ABSTRACTS

1. Imaging

1.1 **Comparative resolution, gain and depth-of-field measurements in B-mode and short-lag spatial coherence images**, Muyinatu A. Lediju, Jeremy Dahl and Gregg E. Trahey, *Duke University, Durham, NC, muyinatu.lediju@duke.edu.*

The spatial coherence of backscattered ultrasound waves is predicted by the van Cittert Zernike Theorem. This theorem is the basis for the derivation of spatial coherence functions as the Fourier transform of the square of the product of a source function (or target) and the lateral transmit beam pressure. Experimentally, spatial coherence functions are displayed as the average post-delayed correlations between rf echoes received by individual elements, as a function of element separation, or element lag. We utilize information in the first few lags of spatial coherence functions to implement a novel technique termed Short-Lag Spatial Coherence (SLSC) imaging.

The theory was implemented to predict the expected spatial coherence of a variety of source functions, including lesions, sine waves with a range of frequencies and step targets. Field II was used to simulate received channel signals from these same imaging targets. Experimental phantom and clinical individual channel signals were acquired using the Axius Direct Diagnostic User Interface (Siemens Medical Solutions USA, Inc., Issaquah, WA), in conjunction with a synthetic receive-aperture technique. Spatial-coherence functions were computed for short lags (typically 1-30% of the transmit aperture). The resulting SLSC function computed at each axial and lateral resolution cell was summed and the summed values were displayed as SLSC images. For simulation and experimental data, matched B-mode images were constructed with the same individual channel data using conventional delay-and-sum methods. Resolution was measured via the numerical differentiation of step targets and the autocorrelation of image texture (i.e., speckle in B-mode images). Results from the various sine-wave input frequencies were used to create SLSC image transfer functions. SLSC images show better resolution than B-mode images for most short-lag values. Transfer function results revealed that SLSC images and B-mode images have comparable gain at the focus for most input frequencies, with theory and simulations having notable agreement. We also report on SNR as a function of depth in matched simulated and experimental B-mode and SLSC images.

1.2 **Harmonic coherence imaging using short-lag spatial coherence: demonstration of basic principles and experimental and simulation results**, Jeremy J. Dahl,[1] Gianmarco F. Pinton[2] and Gregg E. Trahey,[1] *[1]Department of Biomedical Engineering, Duke University, Durham, NC and [2]Institut Langevin, ESPCI, Paris, France.*

Short-lag spatial coherence (SLSC) imaging is a new imaging technique that is based on the coherence of backscattered waves at small spatial separations. The primary application of SLSC imaging is clutter reduction, although SLSC imaging typically shows favorable imaging characteristics such as improved contrast-to-noise ratio (CNR) and signal-to-noise ratio (SNR) compared to conventional B-mode imaging even when no noise is present. SLSC images are formed by integrating the spatial coherence function over the short-lag region. Image clutter, which appears as an omnidirectional source in the backscatter, has low spatial coherence and is thus suppressed. Conventional harmonic imaging methods also suppress image clutter, although the mechanism is entirely different. Harmonic imaging methods suppress clutter because the harmonic signals are generated further downstream from tissue layers that potentially trap the acoustic pulse and produce reverberation clutter.

Conventional harmonic imaging, however, is not mutually exclusive to SLSC imaging and therefore the two techniques can be combined.

We introduce a harmonic version of the SLSC imaging (HSLSC) technique. Because the same signals that are used to construct B-mode images are also used to construct SLSC images, the benefits obtained with harmonic imaging are also applicable to SLSC imaging. We compare the characteristics of fundamental and harmonic spatial coherence functions and demonstrate the effects of aberration and clutter on these functions using a full-wave, nonlinear acoustic (FWNA) simulation method. In addition, we use the FWNA simulator to compare B-mode, harmonic B-mode, SLSC and HSLSC imaging in a variety of imaging tasks, including lesion detectability both with and without realistic models of human abdominal layers and in models of heart chambers. We also demonstrate HSLSC imaging in tissue-mimicking phantoms and human liver. On average, SLSC and HSLSC yielded better detectability than their B-mode counterparts while the harmonic imaging modes yielded better detectability than the fundamental imaging modes. For example, in the heart chamber model, a potential thrombus with -12 dB magnitude relative to the chamber wall demonstrated a CNR of 0.36, 1.26, 1.38 and 2.32 in the fundamental B-mode, fundamental SLSC, harmonic B-mode and HSLSC images, respectively. The speckle SNR of the thrombus was 2.07, 2.70, 1.59 and 2.55 for the same imaging modes, respectively. We conclude that HSLSC imaging is a viable imaging method for clutter reduction and can improve the performance of SLSC imaging by minimizing the impact of clutter in the backscattered signals. Supported by NIH grant R21-EB008481 from the National Institute of Biomedical Imaging and Bioengineering. In-kind and technical support provided by the Ultrasound Division at Siemens Medical Solutions USA, Inc.

1.3 **Performance evaluation of short-lag spatial coherence imaging in the presence of acoustical noise**, Marko Jakovljevic, Dongwoon Hyun, Gregg Trahey and Jeremy Dahl, *Duke University, Durham, NC.*

We have recently developed a novel beamforming technique called short-lag-spatial-coherence (SLSC) imaging and applied it to suppress the effects of clutter in ultrasound images. The images are formed by utilizing small spatial differences in the coherence function of backscattered ultrasound. In this paper, we utilize simulations to evaluate the performance of SLSC imaging under different noise levels and compare it to the conventional B-mode imaging. Specifically, simulations in Field II, a linear acoustic simulation method and a full-wave nonlinear acoustic (FWNA) simulation method were used to demonstrate the detection of lesions of varying sizes and contrasts with and without acoustical interference in the backscattered data. In addition, *in vivo* data was acquired on human liver vasculature where the acoustical noise level varied across the patients.

Matched SLSC and B-mode images were formed from the simulated and *in vivo* data and image contrast, CNR and SNR were calculated. Simulation results show that in noise-free conditions, B-mode and SLSC images are nearly equivalent in lesion detection, based on the contrast-to-noise ratio (CNR) of the lesion. However, SLSC images have higher contrast and CNR than their B-mode counterparts with the addition on acoustical clutter. This is due to the fact that SLSC suppresses incoherent echoes arising from the acoustical clutter. The image quality metrics of *in vivo* images are consistent with those of simulation images. SLSC images show better visualization of liver vasculature in the presence of clutter while in some cases they indicate the presence of the structures not visible in the B-mode images. We also discuss the potential applications, limitations, and tradeoffs of SLSC imaging. Supported by NIH grants R21-EB008481 from the National Institute of Biomedical Imaging and Bioengineering and R01-CA114093-04S1 from the National Cancer Institute. The au-

thors wish to thank the Ultrasound Division at Siemens Medical Solutions USA, Inc. for their in-kind and technical support.

1.4 **Super-resolution imaging of a large number of scatterers using time reversal and MUSIC**, Yassin Labyed and Lianjie Huang, *Los Alamos National Laboratory, Mail Stop D443, Los Alamos, NM 87545,yassin@lanl.gov.*

In time-reversal ultrasound imaging, point scatterers or unknown targets smaller than the ultrasound wavelength are sequentially probed using N transducer elements and the backscattered signals are measured at the N element locations. This system is characterized at each frequency by the transfer matrix $K_{i,j}$, with i and j ranging from 1 to N. The transfer matrix is used to compute the Hermitian time reversal matrix $T=K^{\dagger} K$ whose nonzero eigenvalues can be shown to correspond in a one-to-one manner with the different targets. Furthermore, the eigenvalues are proportional to the reflectivities of the targets. In particular, exciting the array by one of the eigenvectors focuses the generated wavefield on the associated target. Therefore, if the diffraction impulse response for each element is known for the medium in which the targets are embedded, an image of the target locations can be generated. Using Multiple Signal Classification (MUSIC) in conjunction with time-reversal processing has been shown to yield images with subwavelength resolution.

Previous studies on time-reversal and MUSIC imaging were conducted only for the case where the number of targets is smaller than the number of transducer elements. In addition, the diffraction impulse responses of the transducer elements were approximated with the Green's function of the background medium. We develop a new technique based on time reversal and MUSIC for detecting scatterers when the number of imaging targets is larger than the number of transducer elements. Our new imaging method is based on dividing the image plane into subregions and calculating the time reversal matrix from the windowed backscattered signals originating from each subregion. We further improve image resolution using the diffraction impulse responses of the transducer elements.

Computer simulations and experiments with a synthetic aperture linear array on phantoms containing glass microspheres showed that when the number of targets is larger than the number of transducer elements, a single eigenvector no longer focuses ultrasound energy on one single target but rather on several targets with an efficiency that is quantified by the associated eigenvalue. However, our new technique can locate all the targets and provide images with a resolution of approximately /12. In addition, highly accurate selective focusing on each target is achieved. The results also showed that compensating for the transducer elements impulse responses decreases the errors in target localization and improves image resolution. Supported by the Breast Cancer Research Program of DoD Congressionally Directed Medical Research Programs.

1.5 **Imaging small targets using synthetic-aperture ultrasound,** Lianjie Huang,[1] Yassin Labyed,[1] Michael Williamson,[2] Robert Rosenberg,[2] Philip Heintz[2] and Daniel Sandoval,[2] *[1]Los Alamos National Laboratory, Los Alamos, NM 87545 and [2]Department of Radiology, University of New Mexico, Albuquerque, NM 87131, ljh@lanl.gov.*

We investigate the capabilities of synthetic-aperture ultrasound for imaging small targets using an investigational system from InnerVision Medical Technologies. Current clinical ultrasound lacks of the capability of imaging small targets such as breast microcalcifications. Synthetic-aperture ultrasound has recently developed as a promising tool to improve the capabilities of medical ultrasound.

Microcalcifications are tiny specks of mineral deposits (calcium). They are the first sign of breast cancer in more than 30% of all cases. For example, ductal carcinoma in situ (DCIS) represents approximately 20% of all breast cancers detected by mammography and approxi-

mately 95% of all DCIS is diagnosed because of mammographically-detected microcalcifications. The size of breast microcalcifications ranges approximately from 0.1 mm to 0.5 mm. They can be scattered throughout the mammary gland, or occur in clusters. They may or may not be associated with a tumor; therefore, they must be detected and characterized accurately according to their size, number, distribution and morphology to determine if they are benign or malignant.

We use two different tissue-equivalent phantoms to study the imaging capabilities of InnerVision DAS009, a real-time synthetic-aperture ultrasound system, for imaging small targets. The center frequency used is either 5 MHz or 8 MHz. The two phantoms contain line targets with a diameter of 0.05 mm. We use InnerVision DAS009 to image the two phantoms and compare the results with those obtained from clinical scanners Acuson Sequoia 512 and Siemens S2000. In addition, we investigate the imaging capabilities of synthetic-aperture ultrasound using each physical element or virtual source of phased multi-elements to emit unfocused ultrasound. We will use InnerVision DAS009 for *in vivo* studies of breast microcalcification detection. Supported by the Breast Cancer Research Program grant #BC085221 of the U.S. DoD Congressionally Directed Medical Research Programs.

