a small area; the force is applied to the rectal wall by the transrectal probe in prostate elastography. Furthermore, the cylindrical shape of the probe means that applied stress rapidly decreases away from the center of the application area, unlike compression using a planar surface; this worsens the nonuniform nature of the stress distribution.

We developed a preliminary finite-element model (FEM) to simulate the compression of the prostate. The prostate is modeled as an oval-shaped organ with a homogeneous Young's modulus of 60 kPa. A stiffer tumor was modeled in the anterior region with a Young's modulus of 250 kPa. In this model, a force is applied on the rectal wall to deform the prostate. We computed strain from the resultant displacements.

Our initial results show that strain is maximal directly beneath the probe and deceases very rapidly with increasing depth as well as lateral distance. Because of this rapid drop-off in strain, lesions that are directly underneath the probe are clearly visible. Depicting a stiff lesion will be more difficult in the lower-strain areas, e.g., at larger depth and away from the lateral center.

An understanding of prostate deformation in elastography applications will help us in developing novel approaches to produce strain patterns in the prostate that facilitates visualization of lesions.

7.8 **Prostate tissue characterization by ultrasound spectral methods and elastography**, Ervis Sofroni,[1,2] Naum Papanicolau,[1,2] Sara Iraji,[1,2] Martin Yaffe,[2] Hans Chung[1] and Gregory J. Czarnota,[1,2] *[1]Department of Radiation Oncology, Sunnybrook Health Sciences Centre and University of Toronto and [2]Imaging Research, Sunnybrook Health Sciences Centre, and Department of Medical Biophysics, University of Toronto, Toronto, Canada,gregory.czarnota@gmail.com.*

Current accepted methodologies used for detection of the prostate tumor involve measurements of prostate specific antigen (PSA) levels, ultimately leading to ultrasound guided biopsies. The goal of our research study is to investigate the use of transrectal ultrasound as a noninvasive imaging modality for the detection prostate tumors using multiparameter spectroscopic analysis of the ultrasound radiofrequency (rf) signal in combination with ultrasound elastographic imaging of the prostate with correlative whole-mount histopathology after radical prostatectomy.

Ten patients with prostate cancer were subjected to transrectal conventional low-frequency ultrasound scans prior to undergoing radical prostatectomy. The scans were performed with an Ultrasonix RP ultrasound system using a transrectal biplane probe with 128

elements per plane with a 7 MHz center frequency for the linear transducer and 6.7 MHz for the curved transducer. The curvilinear transducer was used to collect equidistant (0.5 cm) transverse slices with a pulsing frequency of 10 MHz and a sampling frequency of 40 MHz for rf data collection. Planes of data were collected with the linear transducer at the center of the prostate with 20 separations using the same frequency settings. Parallel to acquiring rf data, complementary elastrography data were acquired at each step for comparison. Radical prostatectomy specimens were prepared by whole mount histopathology with specimens sliced in 0.5 cm equidistant slices perpendicular to the urethra and stained with hemotoxylin and eosin for comparison. Spectroscopic analysis[1,2] was carried out using custom software and normalized using a glass bead phantom to remove system artifacts. Analysis of the averaged power spectrum was performed using a 6 dB window and linear regression to extract the midband fit, 0-MHz intercept and the slope of the best fit line. Parametric maps were generated for each of the three spectral parameters. The spectral parameter maps, as well as the elastography map, were then compared with the histopathology images in order to measure disease detection for each of the parameters.

Preliminary results indicate that relative changes in the spectral parameters correlate to disease in the corresponding whole mount sections. A relative decrease in the mid-band fit parameter of 5-10 dBr corresponded to areas where disease was present in the whole mount sections. Spectral slope, however, was relatively invariant. A decrease in the 0-MHz intercept as an indication of the concentration of acoustic scatterers corresponded well with the whole mount histology sections. Preliminary qualitative results of the elastography data indicated areas of increased tissue stiffness in the presence of bulky prostate tumors and were validated by the presence of gross tumor in the corresponding whole mount sections.

Our preliminary data shows promise in the ability to create parametric maps both in 2D and 3D by combining multiple complementary parameters in order to achieve a high degree of accuracy in delineating areas where disease is present. The ability to calibrate and fine-tune spectral, and electrographic parameters in combination with PSA and other patient specific data can potentially lead to improvements in early noninvasive prostate cancer detection.

(1) *Cancer Biomark 4,* 201-212 (2008). (2) *J Acoust Soc Am 73*, 1366-1373 (1983).