1.6 **Quantitative tracking of tendon motion from ultrasonic images using curved M-mode**, Paul Otto,[1] Lindsey Curatalo,[2] Avinash Eranki,[1] Laura Prosser,[2] Diane Damiano,[2] Katharine Alter[2] and Siddhartha Sikdar,[1,3] *[1]Department of Electrical and Computer Engineering, George Mason University, Fairfax, VA 22030 and [2]Functional and Applied Biomechanics Section, Rehabilitation Medicine Department, National Institutes of Health, Bethesda, MD 20892, ssikdar@gmu.edu.*

Background: Neurological diseases such as cerebral palsy (CP) lead to gait impairments. Footdrop is one impairment where the patient is unable to adequately perform ankle dorsiflexion (i.e., lift their toes). Patients attempt to compensate for this by flexing or circumducting their hip to achieve better toe clearance during the swing phase of gait but may still catch their toes leading to tripping and falling. Typical treatment for footdrop includes ankle orthoses that block plantarflexion throughout the gait cycle. Functional electrical stimulation is an alternative to traditional ankle orthoses that delivers surface electrical stimulation to the common peroneal nerve to provide dorsiflexion during the swing phase of gait without limiting plantarflexor power. Traditionally, joint kinematics, dynamometry and electromyographic data have been used as clinical outcome measures for assessing footdrop. Quantitative methods for direct measurements of tendon kinematics may lead to improved clinical outcome measures. In recent years, ultrasound imaging (US) has become an important tool for direct assessment of length, shape and deformation of muscles and tendons. There is a need for validated methods that can be used in an office-based setting using commercially-available equipment.

Objective: The objective of this study is to validate an US-based algorithm for tendon tissue tracking that can be used with conventional real-time B-mode imagery. Our algorithm tracks tendon motion in a curved M-mode image generated by resampling the ultrasound images along the tendon using a parametric curve. This semi-automatic method enables a quantitative characterization of motion along the length of the tendon.

Methods: Children and adolescents ($N = 7$) with spastic CP who ambulate independently with no assistive device (Gross Motor Function Classification Scale level I & II) were evaluated. All participants had unilateral footdrop as determined by clinical observation of barefoot walking. The patients were seated in an upright position and asked to perform repeated dorsiflexion and relaxation. The tibialis anterior tendon was imaged using an Ultrasonix SonixTouch US system and a 5-14 MHz linear array transducer. The US transducer was sta-

bilized over the tendon using a custom Neoprene cuff. Simultaneously, the ankle joint motion was monitored using a Vicon 612 3D motion capture system.

The reconstructed B-mode image sequence was analyzed offline using Matlab. The tissue-motion detection method can be divided into two steps: resampling followed by motion estimation. We modeled the tendon using a curved spline with equally-spaced sample points. This spline is user selectable and placed over the tendon in the ultrasound image. The US image sequence is then resampled at equally-spaced points along the spline to generate a curved M-mode image. The tendon motion in this curved M-mode image is quantified by speckle tracking using a normalized cross-correlation to generate a time series of the tendon motion. This time series was then compared with the time series of the ankle joint angle acquired using 3D motion capture for validation. The linear velocity of the tendon and the corresponding joint angular velocity during dorsiflexion was computed as the slope of the tendon displacement and joint angle time series, respectively.

Results and discussion: The linear tendon velocities measured using US showed good correlation with the joint angular velocities measured using 3D motion capture ($R^2 = 0.86$ for linear regression for pooled data over multiple trials). The slope of the linear regression was nearly identical for all seven subjects. The standard deviation of the linear regression slope for each patient was found to be 0.08 for a mean of 0.7, suggesting that the functional radius of movement is approximately the same for all patients. These results show that the linear tendon velocity can be used as a surrogate measure for joint angle kinematics. The current standard for gait analysis is 3D motion capture, which requires a specialized gait lab and expensive equipment. Our results indicate that monitoring of tendon kinematics using conventional ultrasound equipment can be used as a surrogate measure. Furthermore, our method enables parametric modeling of the tendon kinematics. We are working on incorporating our methods into a portable US system that can monitor tendon kinematics during gait. Supported in part by Grant Number 0953652 from the National Science Foundation and the intramural research program at the National Institutes of Health Clinical Center.

1.7 **FDA-approved smartphone ultrasound system**, William D. Richard,[1, 2] David M. Zar,[1-3] Sailesh Chutani[3] and Roman Solek[4]   *[1]Washington University in St. Louis, One Brookings Drive, St. Louis, MO 63021, [2]Z&R Technologies, L.L.C., 282 Birchwood Crossing Lane, Maryland Heights, MO 63043, [3]Mobisante, Inc., 16625 Redmond Way, Suite M, Redmond, WA 98052 and [4]Interson Corporation, 7026 Koll Center Parkway, Suite 201, Pleasanton, CA 94566, wdr@wustl.edu.*

The first FDA-approved smartphone ultrasound system is a complete ultrasound system requiring no external batteries or accessories to image in real time anywhere in the world. The entire system consists of a generic Microsoft Windows Mobile smartphone and a Universal Serial Bus (USB) ultrasound probe. The probe connects directly to the smartphone via a passive USB cable, drawing less than 100 mA at 5V, or ½ W, allowing a runtime of up to 90 minutes (or a full day of typical use). Since more than 90% of the world's population lives within range a cell tower, practitioners in remote areas can instantly share diagnostic images with colleagues around the globe. We briefly review the system architecture, describe the user interface and present clinical images obtained using the system. Supported in part by Microsoft Research through the Cell Phone as a Platform for Healthcare initiative.

1.8 **High-resolution ultrasonic method for 3D fingerprint imaging**, R.Gr. Maev, F. Severin and Moen Uddini, *The Institute for Diagnostic Imaging Research, 688 University Avenue W. Windsor, Ontario, CANADA N9A 5R5, seviarzy@uwindsor.ca.*

This work introduces a newer development of the ultrasonic fingerprint imaging for biometrics purposes. The proposed method includes high-resolution pulse-echo scanning

with a spherically-focused 50 MHz acoustic lens. This allows us to obtain a 3D set of acoustic data that can be used for both fingerprints identification and tissue examination. Further processing includes noise reduction and its presentation in a form of B- and C-scans. This gives total control over the visualization options. Internal structure of the near sub-skin region can be reconstructed and analyzed. In particular, the distribution of the sweat pores (which are located along the ridges) can be easily visualized by setting the C-scan gate on proper depth under the skin surface. The optimized setups, acoustic parameters of the system, signal and image processing options are discussed thorough. As result, obtained acoustic images could be used as a recognizable source of information in tissue characterization and biometric identification.

1.9 **Characterization of the spatial resolution of different high-frequency imaging systems using a novel anechoic-sphere phantom**, Erwan Filoux,[1] Jonathan Mamou,[1] Orlando Aristizabal[2] and Jeffrey A. Ketterling,[1] *[1]Riverside Research, Lizzi Center for Biomedical Engineering, 156 William Street, New York, NY 10038 and [2]Skirball Institute of Biomolecular Medicine, New York University School of Medicine, 540 First Avenue, New York, NY 10016.*

The spatial resolution of high-frequency ultrasound (HFU, >20 MHz) imaging systems is usually determined using wires perpendicular to the beam. Recently, two tissue-mimicking phantoms (TMPs) were developed to estimate the three-dimensional (3D) resolution. Each of the TMPs contained randomly-distributed anechoic spheres with diameters ranging from 0.1 to 1.09 mm. The ability of an HFU system to detect these spheres against a speckle background provides a realistic estimation of its 3D spatial resolution. In the present study, these TMPs were used with HFU systems using single-element transducers, linear arrays and annular arrays. The TMPs were scanned using a VisualSonics(tm) Vevo 770 and Vevo 2100 and a custom HFU system based on a 5-element annular array. All transducers had a nominal center frequency of 40 MHz and similar axial and lateral resolutions. Results obtained with the custom system, using synthetic focusing and chirp-coded excitation, were compared to those of the Vevo systems in terms of sphere detection, i.e., 3D spatial resolution, and contrast-to-noise ratio (CNR). Resulting B-mode images indicated that only the annular-array transducer was able to detect the 0.2 mm spheres over at least 7 mm within the phantoms. The annular array excited by a chirp-coded signal provided images of the highest contrast, with a maximum CNR of 1.8 at the focus, compared to 1.3 when using impulse excitation and 1.6 with the single-element transducer and linear array. These results showed that the axisymmetrical radiation pattern of annular arrays provide improved detection capabilities compared to linear arrays when imaging *in-vivo* structures in tissues.

2.   Quantitative Ultrasound 1

2.1 **Acoustic microscopy imaging of breast tumors**, E. Yu. Maeva and I. Seviaryna, *Institute for Diagnostic Imaging Research, University of Windsor, 401 Sunset Ave., Windsor, Ontario N9B 3P4 Canada, seviary@uwindsor.ca.*

At surgery time, surgeons sometimes have difficulty determining if they achieved an adequate margin of normal tissue around the excised tumor. Methods of Scanning Acoustic Microscopy (SAM) were used to visualize structures in thickly-sliced not-fixed or fixed/not-stained specimens. Specimens of human breast containing ductal carcinoma tumors with 2–3 cm lateral dimensions and 2–4 mm thicknesses were examined by pulse-echo scanning acoustic microscopes with 25-100 MHz spherically-focused lenses. Two different acoustic microscopes working in sound speed, sound attenuation and acoustic impedance modes

were used. By selectively gating the reflected signal, the images of the internal tissue structures were obtained and three-dimensional analysis of the samples was performed. Compared with subsequently-prepared conventional permanent slides from the same specimens, the acoustic images show good correlation of disease-free margins. The obtained results prove SAM potentials as an adjunctive method for pathologists to rapidly determine tumor size and resection margin status during intraoperative consultation and provide more complete specimen assessment during gross examination.

2.2 **Detection of metastases in dissected lymph nodes of colorectal, gastric and breast-cancer patients using high-frequency ultrasound**, Ernest J. Feleppa,[1] Jonathan Mamou,[1] Emi Saegusa-Beecroft,[2] Alain Coron,[3] Michael Oelze,[4] Tadashi Yamaguchi,[5] Junji Machi,[2] Masaki Hata,[2] Eugene Yanagihara[2] and Pascal Laugier,[3] *[1]Riverside Research, New York, NY, [2]University of Hawaii and Kuakini Medical Center, Honolulu, HI, [3]Université Pierre et Marie Curie and CNRS, Paris, France, [4]University of Illinois, Urbana Champaign, IL and [5]Chiba University, Chiba, Japan.*

A reliable means of detecting metastases in regional lymph nodes is essential for accurate staging of cancer and effective planning of therapy. Current standard time-consuming histopathology methods appear to have high false-negative rates for metastases that are 2 mm or smaller. We have been investigating high-frequency (HF) quantitative ultrasound (QUS) methods to provide a rapid and reliable means of detecting metastases in dissected nodes based on their ultrasound-scattering properties.

We acquired HF ultrasound and histological data from lymph nodes dissected from patients with colorectal, breast, gastric and other cancers. Freshly-dissected nodes were scanned in a saline water bath using a raster pattern to acquire 3-D rf echo-signal data. Scans utilized a broadband, F-2, 25.6-MHz, single-element transducer with scan vectors separated by 25 μm in *x* and *y* 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 more than 240 nodes, including abdominal nodes of colorectal and gastric cancer patients and axillary nodes of breast-cancer patients. 3-D images generated from rf data were segmented semiautomatically to select nodal tissue for analysis. Echo signals from nodal tissue were processed to yield QUS estimates, which included B-mode envelope-signal statistical features. Different histological node architectures were observed and different QUS results were obtained for abdominal compared to axillary nodes.

Linea- 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. Classification performance was assessed for individual estimates and various linear combinations of estimates. ROC results for axillary as well as abdominal nodes showed excellent classification. For abdominal nodes, the areas under the ROC curves approached 1.0 for a combination of all QUS estimates. Slightly- poorer results were obtained for axillary nodes. Images based on QUS parameters showed an excellent ability to depict metastatic foci.

These encouraging initial results suggest that HF QUS methods may provide a clinically-valuable means of detecting small metastatic cancers in dissected lymph nodes that might not be detected using standard pathology procedures. The ability of HF QUS to reveal otherwise-missed metastases will enable pathologists to more-efficiently focus histological effort on cancer-containing regions of nodes. Future studies will investigate the applicabil-

ity of these methods to detection of nodal metastases *in situ*. Supported in part by NIH/NCI grant CA100183.

2.3 Cross-platform comparison of backscatter coefficient from four clinical imaging systems in four well-characterized phantoms, Lauren A. Wirtzfeld,[1] Kibo Nam,[2] Goutam Ghoshal,[1] Viksit Kumar,[3] Ivan M. Rosado-Mendez,[2] Alexander D. Pawlicki,[1] Ernest L. Madsen,[2] Timothy A. Bigelow,[3] Michael L. Oelze,[1] James A. Zagzebski,[2] 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 and [3]Department of Mechanical Engineering, Iowa State University, Ames, IA, wdo@uiuc.edu.*

The ability to reproducibly estimate the backscatter coefficient (BSC) across different clinical imaging systems is critical to moving quantitative ultrasound (QUS) imaging into a clinical setting. In our previous QUS studies of physical phantoms, agreement in BSC estimates was demonstrated across different single-element laboratory systems. Also, BSC estimates were in agreement with scattering theory. The goal of this study was to compare the BSC obtained from four different clinical imaging systems using the same well-characterized phantoms. The four imaging systems were an Ultrasonix RP; a Zonare Z.one scan engine; a Siemens Acuson S2000; and a VisualSonics Vevo2100.

All phantoms employed have been previously described and well characterized with single-element data from two institutions (UIUC,[(1)] UW[(2)]). For the current study from three institutions (UIUC, UW, ISU), four phantoms were imaged. Three of the phantoms consisted of weakly -scattering agar spheres of various diameters, nominally between 90 and 212 μm, each exhibiting oscillatory behavior in BSC vs frequency that is characteristic of the sphere sizes. One phantom contained glass bead scatterers, measuring 41±0.2 μm in diameter. Data from all systems accurately reproduced the different BSC vs frequency shapes. Excellent cross-platform quantitative agreement was observed across all four imaging systems for BSC measurements in all phantoms, including direct agreement with theory for the glass-bead phantom. Supported by NIH Grant R01CA111289.

(1) *J Acoust Soc Amer 128*, 903 (2010). (2) *Ultrasonic Imaging 32*, 48 (2010).

2.4 Ultrasonic backscatter coefficient measurement agreement across multiple imaging platforms from *in vivo* rodent tumors, Lauren A. Wirtzfeld,[1] Goutam Ghoshal,[1] Ivan M. Rosado-Mendez,[2] Kibo Nam,[2] Viksit Kumar,[3] Alexander D. Pawlicki,[1] Michael A. Kurowski,[1] Nathan R. Hirtz,[4] Emily L. Hartman,[1] Rita J. Miller,[1] Douglas G. Simpson,[4], Timothy A. Bigelow,[3] James A. Zagzebski,[2] 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 Mechanical Engineering, Iowa State University, Ames, IA, [4]Department of Statistics, University of Illinois at Urbana-Champaign, Champaign, IL and [5]Beckman Institute, University of Illinois at Urbana-Champaign, Urbana, IL, wdo@uiuc.edu.*

In order to translate quantitative ultrasound (QUS) techniques to the clinic, it is necessary to demonstrate that the QUS measurement results are platform independent. The backscatter coefficient (BSC) is a fundamental parameter that describes scattering on an absolute scale and a parameter from which several other important QUS parameters are calculated. Therefore, demonstrating agreement between the BSC estimates using different systems is significant. This study is an intercomparison of BSC estimates acquired by different groups from two *in vivo* tumor models, an orthotopic mouse mammary carcinoma (4T1) and a spontaneous rat-mammary fibroadenoma. The ultrasound systems employed included three

clinical imaging systems: an Ultrasonix RP; a Zonare Z.one scan engine diagnostic system and a Siemns Acuson S2000, as well as a preclinical animal imaging system, a VisualSonics Vevo2100. Radiofrequency (rf) echo data spanning the 2–14 MHz frequency range were acquired in three dimensions from all animals using each system. Each research group (UIUC, UW, ISU) processed their rf data independently, and the resulting BSCs were compared. Good agreement was observed in BSCs across all imaging systems. Variations in BSCs were observed across different fibroadenomas, which could have been due to the heterogeneity within and between tumors. On the other hand, the carcinomas are very uniform tumors and good agreement was observed in BSC estimates between systems and for different tumor samples. This type of agreement enables QUS results to be compared between systems. We will now begin investigating how characteristic differences between different pathologies correspond to different QUS results. This work was supported by NIH Grant R01CA111289.

2.5 **Detection of layers of aligned collagen in human cervical tissue using ultrasound**, Lisa M. Reusch,[1] Helen Feltovich,[2] Lindsey Carlson,[1] Jeremy J. Dahl,[3] Mark L. Palmeri,[3] Kevin Eliceiri[4] and Timothy J. Hall,[1] *[1]Medical Physics, University of Wisconsin - Madison, Madison, WI, [2]Maternal Fetal Medicine, Intermountain Healthcare, Park City, UT, [3]Biomedical Engineering, Duke University, Durham, NC and [4]Laboratory for Optical and Computational Instrumentation, University of Wisconsin-Madison, Madison, WI, lmmcguire@wisc.edu.*

Objectives: Spontaneous preterm birth rates have not changed in a century despite extensive research. Collagen alignment in the cervix contributes to cervical strength and undergoes rearrangement long before gross changes (shortening, softening) can be seen; thus, understanding cervical microstructure is an important first step to understanding cervical dysfunction. A quantitative assessment of these changes in women has been challenging due to a lack of noninvasive technology sophisticated enough to interrogate the microstructure of the cervix. We aim to develop such a technique using quantitative ultrasound (QUS) and acoustic-radiation-force-impulse (ARFI) measurements. We corroborate our ultrasound findings with multiphoton optical microscopy.

Methods: Hysterectomy specimens ($n = 5$) were scanned using a Siemens Acuson S2000 ultrasound system equipped with a prototype intracavity transducer (Siemens Medical Solutions USA, Malvern, PA, USA). Radiofrequency (rf) data were acquired with the endocervical canal parallel to the transducer aperture. transmit and receive angles were changed through electronic control to assess anisotropic acoustic propagation. Backscattered data were collected for steering angles between ±40º in steps of 4º. The total backscattered power (BSP) was computed for each angle by integrating the power spectra. Data from a phantom with spherical scatterers were used for system calibration. ARFI measurements were collected at steering angles of 0º, ±20º and ±40º and displacements were estimated using a cross-correlation method. Shear sounds speeds are estimated from the time-to-peak values. Lastly, the tissue was sectioned and imaged using second harmonic generation (SHG) imaging.

Results: The two different US assessment techniques (QUS, ARFI) show a change in properties as the distance away from the endocervical canal increases. In particular, at a distance of about 6 mm away from the canal, the loss in BSP as a function of beam steering changes and the shear sound speed increases. Additionally, the SHG images show a qualitative change in the apparent collagen organization at a depth that is consistent with the change in US properties. This change in acoustical and optical properties indicates that we are detecting the presence of at least one layer within the cervix. Ongoing work aims to quantify the difference between cervices that have given birth to ones that have not and to quantify the

collagen alignment in the SHG images using a curvelets-based analysis. Supported by NIH grants R21HD061896 and R21HD063031.

3. Shear-Wave Imaging

3.1 **Using quantitative shear-wave elasticity imaging techniques to noninvasively characterize liver fibrosis**, Mark L. Palmeri,[1] Ned C. Rouze,[1] Michael H. Wang,[1] Manal Abdelmalek,[2] Cynthia Guy[3] and Kathryn R. Nightingale,[1] *[1]Department of Biomedical Engineering, Duke University, [2]Division of Gastroenterology, Duke University Medical Center and [3]Department of Pathology, Duke University Medical Center, Durham, NC, mark.palmeri@ duke.edu* (overview).

Liver fibrosis can result from alcoholic and nonalcoholic etiologies and affects millions of patients each year who must be evaluated for disease progression and candidacy for liver transplant or other therapeutic interventions. The current gold standard for liver fibrosis characterization is liver biopsy but this invasive procedure is costly and has the risks of infection and hemorrhage in addition to patient pain and discomfort. Over the past 10 years, there have been efforts to characterize liver fibrosis using noninvasive imaging techniques, such as acoustic-radiation-force-based shear-wave elasticity imaging, to provide the clinician with a bedside tool to evaluate liver health in a clinic setting. Recognizing that fibrotic tissue can be stiffer than healthy tissue, liver fibrosis can be indirectly characterized by estimating its stiffness through estimation of shear wave speed. Acoustic Radiation Force Impulse (ARFI) shear-wave imaging is one such modality that has been developed and studied for such noninvasive liver fibrosis measurement.

Shear waves are generated using impulsive, focused acoustic-radiation-force excitations and the speed of those propagating shear waves is estimated using a variety of time-of-flight (TOF) algorithms. We have implemented custom ARFI shear wave imaging sequences using a Siemens CH4-1 curvilinear transducer on a Siemens SONOLINE Antares™ scanner. The radiation force excitations were focused at 49 mm with an F/2 focal configuration to deliver a 180 μs excitation at 2.0 MHz. Shear waves were tracked using 3.0 MHz tracking beams and 4:1 parallel receive spanning 20 mm laterally-offset from the radiation-force excitation at a prf of 4.8 kHz. We have explored several algorithms to robustly reconstruct shear wave speeds under assumption of homogeneity of the liver and *a priori* knowledge of the direction of shear-wave propagation. An overview of our Lateral TTP, RANSAC, and Radon-sum transformation methods will be presented in the context of a 172 patient retrospective/prospective study looking at liver fibrosis in Non-alcoholic Fatty Liver Disease (NAFLD) patients. Significant fibrosis (F3-4) is able to be differentiated from insignificant-to-mild fibrosis (F0-2) with 90% sensitivity and specificity using a shear-stiffness threshold of 4.24 kPa. Liver shear stiffness was not dependent on hepatocyte ballooning, inflammation nor imaging location.

Future directions for shear-wave elasticity imaging include the visualization of structures that violate the homogeneity assumptions that were utilized in the liver-fibrosis studies. The homogeneous TOF reconstruction algorithms require modification to accommodate shear-wave reflections from stiffness interfaces. We have utilized shear-wave leading-edge algorithms with smaller spatial-reconstruction kernels to reduce the artifacts associated with shear-wave reflections and we have been able to generate accurate quantitative stiffness images of spherical inclusions in simulation and phantoms. Quantitative shear-wave images suffer from decreased spatial resolution that is dependent on the kernel size, with CNRs that are approximately half that of qualitative ARFI images using similar radiation-force excita-

tions (6.2 vs. 11.5). Combining the higher resolution of qualitative elasticity images with the quantitative shear-wave images will allow for additional characterization of liver lesions to be performed in the clinical setting. Supported by NIH grants R01 EB-002132 and R01 CA142824.

3.2 **Vibration Elastography: overview and clinical results**, Kevin J. Parker, Zaegoo Hah and Deborah Rubens, *Rochester Center for Biomedical Ultrasound, University of Rochester, Hopeman Hall 203, Rochester NY 14627-0126, kevin.parker@rochester.edu* (invited).