8. Imaging

8.1 **Sources and characterization of ultrasonic imaging clutter using a nonlinear, full-wave simulation method**, Jeremy Dahl and Harshawardhan Deshpande, *Department of Biomedical Engineering, Duke University, Durham, NC, jjd@duke.edu.*

Clutter is a well known image degradation mechanism in ultrasonic imaging that is patient and organ dependent but is more prevalent in patients that are overweight or obese. In clinical settings, clutter is problematic because it obscures important anatomical details and makes physiological measurements difficult or impossible. The number of suboptimal and inadequate imaging exams has been due to the increase in overweight and obese individuals throughout the world's population in the last 20 years.

Despite widespread agreement on the sources of ultrasonic clutter, there have been very few studies on the sources of clutter and the contribution of each source to the overall clutter in the image. We have performed simulations of clutter using a nonlinear, full-wave method to demonstrate the characteristics and sources of ultrasonic clutter. In these simulations, representations of human abdominal layers, created from histological stains of actual human abdominal layers, were placed at the surface of the transducer to create realistic,

near-field, heterogeneous tissue. Variations in tissue compression, sound speeds and densities were applied to measure the effects on clutter generation. Anechoic cysts were also simulated to demonstrate the characteristics of the clutter in conventional and tissue harmonic imaging. In addition to simulations, we have performed *in vivo* experimental studies in human bladders and livers that isolate the main sources of clutter and their characteristics.

The results of both simulation and *in vivo* experiments show that clutter resulting from near-field tissue layers are spatially coherent with respect to axial motion or compression. Conversely, the same near-field clutter is shown to be incoherent in the sampled pressure field. For *in vivo* human bladder, the contribution of off-axis clutter resulting from the tails of the point-spread-function (i.e., the isochronous volume) is shown to be relatively small (<5%) compared to the contribution of clutter associated with near-field layers (approximately 68%) at the focal depth of the transmit pulse. The simulations indicate a greater amount of clutter resulting from near-field heterogeneous tissue compared to aberration or off-axis scattering. Simulations also demonstrated decreased clutter resulting from tissue compression. The results of the *in-vivo* human studies are consistent with the conclusions drawn from the simulated images of anechoic regions in that it is shown that the dominating mechanism of clutter is associated with multiple reflections in the near-field tissue layers. Clutter due to off-axis scattering dominates only when an interfering target is close to the imaging target.

This work is supported by the NIH grant R21-EB008481 from the National Institute of Biomedical Imaging and Bioengineering. In-kind and technical support was provided by the Ultrasound Division at Siemens Medical Solutions USA, Inc.

8.2 **Progress towards high-frequency annular-array imaging in real-time**, Erwan Filoux, Orlando Aristizábal, Jonathan Mamou and Jeffrey A. Ketterling, *Riverside Research Institute, Lizzi Center for Biomedical Engineering, 156 William St., New York, NY 10038, jketterling@rri-usa.org.*

Annular arrays allow for an increased depth of field with a relatively low number of array elements. We have been developing 20 and 40 MHz, five-element arrays made of PVDF and P(VDF-TrFE) piezopolymer films. The films had one electroded side and one side bonded to a copper-clad polyimide film that had an array pattern etched on its copper surface. Image data were acquired with a five-pass approach that permitted collection of all 25 transmit-to-receive element pairs. The collected data were synthetically focused to form a final image. In this talk, we describe progress towards a real-time, high-frequency annular-array imaging system. The original prototype system required about 60 seconds to acquire all of the image data prior to synthetic focusing. The current system is able to acquire the same data in 0.5 s. The current scan system also permits the implementation of coded-excitation imaging to improve the image signal-to-noise ratio, gated-imaging techniques to create effective real-time cineloops and single-element real-time imaging to position the annular arrays over a region of interest. With the current system, we are able to acquire *in vivo*, *in utero* data from gestating mouse embryos. Examples of the different imaging modes will be given, including human subject scans.

9. Ultrasound Computed Tomography

9.1 **Progress in ultrasound computed tomography**, Michael P. Andre, *Department of Radiology, VA Healthcare System, University of California, San Diego, CA, mandre@ucsd.edu* (invited overview).