We present the evolution of elastographic techniques that employ sinusoidal vibrations as inputs and derive images of relative or absolute stiffness as an output. The earliest images and theoretical foundations are described, along with the proliferation of techniques over a decade. Finally, the development of crawling waves, which are interference patterns of shear waves, is described. Crawling waves can be generated by applying two vibration sources, and examples are compared from mechanical contact sources and radiation-force sources. Finally, clinical results in the prostate, liver and thyroid are demonstrated. The accuracy of cancer detection in the prostate is now surpassing 80% using some of these elastographic techniques. This provides a great improvement over B-scan imaging and is useful for guiding, but not yet replacing, needle biopsy.

3.3 **Exploration of the human cervix using acoustic-radiation-force-impulse measurements**, Lisa M. Reusch,[1] Helen Feltovich,[1,2] Lindsey C. Carlson,[1] Jeremy J. Dahl,[3] Mark L. Palmeri[3] and Timothy J. Hall,[1] *[1]University of Wisconsin-Madison, Medical Physics, Madison, WI, [2]Intermountain Healthcare, Maternal-Fetal Medicine, Provo, UT [3] and Biomedical Engineering, Duke University, Durham, NC, lmmcguire@wisc.edu* (invited) .

Objective: Despite decades of research, preterm birth has been, and still remains, a problem. Progress has been hindered by a lack of understanding of the cervix due, in part, to a lack of noninvasive assessment techniques precise enough to interrogate the cervical microstructure. An additional challenge to understanding the cervix is the complexity of the cervix itself; cervical collagen is organized into layers of aligned collagen of differing orientation. This organization contributes much of the cervical strength but also means the cervix is very inhomogeneous and anisotropic. Cervical collagen also undergoes rearrangement leading to shortening and softening of the cervix but this rearrangement occurs long before these large-scale changes can be seen. Acoustic-radiation-force-impulse (ARFI) techniques are good candidates for assessing the strength of the cervix noninvasively, and, in particular, for detecting small changes in the cervix before gross changes are evident.

Method: Five hysterectomy specimens were collected from patients undergoing hysterectomy for benign reasons. The cervical samples were scanned using a Siemens Acuson S2000 ultrasound machine equipped with a prototype intracavity transducer (Siemens Medical Solutions USA, Malvern, PA, USA). ARFI data were acquired with the endocervical canal parallel to the transducer aperture at beam steering angles of 0º, ±20º and ±40º. Displacements were estimated using a cross-correlation method and shear-sounds speeds were calculated using a lateral time-to-peak method.

Results: Images of the displacements show clear evidence of layering within the cervix. Specifically, two regions with differing shear-sound speeds were found. The first region, which covers roughly the inner 6 mm of the cervix, has a lower shear-sound speed of about 2 m/s. The second region covers the rest of the radius of the cervix (from ~6 mm to the outer edge) and has a shear-sound speed of about 5 m/s. Of particular interest is that we seem to be able to measure local properties as opposed to only measuring average behavior, making ARFI measurement techniques good methods for quantitative assessment of the stiffness

(and, therefore, strength) of the cervix, as well as measuring changes that occur in different regions of the cervix. Further work involves modeling of the cervix to examine the effect of boundaries on shear-wave propagation, measuring the backscattered echo signal to analyze the anisotropy and corroborating the ultrasound results with images taken using multi-photon optical techniques. Supported by NIH grant R21HD063031.

3.4 **Measurements of viscoelastic properties of myocardium using wave-propagation methods**, Matthew W. Urban, Cristina Pislaru, Ivan Nenadic and James F. Greenleaf, *Department of Physiology and Biomedical Engineering, Mayo Clinic College of Medicine, Rochester, MN 55905, urban.matthew@mayo.edu* (invited).

Background: Diastolic dysfunction is the impaired ability of the heart to fill and maintain its stroke volume at physiologic filling pressures and is due to abnormal ventricular relaxation and/or stiffness. Knowledge of the quantitative values of the viscoelastic properties of the myocardium would provide the clinician a tool to evaluate directly myocardial properties in patients.

Objective: The goal of this work is to develop a noninvasive method using wave propagation techniques to measure mechanical properties of the myocardium *in vivo*.

Methods: We modeled the left-ventricular wall as a viscoelastic plate (Voigt model) with dispersive shear-wave characteristics and applied Lamb wave theory to estimate viscoelastic material properties. We call this method Lamb wave Dispersion Ultrasound Vibrometry (LDUV). The method was first validated *in vitro* in gelatin and urethane rubber phantoms and then tested in eight pigs in an open-chest preparation. The *in vitro* results were compared with results from an embedded-sphere test. Initial *in vivo* tests were performed using a mechanical actuator to create harmonic (50-350 Hz), propagating mechanical waves in the myocardial wall and a Sonix RP system to track the wave motion (acquisition rate: ~2500 Hz). Data were acquired over several cardiac cycles. Dispersion curves were fit with a viscoelastic, antisymmetric Lamb wave model to obtain estimates of the shear elasticity, μ_1, and viscosity, μ_2. Myocardial elasticity was also measured using an independent invasive method (i.e., pressure-segment length). We have also performed measurements in pigs using ultrasound radiation force (Verasonics system) to induce wall vibrations and measure wave propagation in one quick measurement (6-12 ms data acquisition, frame rate 4000- 8000 Hz), from both direct (open-chest) and transthoracic approaches.

Results: The mean and standard deviations of the *in vitro* LDUV results in gelatin ($\mu_1 = 15.9 \pm 0.5$ kPa and $\mu_2 = 0.7 \pm 0.4$ Pa s) and urethane phantoms ($\mu_1 = 45.1 \pm 1.4$ kPa and $\mu_2 = 6.5 \pm 0.8$ Pa s) compared well with the validation test using an embedded sphere in gelatin ($\mu_1 = 16.6 \pm 0.3$ kPa and $\mu_2 = 0.5 \pm 0.02$ Pa s) and urethane samples ($\mu_1 = 46.6 \pm 3.2$ kPa and $\mu_2 = 5.7 \pm 0.8$ Pa s). *In vivo*, we evaluated the shear elasticity and viscosity in both diastole and systole. The mean and standard deviation of μ_1 in diastole and systole was 1.81 ± 0.86 and 21.14 ± 8.25 kPa, respectively. The mean and standard deviation of μ_2 in diastole and systole was 2.76 ± 0.60 and 4.16 ± 4.62 Pa s, respectively. We found excellent agreement between the elastic term measured by LDUV and the shear-elastic modulus measured by pressure-segment length analysis. The measurements made using radiation-force-induced waves (Verasonics) were in agreement with those made with the mechanical actuator; however, data were more noisy and precision of measurements was lower, and, thus, more refinements are needed.

Conclusion: We demonstrated that LDUV measurements and Lamb wave theory allow us to estimate viscoelasticity of the myocardial wall *in vivo* throughout the course of the cardiac cycle. Supported in part by grant EB002167 from the NIH.

3.5 Rapid acquisition of ARFI-induced shear-wave velocity estimates using temporally-interleaved displacement tracking, Peter J. Hollender, Richard R. Bouchar and Gregg E. Trahey, *Duke University, Durham, NC, peter.hollender@duke.edu.*

Shear-wave velocimetry of ARFI-induced transverse waves has been demonstrated to be a viable way to estimate the shear modulus of viscoelastic media. To measure the shear-speed of these transverse waves, the off-axis response of the target region must be tracked to image wave propagation. A wider region of tracking will reduce jitter in the velocity estimate but traditionally requires superimposing the response of multiple excitations and thus increases susceptibility to motion artifact. By interleaving multiple tracking locations after a single excitation, temporal sampling of each lateral location is sacrificed to obtain estimates quasi-simultaneously for a wide field of view. The tradeoff between jitter reduced by the wide field of view and that introduced by reduced temporal sampling is shown to be favorable when motion is present. An analysis of this method's optimization and its application is presented with elastic phantom verification and *in vivo* validation with intracardiac data from *canine* studies. Supported by NIH Medical Imaging Training Grant EB001040, NIH 5R37HL096023 and NIHR01EB01248.

3.6 Acoustical near-field imaging by dynamic strains analysis over the Lamb-wave field, Kano Teramoto, Ryoji Inoue, Mahbub Hasan and Tawhidul Islam Khan, *Department of Advanced Technology Fusion, Saga University, Japan, tera@me.saga-u.ac.jp.*

Quantitative acoustical imaging methods are used or developed to classify the tumor regions. These methods estimate the characteristics of the tissue elasticity of a region of interest having some inhomogeneity with respect to the surrounding soft tissues.

The goal of this study is to propose a novel near-field imaging method for shear-wave elastography and subwavelength imaging. The proposed method utilizes the determinant of a covariance matrix composed of the orthogonal pair of the shear strains. Applied on the surface of tissues, a mechanical vibration excites several kinds of waves: (a) pressure and shear waves propagating in the medium, (b) a Rayleigh wave that is confined to the surface of the medium and (c) symmetric and anti-symmetric Lamb-waves traveling along the skin layer. The first two waves are utilized for traditional ultrasonic techniques, such as pulse-echo methods. In contrast to these classical techniques, in which the wavelength is shorter than the thickness of skin, the Lamb-wave has the advantage of propagating over a large area, thus inspecting the entire tissue. In this study, the problem of reconstructing a super-resolved image of stiffer region is considered.

The image reconstruction theory can be summarized as follows. (1) The distributions of the normal displacement of the skin surface are governed by the 2-dimensional wave equation. (2) When the single propagating wave exists on the surface of the tissue without any stiffer regions, the orthogonal pair of the out-of-surface shear strains are linearly dependent each other. Therefore, the determinant of a covariance matrix, which is composed of the orthogonal pair of the shear strains, becomes zero. (3) When a region of interest having some inhomogeity exists, the scattered wave field arises in the Lamb-wave field. Consequently, the determinant becomes larger than zero because of the independency between the orthogonal pair.

Towards that goal, we have been evaluating the proposed imaging method by comparing the theoretical analyses with several acoustical experiments *in vitro*. In the experiments, the specimen is excited with 36 kHz frequency with 36 mm wavelength. The distributions of normal displacements are observed by a laser interferometer. The orthogonal pair of out-of-surface shear strains is obtained by subtracting x and y directionally adjacent displacements, respectively. From the experimental results, subwavelength, 2 mm resolution is confirmed. Supported by Grant-in-Aid for Scientific Research (KAKENHI 22560421) from JSPS and MEXT of the Japanese Government.

3.7 **Tracking shear wave propagation in 3D using a real-time volumetric imaging ultrasound transducer**, Michael Wang, Brett Byram, Mark Palmeri, Ned Rouze and Kathryn Nightingale, *Department of Biomedical Engineering, Duke University, Durham, NC, mhw12@duke.edu.*

Tissue displacement due to acoustic-radiation-force impulse (ARFI) excitation can only be monitored in one cross-sectional plane of the anatomy using conventional 1D array ultrasound transducers. As a result, stiffness estimation can only be performed within 2D planes, which hinders full appreciation of the 3D nature of the anatomy. With the recent availability of matrix-array ultrasound transducers, acquisition of displacement fields within a volume of tissue in real-time is now possible. There are several potential advantages in using a matrix-array transducer for monitoring ARFI displacements, including: (1) the ability to track shear-wave propagation in multiple directions to reveal stiffness anisotropy and (2) the ability to measure ARFI response over a larger tissue volume, increasing the amount of high SNR data available for stiffness reconstruction.

A system capable of tracking ARFI-induced shear-wave propagation in 3D is presented. An annular focused HIFU piston transducer (H-101, Sonic Concepts, Bothell, WA) is used for generating radiation-force excitation (1.1 MHz, f/1, 60 mm focal depth). A 2D matrix-array transducer (4Z1C, Siemens Healthcare, Ultrasound Business Unit, Mountain View, CA) inserted in the central opening of the HIFU piston was used for monitoring the resulting ARFI displacement. The face of the 4Z1C was flush with the radiating surface of the piston. Shear waves were induced in a homogeneous phantom ($E = 4.5$ kPa) using a 1000 cycle push pulse (0.9 ms duration) with an I_{sppa} value of 4100 W/cm^2 (in water). Displacement tracking was performed at a center frequency of 2.5 MHz using a 10×12 (lateral × elevation) rectangular grid of receive beams. The spatial extent of this tracking region was 16.5 × 20 mm (lateral × elevation) at the push focal depth of 60 mm. The push axis was located at one corner of the tracking region, allowing displacements in one quadrant surrounding the push to be observed. 30:1 parallel receive was used to beamform 5×6 beam locations for every transmit, enabling a volume rate of 2 kHz to be achieved. With this imaging configuration, shear-wave propagation away from the push in all directions within a 90º field of view in the lateral-elevation plane are observed, for the very first time. Further optimization of imaging parameters is being performed to increase the field of view and volume rate. Shear-wave speed reconstruction algorithms, which take advantage of the additional data available from tracking shear wave propagation in multiple directions, are being investigated. Supported by NIH grants R01 EB-002132 and R01 CA142824.

4.   Quantitative Ultrasound 2/Bone

4.1 **Comparison of the backscattered power loss in multiparous versus nulliparous cervices,** Lisa M Reusch,[1] Helen Feltovich,[1] Lindsey C. Carlson,[1] Kevin Eliceiri[3] and Timothy J Hall,[1] *[1]Medical Physics, University of Wisconsin, Madison, WI, [2]Maternal-Fetal Medicine, Intermountain Healthcare, Provo, UT and [3]Laboratory for Optical and Computational Imaging, University of Wisconsin, Madison, WI, lmmcguire@wisc.edu.*

Objective: The lack of noninvasive technology sophisticated enough to interrogate the microstructure of the cervix hinders quantitative assessment of the cervix, resulting in the ongoing problem of preterm birth. Understanding the cervical microstructure is necessary to understand cervical dysfunction. The strength of the cervix comes from collagen alignment and in order to develop a comprehensive understanding of the cervical microstructure, we use quantitative ultrasound techniques to detect alignment in cervical collagen.

Methods: Radiofrequency (rf) echo data were collected with a Siemens Acuson S2000 ultrasound machine using a prototype intracavity transducer (Siemens Medical Solutions USA, Malvern, PA, USA). The transducer was operated as a linear array and the beam was electronically steered between ±40º in steps of 4º. Backscattered power (BSP) for each angle was calculated from the rf echo data by Fourier transform and the power spectra integrated. Data from five hysterectomy specimens were collected. Three of the subjects had never had babies (nulliparous) and two of the subjects had given birth at least once (multiparous). Data from a phantom containing spherical scatterers were also collected at the same time to account for changes in the transducer's sensitivity and effective aperture. BSP loss from the cervical specimens was compared to the BSP loss in the phantom to examine deviations from isotropic scattering. BSP loss from the multiparous cervices was also compared to the nulliparous cervices.

Results: A monotonically-increasing loss of BSP as a function of steering angle occurred in both tissue and phantom; however, the cervical tissue showed 20-60dB excess power loss compared to the phantom. This is consistent with the presence of anisotropic scattering structures. Interestingly, comparison of multiparous to nulliparous samples showed greater power loss in the latter. Additionally, the BSP loss in nulliparous cervices is symmetric about 0° steering angle whereas the BSP loss in the multiparous cervices is much more asymmetric. Results show that not only are these methods good for detecting organization in cervical collagen but that we can also detect differences between cervices. Ongoing studies further investigate differences between multiparous and nulliparous cervices using ARFI as well as multiphoton optical imaging techniques. Supported by NIH grant R21HD- 061896.

4.2 **Three-dimensional impedance map analysis and comparison of normal and fatty rabbit liver**, Alexander D. Pawlicki, Alexander J. Dapore, Sandhya Sarwate and William D. O'Brien, Jr., *Bioacoustics Research Laboratory, Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, Urbana, IL.*

Three-dimensional impedance maps (3DZMs) are virtual (computational) data sets of real tissue that can be used to study fundamental ultrasonic properties. 3DZMs are created from a series of adjacent histological tissue slide images that have been realigned to one another using a registration scheme. Each pixel is assigned an impedance value to create a 3D map of acoustic impedance. The recreated tissue volume is a valuable tool for estimation of ultrasound backscatter and quantitative ultrasound (QUS) parameters such as the effective scatterer diameter (ESD). The ultimate goal of 3DZMs is to help identity the acoustic scattering sites of tissue and aid in developing more accurate models of scattering and interaction with tissue microstructure.

In a previous experiment, a sample of fatty rabbit liver was chemically fixed and scanned with single-element ultrasound transducers ranging in center frequencies from 7.5 to 65 MHz. A total of 24 3DZMs were then made from the sample and the ESD was estimated using the fluid-filled sphere form factor model. The results showed that when weighting the estimation toward smaller scatterer sizes, the ESD was 7.04 ± 1.30 μm, which corresponds closely to the size of the liver cell nucleus of the actual tissue. This result suggests that the liver cell nucleus could be the primary source of scattering in fatty liver.

As a continuation to the experiment described above, the same ultrasound scans and histology processing were performed on a sample of normal (nonfatty) fixed rabbit liver to investigate the acoustic backscatter and the estimated ESD of normal liver. The 3DZM technique has the potential to be a powerful tool in diagnosis of fatty liver disease because of the ability to both visually and quantitatively assess the properties of tissue microstructure. In addition to the extreme cases of normal and fully-developed fatty liver, intermediate

stages of the disease progression can also be studied to determine the dependence of ultrasound scattering as the fat content of the tissue changes. Supported by NIH R01CA111289.

4.3 **Improvements in measurements of BUA and SOS in human calcaneus**, Keith A. Wear, *Food and Drug Administration, 10903 New Hampshire Blvd, Silver Spring, MD, 20993.*

Although calcaneal broadband ultrasound attenuation (BUA) and speed-of-sound (SOS) are good predictors of osteoporotic fracture risk, BUA and SOS measurements exhibit substantial inter-system variability. The objectives of this work were to (1) compare phase insensitive (PI) detection, which suppresses phase cancellation, and conventional phase sensitive (PS) detection for measurement of BUA and (2) test a compensation formula for reducing variability in SOS measurements. Data from 16 human calcaneus samples *in vitro* and 73 women *in vivo* were acquired using a GE Lunar Achilles Insight bone sonometer. Radiofrequency data were processed off-line using both PI and PS algorithms. BUA measurements (mean ± sd) were 22.1 ± 15.8 dB/MHz (PS) and 17.6 ± 7.2 (PI) *in vitro* and 81.4 ± 21.4 dB/MHz (PS) and 67.2 ± 9.7 dB/MHz (PI) in *vivo*. Compensation of SOS measurements reduced (1) average transit-time-marker-related SOS variability by 75% in 73 women and (2) bandwidth-related SOS variability by 80% in a bone-mimicking phantom. These new methods may enable a substantial improvement in consistency in bone sonometry. The mention of commercial products, their sources or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the Department of Health and Human Services.

4.4 **Using Bayesian methods to characterize the presence of attenuation artifacts arising from overlapping fast and slow waves in cancellous bone,** Amber M. Nelson,[1] Joseph J. Hoffman,[1] Mark R. Holland,[1] Katsunori Mizuno,[2] Yoshiki Nagatani,[3] Mami Matsu kawa[2] and James G. Miller,[1] *[1]Washington University in St. Louis, St. Louis, MO, [2]Doshisha University, Japan and [3]Kobe City College of Technology, Japan, james.g.miller@ wustl.edu.*

Objective: The goal of this study was to investigate the attenuation behavior of overlapping fast and slow waves in cancellous bone, using Bayesian parameters estimated from experimentally-obtained waveforms.

Methods: Simulated data with Bayesian parameters were generated using a propagation model including both fast and slow waves. The fast and slow waves were generated for bone thicknesses that systematically varied from 15 mm to 5 mm in 1 mm increments. Two analysis methods for determining the attenuation as a function of propagation distance were applied. The first was a time-domain analysis using the amplitudes of the first peak of the mixed waveform. The second was a frequency-domain analysis method applied to the separated fast and slow waves. Two sets of Bayesian parameters were obtained from experimental waveforms that passed through two different sample thicknesses.

Results: In the time-domain analysis, the apparent attenuation of the fast wave is larger at the beginning and gradually decreases as the wave travels farther into the bone. In simulation, frequency-domain analysis of the separated waves provides attenuation coefficients for each wave mode that do not depend on the propagation distance.

Discussion: The simulated data indicate that the apparent dependence of the attenuation properties on propagation distance can arise from analyzing the unseparated signal with time-domain analysis. Phase cancellation at the face of a phase-sensitive receiver can also yield apparent attenuation properties that appear to vary with propagation distance, which might be associated with different values of Bayesian parameters for different propagation lengths. Supported in part by NIH R01 AR057433.

4.5 **Ultrasonic manipulation of bone cells, *in vivo* adaptation and tissue mechanical strength,** Yi-Xian Qin, Shu Zhang, Suzanne Ferreri and Jacky Cheng, *Department of Biomedical Engineering, Stony Brook University, Stony Brook, NY, Yi-Xian.Qin@sunysb.edu.*

Introduction: It is well documented that ultrasound, as a mechanical signal, can produce a wide variety of biological effects *in vitro* and *in vivo*. The purpose of the current study was to (1) develop a methodology to allow for *in-vitro* manipulation of osteoblastic cells using acoustic-radiation force generated by ultrasound, (2) use this methodology to determine the morphological and biological responses of bone cells to ultrasound and (3) mitigate bone loss under estrogen-deficient osteopenia.

Methods: In-vitro cellular manipulation: We used a therapy- focused transducer that had a spherical cap with 64 mm diameter and 62.64 mm focal length. MC3T3-E1 osteoblastic cells were cultured in   -MEM containing 1% penicillin-streptomycin and 10% decomplemented newborn calf serum. *In-vivo ovx model*: 72, 16 y.o. Sprague-Dawley rats were divided into six groups; baseline control, age-matched control, OVX control, OVX + 5 mW/cm^2 ultrasound (US), OVX + 30 mW/cm^2 US and OVX + 100 mW/cm^2 US. Low-intensity pulsed ultrasound (LIPUS) was delivered transdermally at the L4/L5 vertebrae, using gel-coupled plane-wave US transducers. The signal was applied 20 min/day, 5 days/ week for 4 weeks.

Results: *In-vitro* cellular response: The methodology allowed manipulation of MC3T3-E1 cells by an acoustic-radiation force. The deformation of cell membranes was observed by the US manipulation, which appeared after 15 s treatment with 6 W pulsed ultrasound. We also imaged the movement of primary cilia, which showed corresponding movement when subjected to pulsed ultrasound. *In-vivo* response: LIPUS treatment significantly increased BVF compared to OVX controls for the 100 mW/cm^2 -treated group. Interestingly, the 100mW/cm^2 -treated groups showed a significant improvement over the 5mW/cm^2- treated group.

Discussion: The observed primary cilia can be moved dynamically by the acoustic force. These findings support the hypothesis that LIPUS can inhibit bone loss and preserve bone strength under conditions of estrogen-deficient osteopenia.