Ultrasound imaging is an indispensable tool of medical imaging that has sustained remarkable growth over the past several decades. It is interesting to note that despite undergoing many significant technical advancements over this period, the basic imaging paradigm of medical ultrasound has remained unchanged; namely, image formation results from transmission-reception of 180 backscatter assuming straight-line propagation. For more than 25 years, quantitative Ultrasound Computed Tomography (USCT), which attempts to create images from both transmitted and scattered signals, has been researched by several groups mainly for breast imaging with varying degrees of success. It can be shown that conventional ultrasound imaging is actually a subset of USCT and to this end a brief historical perspective on the pioneering works of many scientists will be presented, including some present at this conference.

While modern ultrasound imaging provides a two-dimensional map of relative tissue 'echogenicity,' USCT attempts to compute quantitative three-dimensional maps of tissue acoustic properties, usually sound speed, attenuation, compressibility, scatter density, etc., as approximations of components of the wave equation. These methods account for refraction, attenuation, multiple scattering and more. Significantly, laboratory and *in vivo* measurements have suggested that in breast tissue, benign lesions and cancerous lesions may be identified by these inherent acoustic properties (particularly sound speed and attenuation). In general, due to limitations of instrumentation and algorithms, the early methods used two-dimensional linearization techniques to solve what is inherently a nonlinear three-dimensional problem that necessitates capture of a large segment of the scatter field around the object. From this early work, it is now clear that the range of tissue properties encountered in the breast is sufficiently large that linear approximations lead to severe artifacts and inadequate spatial resolution. New methods capable of implementing advanced USCT algorithms are being tested in patients and are progressing towards clinical use. A review of these new scanner systems will be presented.

In recent years, variants of such a breast scanner, developed by Techniscan Medical Systems, Inc. (Salt Lake City, Utah), were installed at the University of California, San Diego to evaluate clinical feasibility of using USCT to analyze and detect breast masses as well as monitor changes due to therapies. The current system uses a multifrequency nonlinear 3D inverse-scattering algorithm. Until very recently, the engineering technology and mathematical methods for full-wave inverse-scattering 3D tomography have been so complex that practical results in humans were not realized. To solve the numerically ill-conditioned problem of full-wave inversion, discrete frequency domain data is used by a 3D inverse-scattering algorithm that incorporates multiple scattering within and between the planes. Despite computational complexity of the problem, the method solves an accurate approximation to the full Helmholtz equation. The full inversion is now completed within approximately 30 minutes with a new GPU cluster; this is a remarkable accomplishment given the computation cost is very large. In its current form, 3D volumes of the entire breast are reconstructed as accurate maps of sound speed, attenuation and aberration-corrected reflectivity.

Additional motivation for this continued interest in USCT is that conventional breast sonography is a notoriously difficult exam to perform. The quality of the results is highly dependent on the skill of the operator as well as technical features of the scanner. In order to obtain the needed high resolution the field of view in sonography is very small, which greatly complicates interpretation and localization of a mass. USCT promises an essentially automated whole-breast scanning system that does not depend on operator expertise. Furthermore, the images present a global view of the entire breast in 3D, facilitating comparison to prior exams as well as to mammography and MRI. Several examples of clinical results will be presented.

9.2 **3D USCT II: Prototype for 3D data acquisition with a semi-elipsoidal aperture**, N.V. m, M. Zapf and H. Gemmeke, *Karlsruhe Institute of Technology, Institute for Data Processing and Electronics, Karlsruhe, Germany, nicole.ruiter@kit.edu* (invited).

Most ultrasound computer tomography (USCT) systems implement unfocussed data acquisition to reconstruct optimally-focussed reflection images by synthetic aperture post-beamforming and to achieve fast data acquisition. However, these systems are generally only unfocussed in 2D; the elevation dimension is focussed. The main drawbacks are a large slice thickness with limited depth of field, the loss of out-of-plane reflections and a large number of movement steps to acquire a stack of images of the whole volume.

A system for 3D data acquisition requires a number of transducers approximately two orders of magnitude larger than 2D systems. In order to approximate a spherical wavefront, the individual transducer area has to be small, which leads to low sound pressure and low signal-to-noise ratio (SNR). For *in-vivo* imaging, the data acquisition time has to be short to prevent patient movement.

We built a first experimental set-up for 3D USCT to investigate the feasibility of such a system. We chose a sparse aperture approach: 1,920 transducers are grouped on a cylindrical aperture (18 cm diameter, 15 cm height) and can be rotated to reduce the sparseness. Six rotations are carried out in total. Pulses of 2.4 MHz center frequency and 2 MHz bandwidth are applied. The pulse shape can be coded to increase the SNR. The resulting point spread function (PSF) is anisotropic ((0.2 mm)² 0.9 mm) due to the limited aperture height of the cylinder. As expected with a sparse aperture, the image contrast is reduced by grating lobes but the contrast could be significantly increased during reconstruction.