5. Tumor Monitoring

5.1 **Three-dimensional power Doppler ultrasound for characterizing tumor vascular response to radiation**, Ahmed El Kaffas,[1,2] Anoja Giles[1,2] and Gregory J. Czarnota,[1,2] [1]*Imaging Research and Radiation Oncology, Sunnybrook Health Sciences Centre, 2075 Bayview Ave. and* [2]*Departments of Radiation Oncology and Medical Biophysics, University of Toronto, 2075 Bayview Ave., Toronto, ON, Canada, M4N 3M5, gregory.czarnota@ gmail.com.*

High-frequency power Doppler ultrasound is a noninvasive vascular imaging modality ideal for quantitative assessment of vascularity in preclinical tumor models. Advantages of power Doppler over other Doppler techniques include minimal transducer angle dependence, no aliasing and increased sensitivity to slow blood flow as compared to mean frequency techniques. While contrast-enhanced ultrasound methods allow for detection of smaller blood vessels and even slower flows, power Doppler has the advantage of being logistically more feasible for studies involving a large number of samples and allows obtaining data for full 3D tumor volumes. The aim of this work is to utilize high-frequency 3D

power Doppler ultrasound to assess tumor response to vascular targeting therapies in complement to standard tissue-characterization methods.

Breast cancer MDA-MB-231 xenografts were treated with single radiation doses of 0 to 16 Gy alone, or in combination with Sutent, an antiangiogenic agent. Three-dimensional power Doppler ultrasound data were acquired before and 24 hours after treatment using a 25 MHz transducer and a VEVO770. To assess tumor vascular response, we have developed a number of parameters that includes the vascularity index (VI: percent flow signal per tumor volume), vessel dimensions (two and three dimensions), vessel shape and branching and the distribution of flow signal throughout tumor.

As anticipated, the VI decreased by more than 50% when tumors were treated with single large doses of radiation greater than 8 Gy. However, this did not occur for lower radiation doses while Sutent appeared to enhance the radioresistance of tumor blood vessels. A change in vessel sizes was also observed after radiation therapy and Sutent therapy with good correlation between the power Doppler analyses and histopathology with blood vessel marker staining. Analyses with quantitative ultrasound methods and TUNEL staining indicate an enhanced dose-dependent increase in tumor cell death when radiation was combined with Sutent. These results indicate that Sutent treatment may radiosensitize tumors by altering the tumor microenvironment.

5.2 **Quantitative ultrasound and diffuse optical spectroscopy evaluations of treatment response in patients with locally advanced breast cancer receiving chemotherapy**, Omar Falou,[1,2] Naum Papanicolau,[1,2] Hany Soliman,[1,2] Jacqueline Spayne,[1,2] Rebecca Dent,[3] Martin Yaffe,[1,2] Michael C. Kolios[4] and Gregory J. Czarnota,[1,2] *[1]Imaging Research and Radiation Oncology, Sunnybrook Health Sciences Centre, [2]Departments of Radiation Oncology and Medical Biophysics, University of Toronto, [3]Department of Medical Oncology, Sunnybrook Health Sciences Centre and [4]Department of Physics, Ryerson University, Toronto, ON, Canada, gregory.czarnota@gmail.com.*

The necessity for a noninvasive and inexpensive imaging modality to both diagnose and monitor treatment response has led to renewed interest in the potential of ultrasound and optical imaging. The aim of this study is to investigate the potential of both quantitative ultrasound and diffuse optical spectroscopy (DOS) for monitoring of patients with locally advanced breast cancer (LABC) undergoing chemotherapy.

Fifteen women receiving neoadjuvant treatment for breast cancer had the affected breast scanned six times: before, 1 week, 2 weeks, 4 weeks and 8 weeks following initiation of the treatment and prior to surgery. A similar cohort of women had their breast scanned with quantitative ultrasound at the same times to track tumour responses with spectral parameters. A Sonix RP (Ultrasonix Medical Corporation, Richmond, BC, Canada) ultrasound device was used to collect B-mode and three-dimensional radiofrequency data of the tumor using an L15-5 6.0 cm transducer stimulated at 10 MHz. For each scan time quantitative ultrasound parameters including mid-bad-fit, spectral slop and 0-MHz intercept were determined. Three-dimensional maps of optical absorption and scattering properties of the tumor at different wavelengths (690 nm, 730 nm, 780 nm and 830 nm) were obtained using a SoftScan commercial tomographic diffuse optical spectroscopy system (ART Inc., Montreal, QC, Canada). Optical properties were converted to functional indices related to tissue microstructure and biochemical composition such as oxygenated hemoglobin, deoxygenated hemoglobin, total hemoglobin, water concentrations and scatter power. Tumor response was evaluated from clinical response and pathological response using whole mount pathology after mastectomy.

Patients who responded to treatment showed an increase in ultrasound backscatter, spectral slope and intercept compared to nonresponders. In terms of optical parameters, re-

sponding patients showed a reduction in deoxyhemoglobin, hemoglobin, total hemoglobin, water concentrations and scatter power compared to nonresponding patients. Both groups of changes occurred within 1-4 weeks of starting chemotherapy in patients who would have an ultimate clinical response. For responders, mid-band fit typically increased by 10   2 dB at 4 weeks time whereas optical parameters indicated a concurrent decrease by 80   5% of total hemoglobin and water content in the tumor. The results indicate that both quantitative ultrasound and diffuse optical spectroscopy have the potential to quantify changes in tumors during treatment and, hence, may provide noninvasive complementary manners to monitor treatment response in patients receiving neoadjuvant chemotherapy for locally-advanced breast cancer.

5.3 **Conventional frequency, quantitative-ultrasound evaluation of tumor cell death response in locally-advanced breast cancer patients to chemotherapy treatment**, Naum Papanicolau,[1,2] Rebecca Dent,[3] Sunil Verma,[3] Maureen Trudeau,[3] Jacqueline Spayne,[2] Sara Iradji,[1] Ervis Sofroni,[1] Justin Lee,[1,2] Martin Yaffe,[1,2] Michael Kolios[4] and Gregory J. Czarnota,[1,2] *[1]Imaging Research and Radiation Oncology, Sunnybrook Health Sciences Centre, [2]Departments of Radiation Oncology and Medical Biophysics, University of Toronto, [3]Department of Medical Oncology, Sunnybrook Health Sciences Centre, Department of Medicine, University of Toronto and [4]Department of Physics, Ryerson University, Toronto, ON, Canada , gregory.czarnota@gmail.com.*

The aim of many cancer therapies is to induce cell death within a target tumor. A substantial body of research using *in vitro* and *in vivo* models has demonstrated that cell death can be detected via quantitative ultrasound techniques. This study investigates for the first time the potential to quantify tumor responses to therapy in patients, using spectral and signal envelope statistics analysis of ultrasound data.

A clinical study was undertaken investigating the efficacy of ultrasound to quantify cell death in tumor responses with cancer treatment. Patients ($n = 20$) with locally-advanced breast cancer received anthracyline and taxane-based chemotherapy treatments over four to six months. The majority of patients went on to have a modified radical mastectomy and correlative whole-mount histopathology. Data collection consisted of acquiring tumor images and radiofrequency data prior to treatment onset and at four times during neoadjuvant chemotherapy (weeks 0, 1, 4, 8 and preoperatively). Data collection was carried out using an Ultrasonix-RP and an L15-5 6cm transducer pulsed at 10 MHz. Data indicated increases of approximately 9 dBr (1.67) maximally in ultrasound backscatter in patients who clinically responded to treatment. Patients assessed as responding poorly demonstrated significantly lower increases (2.3   1.7 dBr). Increases in 0-MHz intercept followed similar trends while increases in spectral slope were observed locally from tumor regions demonstrating increases in tissue echogenicity.

Using spectral parameters, there was a clear separation of patients who had an ultimate complete clinical response at 4-6 months of chemotherapy from clinical partial-responders and nonresponders. This was apparent at week 4 for the mid-band-fit and 0-MHz intercept and at week 1 for the mid-band-fit parameter. This study demonstrates the potential of ultrasound to quantify changes in tumors in response to cancer treatment administration in a clinical setting. The results indicate that such responses can be detected early during a course of chemotherapy and should permit ineffective treatments to be changed to more efficacious, potentially leading to improved treatment outcomes.

5.4 **Quantitative-ultrasound and power-Doppler evaluation of tumor cell death response in bladder-cancer xenograft treated with radiation-enhancing microbubble disruption**, William Tran,[1,2] Alborz Gorjizadeh,[1,2] Naum Papanicolau,[1,2] Sara Iradji[1,2] and Gregory J. Czarnota,[1,2] *[1]Imaging Research and Radiation Oncology, Sunnybrook Health*

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Tumor vascular endothelial cells respond to ultrasound mediated microbubble exposure and are specifically implicated in enhanced tumor response to radiation. We monitored the response of a bladder tumor line to a new microbubble-based radiation sensitizing treatment here using quantitative rf-based and power-Doppler based ultrasound methods.

Tumor vasculature response monitoring was performed in human bladder cancer HT-1376 xenografts in Severe Combined Immuno-Deficient (SCID) mice following ultrasound-mediated microbubble treatment and radiation. Acute response was assessed 24 hours after treatment using power (amplitude) mode Doppler ultrasound using a VEVO-770 Ultrasound operating at 30 MHz. Quantitative ultrasound data was collected using the same system in addition to an Ultrasonix-RP and an L14-5 probe pulsed at 10 MHz. Longitudinal studies monitored tumor response at 7 days, 14 days, 21 days and 28 days using the same imaging techniques. Treatment conditions consisted of ultrasound mediated 0%, 1% and 3% microbubble concentrations and radiation doses of 0 Gray, 2 Gray and 8 Gray to the tumor in both acute and longitudinal studies. Control conditions consisted of 3% microbubble injection to the mouse circulation without ultrasound activation and ultrasound exposure without microbubble injection (11 conditions, n = 102). Quantitative analysis at scheduled time points using power-mode Doppler ultrasound data and spectral ultrasound (rf) analysis revealed reduced microvessel density and tumor cell death in ultrasound microbubble treatment alone and also with combined treatment and radiation.

The present study suggests that induced ischemia and hypovascularization were present within the tumor's core compartment. Immunohistological analysis after tumor extraction at 24 hours or 21-28 days showed treatment efficacy and validated necrotic regions within the center of the tumor. These core regions revealed condensed areas of fibrosis and necrosis (areas where cellular nuclei are sparse, yet cellular components are present). These results were most obvious when microbubble-ultrasound was used in combination with radiation. The results of the study demonstrated that ultrasound mediated microbubble exposure can potentiate radiation sensitivity in tumors and lead to necrosis within the tumor compartment.

5.5 **Tissue characterization of tumor response to microbubble-based vascular disruption using photoacoustic imaging**, Joris Nofiele[1, 2]   Christina Kim,[1, 2]   Azza Al Mahrouki,[1,2] F. Stuart Foster,[1,2] Michael C. Kolios[2,3] and Gregory J. Czarnota,[1,2] *[1]Imaging Research and Radiation Oncology, Sunnybrook Health Sciences Centre, [2]Departments of Radiation Oncology and Medical Biophysics, University of Toronto and [3]Department of Physics, Ryerson University, Toronto, ON, Canada, gregory.czarnota@gmail.com.*

Tumor vasculature has been shown to directly affect the efficiency of radiation therapy, engendering the search for vascular disrupting treatment modalities. We have recently developed such treatment – ultrasound-induced cavitation of microbubbles – and have shown its efficiency as a radiation enhancer, using power Doppler and histology. Here, we have used the hybrid imaging technique of photoacoustics to quantify tumor hemoglobin content, identifying positive correlations with power Doppler and histology measurements.

Prostate tumors were induced in SCID mice in the hind leg and were treated with 2 Gy and 8 Gy radiation combined with 1% (v/v) Definity microbubbles insonified at 580 kPa and 833 kPa with 0.5 MHz ultrasound. Blood flow was measured using power Doppler before and 24 hours following treatment. Hemoglobin content was photoacoustically measured using a VisualSonics LAZR (VisualSonics, Toronto) system at 750 nm and 850 nm light wavelengths, which were more sensitive to deoxygenated and oxygenated hemoglobin respectively, before and 24 hours following treatment. Following treatment, mice were sacri-

ficed and tumors were collected and stained with *in situ* end-labelling (ISEL) to identify and quantify regions of cell death.

The strongest correspondence across all three treatment assessment modalities was found when combining 8Gy of radiation with both ultrasound pressures. With the signal obtained at 750 nm optical stimulus we observed a 20% and 15% decrease in hemoglobin content with 580 kPa and 833 kPa pressures respectively, which corresponded to a 44% and 31% respective decreases in blood flow as measured with power Doppler. Corresponding histology indicated a 45% and 38% relative region of cell death for 580 kPa and 833 kPa pressures, respectively. Data obtained using 850 nm optical stimulus to probe tissue indicated similar trends. Control samples showed a negligible change blood flow and histology indicated minimal cell death (2% of total area).

In summary, measures of hemoglobin paralleled changes in power Doppler indicators of blood flow. Destruction of blood vessels by this therapy lead to decreases in flow and hemoglobin and were associated with increases in cell death as detected histologically.

5.6 **Quantitative and parametric analysis employing conventional frequency ultrasound of cancer treatment effects *in vivo***, Naum Papanicolau,[1,2] Anoja Giles,[1,2] Michael Kolios[3] and Gregory Czarnota,[1,2] *[1]Imaging Research and Radiation Oncology, Sunnybrook Health Sciences Centre, [2]Departments of Radiation Oncology and Medical Biophysics, University of Toronto, and [3]Department of Physics, Ryerson University, Toronto, ON, Canada, gregory.czarnota@gmail.com.*

The intent of cancer therapies is to target and kill tumors in order to halt proliferation of the disease. Current assessment of treatment efficacy is in many cases based solely upon examining large-scale changes in tumor volume, often determined through physical examination. Large-scale changes in tumor structure, such as decreases in volume or structural rigidity, are the result of extensive changes in tumors at the microstructural level, most often through the process of cell death. These microstructural changes often require a significant period of time to manifest in a manner detectable by physical examination, delaying a physicians capacity to determine early treatment efficacy. In this study, we investigate the efficacy of quantitative ultrasound employed at a clinically-relevant frequency to detect microstructural changes in response to cancer-therapy administration.

Solid PC-3 prostate tumors were grown in SCID mice and treated in three groups. The first received ultrasonically-activated microbubble anti-angiogenic treatment, the second received an 8 Gy dose of single fraction, 100 kVp X-ray radiation and the third received administration of both. A varying set of treatment conditions employing the same treatment modalities provided varying degrees of apoptotic cell death that was examined via parametric-image analysis. Tumors were examined via 10 MHz ultrasound prior to treatment and at 24 hours afterwards. Animals were subsequently sacrificed and tumors excised for histopathological analysis using haematoxylin & eosin as well as TUNEL staining.

We observed an increase in ultrasound backscatter 24 hours following anti-angiogenic and radiation treatment administration. Analysis of the normalized power spectra of the 10MHz data yielded an increase of approximately 3.4dBr (0.9), 4.8dBr (0.8) and 5.9dBr (0.9) in the three treatment categories compared to data acquired before treatment. Spectral slope and 0-MHz intercept parameters followed similar trends. Parametric mappings of tumour regions indicated increasing spectral parameters in tumors undergoing larger fractions of cell death as determined using haematoxyline and eosin staining and immunohistochemistry.

This study examined the efficacy of quantitative ultrasound employed at a clinically-relevant frequency to detect changes in tissue microstructure in response to cancer therapy administration. The advent of a manner capable of noninvasively detecting changes in tumor

microstructure in response to cancer treatment administration would potentiate early assessment of treatment response and enable physicians to customize treatment based upon an individual patient response early in the treatment course.

6. Contrast

6.1 **High-frequency response of polymer-shelled ultrasound contrast agents: influence of shell parameters**, Jeffrey A. Ketterling,[1] Parag V. Chitnis,[1] Sujeeth Raj Koppolu,[2] Jonathan Mamou[1] and Daniel Gross,[1] *[1]Lizzi Center for Biomedical Engineering, Riverside Research, New York, NY and [2]Department of Chemical & Biological Engineering, Polytechnic Institute of New York University, Brooklyn, NY* (overview).

Polymer-encapsulated microbubbles represent the newest generation of ultrasound contrast agents (UCAs). These agents are more rigid than other classes of contrast agents, such as lipid-shelled agents, and it has been shown that the agents must be ruptured before they become acoustically active. The process for manufacturing polymer-shelled UCAs facilitates production of tightly-controlled size distributions and small diameters. The small diameters translate to higher resonance frequencies and potentially make the polymer agents suitable for high-frequency (>20 MHz) ultrasound (HFU) applications, such as dermatology, ophthalmology and small-animal imaging. Two types of characterization studies involving four types of UCAs were conducted in order to determine acoustic excitation and shell-material parameters relevant to HFU-induced rupture and nonlinear oscillations of the resulting microbubbles. First, the subharmonic response from individual UCAs was examined using HFU (40 MHz) excitation in an *in-vitro* flow phantom. Second, UCAs were subjected to slowly increasing static overpressure and 'fragility' (e.g., rupture pressure) was recorded. The overpressure-induced rupture exhibited a sharp threshold, which was not size dependent, but was dependent on the shell parameters, such as modulus and thickness. Similar to the overpressure study, the onset of UCA subharmonic activity exhibited a sharp acoustic-pressure threshold, which was also correlated with shell parameters. The results suggest that shell parameters can be adjusted to optimize polymer-shelled UCAs for specific diagnostic and therapeutic applications that rely on ultrasound-mediated UCA destruction. Supported by National Institutes of Health research grant EB006372.

6.2 **On the utility of subharmonic contrast microbubble signals**, F. Forsberg,[1] J.K. Dave,[1,5] V.G. Halldorsdottir,[1,5] J.R. Eisenbrey,[1] J.S. Raichlen,[3] J.B. Liu,[1] C. Miller,[2] J.M. Gonzalez,[2] M.E. McDonald,[4] D.A. Merton,[1] D. Brown[1] and V. Navarro,[2] *Departments of [1]Radiology, [2]Gastroenterology & Hepatology, [3]Medicine and [4]Radiologic Sciences, Thomas Jefferson University, Philadelphia, PA 19107 and [5]School of Biomedical Engineering and Health Systems, Drexel University, Philadelphia PA 191047, flemming.forsberg@jefferson.edu* (invited).

Our group (and others) has been developing contrast-enhanced subharmonic imaging (SHI) for improved depiction of tumor blood flow and to provide quantitative assessment of physiological parameters; in particular, the noninvasive estimation of hydrostatic blood pressures using subharmonic microbubble signals (a method known as SHAPE; U.S. Patent 6,302,845). In SHI. pulses are transmitted at one frequency but only echoes at half that frequency (i.e., the subharmonic) are received. Because the ability to generate subharmonic signals is exclusive to ultrasound contrast agents, SHI offers improved visualization of blood flow with nearly-complete tissue suppression.

Recently, we implemented software for real-time SHI and SHAPE on several commercial ultrasound scanners. Fourteen women with 16 biopsy-proven breast lesions (four malig-

nant) participated in a SHI pilot study, which also involved static and dynamic cumulative maximum intensity (CMI) SHI. The area under the ROC curve (A_z) for the diagnosis of breast cancer was 0.64 for grayscale and PDI, 0.67 with contrast enhanced PDI, 0.76 for mammography, 0.78 for SHI and 0.75 for static CMI-SHI. For dynamic CMI-SHI mode, Az increased to 0.90, which was significantly better than mammography ($p = 0.03$).

In four canines, SHAPE pressure measurements were acquired in the chambers of the heart and compared to an invasive pressure catheter. For two canines, the calibration factor for converting subharmonic signals to pressure (in mmHg/dB) was obtained from the aorta and LV pressure estimates were calculated using the known peak-systolic LV pressures. The maximum absolute errors for the LV diastolic pressures (LVDP) for mean LVDP, minimum LVDP, end LVDP and mean LV pressure were 1.36 to 5.48 mmHg, respectively. Moreover, estimating the peak systolic right ventricular (RV) pressure resulted in errors of 0.0 to 2.3 mmHg. Finally, a human trial of SHAPE in patients with portal hypertension is underway and preliminary results will be presented.

In conclusion, *in vivo* human and canine experiments have demonstrated the feasibility of performing breast SHI as well as cardiac and portal hypertension SHAPE, using commercial ultrasound scanners. The preliminary results are encouraging with SHAPE resolution on the order of 0 to 6 mmHg. Supported in part by U.S. Army Medical Research Material Command under DAMD17-00-1-0464 and W81XWH-08-1-0503 as well as AHA grant no 0655441U, NIH R21 HL081892 and RC1 DK087365 and GE Healthcare, Oslo, Norway.

6.3 **Dynamics of contrast microbubbles and their subharmonic response for non-invasive blood pressure estimation**, Kausik Sarkar,[1] Amit Katiyar[1] and Flemming Forsberg,[2] *[1]Mechanical Engineering, University of Delaware, 130 Academy Street, Newark, DE 19716 and [2]Department of Radiology, Thomas Jefferson University, 132 South 10th Street, Philadelphia, PA 19107, sarkar@udel.edu* (invited).

Estimation of local organ-level blood pressure can help in diagnosing and monitoring heart and vascular diseases. Subharmonic signals from ultrasound contrast microbubbles have been proposed as a noninvasive alternative to the current practice of using manometer-tipped catheters. An approximately 10dB linear decrease in subharmonic component with 25 kPa pressure increase (typical blood pressure variation) has been reported for several contrast microbubbles. In this talk, we will report on a theoretical investigation of the threshold of subharmonic generation and the dependence of subharmonic response on ambient pressure variation.

For a free bubble, there exists a threshold excitation pressure for subharmonic response, the threshold being minimum at twice the resonance frequency of the free bubble. We numerically show that for a number of models — Newtonian and viscoelastic interfacial rheological models developed by our group, a model due to de Jong and coworkers — of encapsulation, the minimum subharmonic threshold occurs near twice the resonance frequency similar to the case of a free bubble. However, for other models — Church-Hoff's linear viscoelastic model, model due to Marmottant et al and our recent strain-softening interfacial rheological model — the minimum threshold deviates from twice the resonance frequency. They have a minimum threshold near the resonance frequency depending on encapsulation parameters, such as elasticity and viscosity.

In the second part, we will show that a reduction of subharmonic with ambient pressure increase occurs only below a certain excitation frequency. Above another critical frequency, the subharmonic signal increases with ambient pressure. In between, the variation is nonmonotonic. Furthermore, where it decreases with ambient pressure, the relationship is linear only above certain excitation pressure. The behavior is explained by analyzing the dependence of resonance frequency of a bubble on the ambient pressure. The dependence of

the critical frequencies on bubble radius and possibly bubble size distribution will be discussed. Behaviors for several models for encapsulated contrast microbubbles will also be reported. Supported by NSF and NIH.