Our experimental 3D USCT showed that 3D data acquisition is feasible with today's technology if a sparse aperture or long DAQ times may be accepted. The next question is the clinical relevance of such a device. To answer this question, we are currently building a second generation 3D USCT setup with the main aim to image volunteers.

Based on simulations of the 3D PSF, image contrast and illumination, a more optimal aperture in form of a semi-ellipsoid is developed. The semi-ellipsoidal aperture will be equipped with 640 emitters and 1,440 receivers and can be rotated and lifted. We assume that for acceptable image contrast, 3.7 10^6 A-scans or 20 GByte have to be accumulated.

The dedicated DAQ hardware provides 480 parallel channels and 40 GB on-board memory. A minimum DAQ time of 6 s can be reached. Additional time will be needed to move the aperture and for averaging of the signals. The overall DAQ time will be well below 3 min and enable *in vivo* imaging.

The resolution and image contrast of our current system is limited by phase aberration errors and the sparse aperture. In simulations, the resolution, measured by the size and deformation of the 3D PSF, is increased by 62%. The illumination of the breast volume is approximately three times higher than for the cylindrical aperture. Artifacts are decreased by 23%. We expect a reduction of the remaining phase aberration error by temperature monitoring and shorter DAQ duration. The larger opening angle of the new transducers guarantees better speed of sound images. This new generation of 3D USCT will enable optimally-focussed imaging in 3D.

9.3 **Tomographic density imaging**, Roberto J. Lavarello and Michael L. Oelze, *Bioacoustics Research Laboratory, Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, Urbana, IL, 61801, oelze@brl.uiuc.edu* (invited).

Ultrasonic tomography is an imaging technique whose goal is to provide quantitative maps or images of acoustic properties. Algorithms have been developed to reconstruct objects in both two dimensions and three dimensions. Typically, image contrast is based on differences in speed of sound or attenuation. Usually, ultrasonic tomography methods as-

sume density is a constant in the imaging domain in order to reconstruct speed of sound and attenuation images. The present talk will address research conducted to assess the feasibility of density imaging using inverse scattering in lossless media. Two different approaches are currently available in the literature: (1) reconstructing a single functional of speed of sound and density and isolating density information using measurements at two different frequencies, and (2) simultaneously reconstructing two functionals that depend exclusively on compressibility and density changes, respectively. Both approaches suffer from limitations that keep them from being experimentally implemented, i.e., the first approach is too sensitive to the signal-to-noise ratio whereas the second approach requires a very large bandwidth. An improved method, the multiple frequency distorted Born iterative method (MF-DBIM), has been devised by refining the first approach to use multiple frequency information and frequency hopping. Although this method allows the limitations noted above for current density imaging algorithms to be overcome, for certain classes of imaging targets, the convergence of density imaging algorithms is still compromised. Regularization methods were also developed and studied through simulations and experiments in order to extend the applicability of MF-DBIM.

9.4 **Breast imaging with ultrasound tomography: clinical results at the Karmanos Cancer Institute**, Neb Duric, Peter Littrup, Cuiping Li, Lisa Bey-Knight, Olsi Rama, Steve Schmidt, Lukasz Myc, Mark Sak, Bryan Ranger, Jessica Lupinacci and Erik West, *Karmanos Cancer Institute, Wayne State University, 4100 John R. Street, Detroit, MI 48201, duric@karmanos.org (invited).*

We report on a continuing assessment of the imaging performance of an operator-independent breast imaging device based on the principles of ultrasound tomography. The data were collected with a clinical prototype at the Karmanos Cancer Institute in Detroit MI from patients recruited at our breast center. Tomographic sets of images were constructed from the data and used to form 3-D image stacks corresponding to the 3-D volume of the breast. Our techniques generated whole breast reflection images as well as images of the acoustic parameters of sound speed and attenuation. The combination of these images reveals major breast anatomy, including fat, parenchyma, fibrous stroma and masses. The three types of images are intrinsically co-registered because the reconstructions are performed using a common data set acquired by the prototype. Fusion imaging, utilizing thresholding, is shown to visualize mass characterization and facilitates separation of cancer from benign masses. These initial results indicate that operator-independent whole-breast imaging and the detection and characterization of cancerous breast masses are feasible using ultrasound tomography techniques. Clinical applications ranging from risk assessment to detection and treatment monitoring are discussed.

9.5 **Ultrasonic breast-mimicking phantom for pulse-echo and transmission imaging**, Sumedha P. Sinha,[1] Ernest L. Madsen,[2] Gary R. Frank,[2] Paul L. Carson[1] and Mitchell M. Goodsitt,[1] *[1]Radiology, University of Michigan, Ann Arbor, MI 48109 and [2]Medical Physics, University of Wisconsin, Madison, WI 53705, sumedha@umich.edu.*

Automated 3D ultrasound imaging presents good potential for breast cancer screening purposes, especially for women with dense breasts. To retain the resolution of high-frequency ultrasound, we can image the breast from both sides in the mammographic geometry, which we will refer to as dual-sided imaging. This is a novel, feasible technique for a higher-quality image formed by registering and fusing opposite views. Success in registration of dual-sided images will be complicated by low SNR (signal-to-noise ratio) and other artifacts in the central region of the breast where the two views overlap. ‘Shadows’ and ‘en-

hancements' are also prevalent in breast-ultrasound images. These artifacts are anisotropic and highly dependent on the direction of the ultrasound beam.

In order to eventually achieve successful registration of dual-sided *in-vivo* images, we have adopted a multi-step approach, beginning with the simpler, reproducible case of a breast-mimicking phantom containing 39 cancer-like and cyst-like lesions. This phantom simulates the breast compressed in the mammographic cranio-caudal geometry. It is a rectangular solid (length = 18 cm, width = 8.5 cm, height = 6.4 cm), with a 5 cm thick lesion-embedded slab sandwiched between two 7 mm thick aberrating layers. The phantom is bounded by acrylic walls and the scanning windows on the top and bottom are covered with 25 μm thick Saran wrap.

The fat and glandular-mimicking materials are oil-in-gelatin dispersions, while the lesions contain no oil. There are two types of glandular material having slightly different sound speeds. The tissue-mimicking fat has an even lower speed. The oil produces a lowered propagation speed and density and contributes to attenuation. The single hyperechoic lesion contains water-based gelatin with powdered graphite and glass beads (45-53 μm in diameter). The tissue-mimicking subcutaneous fat layers have scalloped surfaces in order to create refraction effects simulating those in an actual human breast. The geometric simplicity of this refracting layer allows for the quantitative analysis and correction of refraction errors.

The 39 lesions are exactly positioned in the tissue-mimicking glandular region. Each zone contains at least four 'cancers' and four 'cysts.' Also, two large double-cone shaped 'cancers,' one large spherical 'cyst' and one large hyperechoic spherical 'cancer' have been included in this phantom. Randomly-positioned knots on three 0.3 mm diameter nylon fibers in the central area of the phantom create more echogenic structural elements. A small (1% by volume) concentration of formalin raises the melting point of the materials (by means of formaldehyde cross-linking) to 100°C and a 5% concentration of 1-propanol is added for preservation.

The first version of this phantom was designed with acoustic properties that appear in the ultrasound literature and was found to produce minimal shadow artifacts. A second phantom with substantially greater contrast in speed of sound, using recently published values from ray-traced ultrasonic CT[(1)] produces image shadows similar to those often seen *in vivo*. This experience helps explain why transmission images of attenuation are so edge enhanced. That is where much or most of the differential attenuation occurs.

(1) In *Medical Imaging 2008: Ultrasonic Imaging and Signal Processing, Proc SPIE,* pp. 692009-692009-9 (2008).

10. Advaced Transducer Technology

10.1 **Transducers for 3-D imaging**, Jesse T. Yen, *USC Viterbi School of Engineering, Department of Biomedical Engineering, 1042 Downey Way University Park, Denney Research Building (DRB) 140, Los Angeles, CA 90089-1111, jesseyen@usc.edu* (invited overview).

This talk will present an overview of the development of array transducers for 3-D imaging. Depending on the clinical application, 2-D matrix arrays from a few hundred elements to more than several thousand elements may be needed. Fabrication of transducers for 3-D imaging faces a number of challenges, primarily the electrical element impedance and interconnect density. The severity of these problems grows as the number of elements grows. For 2-D array elements, their small size leads to high electrical impedance, on the order of

several k , which translates to low pulse-echo sensitivity. The interconnect complexity can have adverse effects on interelement cross talk and pulse-echo performance. Solutions to these challenges by various researchers will be presented. These solutions come in the form sparse arrays, multilayer transducers and fully-sampled matrix arrays with application-specific integrated circuits (ASIC).

Developing sparse array transducers is the most straightforward, since the interconnect requirements are relaxed, but electrical element impedance can still be quite high. The use of multilayer transducers can minimize this problem by reducing the impedance by a factor of N^2 where N is the number of layers. However, multilayer transducers have challenging interlayer connection requirements. Fully-sampled arrays for cardiac and obstetrics have been developed where most of these 2-D arrays have less than 5,000 elements. These probes use custom integrated circuits in the handle to funnel thousands of elements from a fully connected 2-D phased array to 128 system channels. The advantages and disadvantages of these solutions will be presented.

10.2 **Design, integration and use of special ultrasonic transducers for therapeutic guidance and diagnosis**, Douglas N. Stephens, *Dept. of Biomedical Engineering, 451 Health Sciences Dr., GBSF Building, University of California, Davis, Davis, CA 95616, dnstephens@ucdavis.edu* (invited).

10.3 **Forward-looking intracardiac echocardiography catheters using capacitive micromachined ultrasonic transducers**, Amin Nikoozadeh,[1] Ömer Oralkan,[1] Mustafa Gencel,[1] Jung Woo Choe,[1] Douglas N. Stephens,[2] Alan de la Rama,[3] Peter Chen,[3] Kai Thomenius,[4] Aaron Dentinger,[4] Douglas Wildes,[4] Kalyanam Shivkumar,[5] Aan Mahajan,[5] Matthew O'Donnell,[6] David Sahn[7] and Pierre T. Khuri-Yakub,[1] *[1]Stanford University, Stanford , CA 94305, [2]University of California, Davis, CA 95616, [3]St. Jude Medical, Irvine, CA 92614, [4]General Electric Global Research, Niskayuna, NY 12309, [5]University of California, Los Angeles, CA 90095, [6]University of Washington, Seattle, WA 98195 and [7]Oregon Health and Science University, Portland, OR 97239, aminn@stanford.edu* (invited).

Atrial fibrillation is the most common type of cardiac arrhythmia that now affects over 2.2 million adults in the United States alone. Currently, fluoroscopy is the common method for guiding interventional electrophysiological (EP) procedures. However, the radiation exposure involved with the fluoroscopy is hazardous to both the patient and the physician. In addition, it does not provide good soft-tissue resolution, even with the use of contrast agents. In recent years, intracardiac echocardiography (ICE) has proven valuable in real-time guidance of interventional procedures and reducing fluoroscopy exposure time.

We are developing two types of forward-looking ICE catheters using capacitive micromachined ultrasonic transducer (CMUT) technology: Microlinear (ML) catheter and ring catheter. The ML catheter uses a 24-element 1-D CMUT array at the tip for forward-looking phased-array imaging. It provides high-resolution, real-time, 2-D images at a center frequency of 10 MHz. The ring catheter has a 64-element ring CMUT array at the tip that operates at a center frequency of 10 MHz. It provides 3-D, real-time, forward-looking images in front of the catheter tip. In addition, the ring catheter provides a continuous central lumen that runs though the whole length of the catheter. This available space enables convenient delivery of a variety of other devices such as rf ablation catheters, EP diagnostic catheters, biopsy devices, etc. Both the ML and the ring catheters are equipped with front-end electronic circuits that are closely integrated with the CMUT arrays at the tip of the catheter. The custom-designed integrated circuit (IC) is fully compatible with current imaging systems and provides a dedicated preamplifier for each transducer element. The preamplifiers mitigate the adverse effect of long microcoaxial cables on the received signals and improve the

image quality. The first ML and ring catheters are assembled in a 9-F and 12-F catheter shafts, respectively.

In a recent animal study, we demonstrated *in-vivo* images of the heart in a porcine animal model using both catheters. With the ring catheter we also demonstrated 3-D imaging capability using metal spring and nylon wire phantoms. In addition, we used the ring array in a bench-top setup to demonstrate photo-acoustic imaging with a single optical fiber integrated with the ring array through its inner lumen. We have successfully prototyped the first forward-looking catheters based on the CMUT technology and proven the capabilities of this technology for implementing high-frequency miniature transducer arrays with integrated electronics.

This work was supported by the National Institutes of Health under grant 5R01HL067647. IC fabrication was provided by National Semiconductor (Santa Clara, CA).

10.4 **Imaging arrays with improved transmit power capability**, M. J. Zipparo,[1] K. F. Bing[2] and K. R. Nightingale,[3] *[1]W. L. Gore and Associates Inc., 345 Inverness Dr. South, Suite A120, Englewood, CO 80112, [2]Georgia Tech Research Institute, Sensors and Electromagnetic Applications Lab, Atlanta, GA 30332 and [3]Duke University, Department of Biomedical Engineering, PO Box 90281, Durham, NC 27708, katy.nightingale@duke.edu* (invited).

Bonded multilayer ceramics and composites incorporating low loss piezoceramics have been applied to arrays for ultrasound imaging to improve acoustic transmit power levels and to reduce internal heating. Commercially-available hard PZT from multiple vendors has been characterized for microstructure, ability to be processed and electroacoustic properties. Multilayers using the best materials demonstrate the tradeoffs compared to the softer PZT5-H typically used for imaging arrays. Three-layer PZT4 composites exhibit an effective dielectric constant that is three times that of single layer PZT5H, a 50% higher mechanical Q, a 30% lower acoustic impedance and only a 10% lower coupling coefficient. Application of low-loss multilayers to linear-phased and large curved arrays results in equivalent or better element performance. A 3-layer PZT4 composite array achieved the same transmit intensity at 40% lower transmit voltage and with a 35% lower face temperature increase than the PZT-5 control. While B-mode images show similar quality, acoustic radiation force impulse (ARFI) images show increased displacement for a given drive voltage. An increased failure rate for the multilayers following extended operation indicates that further development of the bond process will be necessary. In conclusion, bonded multilayer ceramics and composites allow additional design freedom to optimize arrays and improve the overall performance for increased acoustic output while maintaining image quality.

10.5 **Micromachined single crystal 1-3 composite transducers**, X. Jiang[1] and S. Zhang,[2] *[1]North Carolina State University, Departments of [1]Mechanical and Aerospace Engineering and [2]Biomedical Engineering, Raleigh, NC 27695 and [2] Pennsylvania State University, University Park, PA 16803, xjiang5@ncsu.edu* (invited).

Single crystal piezoelectric materials showed excellent properties for medical ultrasound transducers though research challenges exist in improving phase transition temperature and coercive field.(1) Challenges also exist in fabricating single crystal transducers using conventional dicing technique, especially for high frequency 1-3 composite transducers. We will present new developments on single-crystal piezoelectric transducer materials and the results on a new single-crystal etching technique for transducer fabrications. Ferroelectric single crystals PIN-PMN-PT and PMN-PZT (ternary crystals), retaining high piezoelectric properties of PMN-PT single crystals (binary crystal) but with enhanced temperature stabil-

ity (limited by their rhombohedral to tetragonal phase transition temperature). The phase transition temperature for the new ternary crystals is on the order of 95-150ºC, 30 to 60ºC higher than their binary counterparts; furthermore, the coercive field of the above ternary systems are found to be 4-5kV/cm, double the value of PMN-PT. These new single crystals present great potential for medical ultrasound. For single-crystal transducer fabrications, the recently-discovered piezoelectric-composite-based micromachined ultrasound transducer (PC-MUT) technique utilized deep reactive ion etching (RIE) to form high-aspect-ratio PMN-PT posts without mechanical interaction induced damage and the high-frequency 1-3 composites (15-75 MHz) were successfully fabricated with coupling coefficient of ~ 0.65-0.75.[(2)] High-frequency linear arrays using PC-MUT composites were also studied for medical and NDE imaging. The following progressive results will be presented: (1) 15-75 MHz PMN-PT single crystal 1-3 composite transducer design, fabrication and characterizations. A bandwidth > 80% and significantly-improved sensitivities were obtained from the developed PC-MUT single-element transducers; (2) high-frequency PC-MUT array design, fabrication and characterization. A 64-element, 35 MHZ PC-MUT array was prototyped and characterized, showing promising uniformity, bandwidth and sensitivity. Future research on single crystals and PC-MUT will also be discussed.

(1) In *Handbook of Advanced Dielectric, Piezoelectric and Ferroelectric Materials – Synthesis, Characterization and Applications,* pp.130-157 (2008). (2) Jiang N, et al., in *Proc IEEE Ultrason Symp* (2006).