6.4 **Intravascular subharmonic imaging of atherosclerosis: an *in vivo* pilot study**, A. Sridharan,[1, 2] J.R. Eisenbrey,[1] E.D. deMuinck,[3] M.M. Doyley[4] and F. Forsberg,[1] *[1]Department of Radiology, Thomas Jefferson University, Philadelphia, PA 19107, [2]Department of Electrical and Computer Engineering, Drexel University, Philadelphia PA 19104, [3]Department of Cardiology, Dartmouth Medical School, Hanover, NH 0375 and [4]Department of Electrical and Computer Engineering, University of Rochester, Rochester, NY 14627, flemming.forsberg@jefferson.edu.*

Subharmonic imaging (SHI) of ultrasound contrast microbubbles using intravascular ultrasound (IVUS) provides excellent tissue suppression and a unique opportunity to exclusively image *vasa vasorum* blood flow, which could potentially better identify areas of plaque. In this study, the feasibility of visualizing atherosclerotic plaque neovasculature using parametric SHI IVUS was investigated *in vivo*.

Atherosclerosis was induced in the aorta of two Watanabe Heritable Hyperlipidemic rabbits by a combination of high cholesterol diet and balloon de-endothelization. Following injection of Definity (Lantheus Medical Imaging, N Billerica, MA), radiofrequency (rf) IVUS signals were acquired at 40 MHz using a Galaxy IVUS scanner (Boston Scientific, Natick, MA). SHI (at 20 MHz) was performed off-line by applying an 8th-order bandpass filter to the acquired rf data. Contrast-to-tissue ratios (CTRs) were computed for the vessel relative to the plaque area over four time points. CTRs were also calculated for the tissue-plaque and tissue-vessel from four tissue regions of interest (ROIs) at four time points over the contrast wash-in/wash-out cycle. Parametric images were generated showing cumulative maximum intensity (CMI), time to peak (TTP), perfusion (PER) and time-integrated intensity (TII) for the fundamental and subharmonic data sets and CTR measurements were recalculated for these images. Spectral analysis of the chosen ROIs was also performed based on the rf data.

Injection of contrast bubbles resulted in substantial signal enhancement and improved the delineation between the plaque and vessel lumen. In SHI mode, noticeable tissue suppression occurred (although intensity from the contrast agent was also reduced). No significant improvement in plaque-to-vessel lumen CTR was observed between the subharmonic and fundamental IVUS (2.1 ± 3.64 vs. 2.2 ± 4.20; $p = 0.5$). However, CTR for plaque-tissue was improved (11.8 ± 7.32 vs. 9.9 ± 7.06; p < 0.0001) for SHI relative to fundamental imaging. CMI and TII maps of both fundamental and subharmonic data provided increased CTR relative to nonparametric data sets ($p < 0.002$). Additionally, parametric maps for CMI, PER and TII of SHI IVUS showed significantly-improved vessel lumen to plaque CTR for SHI relative to the fundamental ($p < 0.04$). As expected, the frequency spectra from tissue and vessel lumen showed a signal dominated by the transmit frequency (37-39 MHz). Frequency spectra from vessel lumen, however, showed a larger subharmonic (20-22 MHz) relative to the tissue spectra indicating microbubble generation of subharmonic signals.

In conclusion, parametric SHI IVUS of atherosclerotic plaque is feasible and improves the visualization of atherosclerosis as demonstrated by improvements in the vessel lumen to plaque CTR. Supported in part by NIH grants RO1 HL088523 and RO1 CA 140338.

6.5 **Theoretical and experimental investigation of the dynamics of ultrasound contrast agents: occurrence of higher subharmonics**, Amin Jafari Sojahrood,[1] Raffi Karshafian,[1] Gregory J. Czarnota,[2] Yanjun Gong,[3] Eno Hysi,[1] Tyrone Porter[3] and Michael C. Kolios,[1]

[1]*Department of Physics, Ryerson University, Toronto, ON, Canada,* [2]*Department of Medical Biophysics, University of Toronto and Ontario Cancer Institute, Toronto, Ontario, Canada and* [3]*Department of Mechanical Engineering, Boston University, Boston, MA 02215* (invited).

Background: The nonlinear behavior of ultrasound contrast agents (UCAs) is a key parameter to suppress tissue signal and achieve enhanced blood contrast. Despite the rich nonlinear character of UCAs, their dynamics is very complex. Controlling the behaviour of UCAs is a challenging task especially since there is not enough information about the response of the UCAs to changes in the full control parameter space (UCAs radii, driving frequency and pressure and the shell parameters). On the other hand, limitations in the imaging device may impose another problem as the induced nonlinear behavior frequency response may not be within the bandwidth of the receiver. Complete knowledge on the dynamics of the UCAs will help in optimizing the control parameters to achieve a desirable nonlinear behaviour that can be detected by the imaging system.

Method: In this study, the dynamics of the UCAs is studied theoretically by solving the Hoff model. The results of the numerical simulations were visualized in an efficient manner for a large range of its control parameters. The bifurcations diagrams of the normalized oscillations of UCAs of different sizes were plotted versus the applied pressure. The predicted results were also verified experimentally by sonicating Artenga bubbles and an in-house made lipid shell bubbles with 30 cycle pulses of 25 MHz frequency and pressure amplitudes of 0.1-2.5 MPa using the Vevo770 (VisualSonics, Toronto, Ontario) imaging device. To estimate the bubble size, the ring-down oscillations of the bubbles at their natural resonance frequency and after the 30 cycle driving pulse was analyzed.

Results: Simulations showed that if the bubble sizes are optimized so that their resonance frequency is a fraction (1/3,1/4..) of the sonication frequency, above a certain pressure threshold, the bubbles can emit subharmonics at (1/3,2/3..) of the sonication frequency. This emission is concomitant with an increase in the backscattered pressure, while the bubble oscillations still remain stable. Experimental results showed that the subpopulation of the bubbles that are able to show this behavior scatter sound according to the theoretical predictions (e.g., having three maxima for subharmonics at f/3 and 2f/3) when the size of the bubble is derived from the ring-down analysis based on the same backscattered signal. In addition, size changes in bubbles due to acoustic irradiation were detected in some of the signals.

Discussion and Conclusion: It was shown that through careful UCA size selection and control of the incident pressure, the UCAs can emit signals at higher subharmonics than 1/2. Higher subharmonic signals will increase both the resolution and the sensitivity of the subharmonic imaging method, as these signals have higher frequencies that are closer to the central frequency of the transducer. For a signal which has (f/3 and 2f/3) subharmonics, there are three maxima in the backscattered pressure of the UCAs. This was verified experimentally by analyzing the signal from single bubbles with their size estimated from the ring-down analysis. In some cases, after a few cycles, significant changes in the bubble size were detected due to the ultrasound exposure. This was verified by the change of the signal shape (gradual disappearance of the maximas) and the ring-down analysis.

6.6 **Characterization of single ultrasound contrast agent collapse dynamics using postexcitation rebound signals,** Daniel King and William O'Brien, Jr., *Bioacoustics Research Laboratory, University of Illinois at Urbana-Champaign, 405 N. Mathews Ave., Urbana, IL 61801, daking3@illinois.edu* (invited).

Ultrasound contrast agents (UCAs) respond dynamically to ultrasound pulses. When insonified with sufficiently large peak rarefactional pressures (PRPA), single UCAs undergo inertial collapse that may contain broadband postexcitation emissions following their

principal response to excitation. A double-passive cavitation detection technique, involving the confocal alignment of one transmit and two passive receive transducers, was used to analyze the acoustic response emitted by a UCA from a specific localized volume. This technique allows single UCA behavior in response to large PRPAs to be characterized.

Sufficiently dilute mixtures of commercial (Definity and Optison) and noncommercial microbubbles were prepared such that on average only a single UCA was present within the confocal region. A 3 cycle incident pulse repeating at 10 Hz was varied in frequency from 0.9 to 7.1 MHz and in PRPA up to 6 MPa. The acquired signals were first categorized based on the symmetry of the response and also classified according to the presence or absence of postexcitation signals in the time domain. The postexcitation signal was hypothesized to indicate the transient collapse of the microbubble, an assumption supported by modeling suggesting that postexcitation rebound occurs only after shell rupture and inertial cavitation thresholds have been reached.

The percentage of symmetric signals exhibiting postexcitation emissions was found to increase as PRPA was increased or as frequency was decreased, general trends in agreement with other methods of measuring collapse. Distinct curves indicating the percentage of postexcitation signals as a function of PRPA were observed for different populations of UCAs; the native Definity population was found to have lower PRPA thresholds for postexcitation signals than the native Optison population. These distinctions provide insight into how the collapse behaviors of a given population microbubbles may be influenced by their various properties. Supported by NIH Grant R37 EB002641.

6.7 **Estimating concentration of ultrasound contrast agents with backscatter coefficients,** Scott M. Leithem, William D. O'Brien, Jr. and Michael L. Oelze, *Bioacoustics Research Laboratory, University of Illinois at Urbana-Champaign, 405 N Mathews, Urbana, IL 61801, leithem2@illinois.edu* (invited).

Ultrasound contrast agents (UCAs) are currently used clinically to enhance the contrast of ultrasound images. Recently, however, microbubbles have been explored as a means to enhance therapeutic techniques, such as sonoporation, lithotripsy and high-intensity focused ultrasound (HIFU). Because the effectiveness of these techniques relies on the concentration of bubbles at a target site in the body, it would be beneficial to be able to acquire real-time estimates of UCA concentration noninvasively. A novel method for estimating the concentration of UCAs at a target location, based upon estimates of backscatter coefficient (BSC) at frequencies above resonance of the UCAs, was developed. Calculation of the BSC was accomplished using ultrasonic reference measurements from the back plane wall of a Plexiglas® chamber developed for an experimental flow system. For each trial, an average of 500 snapshots of the ultrasonic backscatter from Definity® microbubbles flowing through the chamber was acquired. Immediately following this procedure, a sample of the UCAs was extracted from the flow path close to the target site in order to optically verify the concentration estimates. Using estimates of the attenuation coefficient through the cloud of bubbles, BSC was calculated as a function of frequency for the 15-25 MHz range. Ultrasonic-based estimates of UCA concentration were obtained by using a Levenberg-Marquardt fitting algorithm to match the calculated BSC to a linear-scattering model. The algorithm was able to converge for all trials in under 0.5 s, indicating that it was effective for providing real-time concentration information. Ultrasonic-based concentration estimates were compared to concentration estimates obtained optically with a hemacytometer. All ultrasonic-based estimates were within one standard deviation of optically-derived estimates. These results indicate that the BSC can be used to estimate the concentration of UCAs. Supported by NIH grant R37EB002641.

7.   Quantitative Ultrasound 3

7.1 **Power-spectral estimation for quantitative ultrasound in the presence of specular echoes**, Adam Luchies, William D. O'Brien, Jr. 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) techniques have been used to relate the power spectrum of the ultrasonic backscatter signal to acoustic and microstructural properties of biological tissues. When the tissue being examined is stochastic, i.e., composed of many randomly-positioned subresolvable scatterers, the backscatter signal power spectrum is estimated by averaging periodograms from adjacently-spaced scan line segments in a data block associated with a specific location in the tissue. Estimating the power spectrum in this manner requires the assumption that each data block contains uniform diffuse scattering, an assumption that is invalidated when a data block includes a nonstationary signal element such as a specular echo.

The goal of this work was to use Welch's method for power spectrum estimation to obtain data-block power-spectral estimates that were unaffected by specular echoes. The Welch method functions by segmenting time-domain signals into overlapping windowed subsections and transforming them into the frequency domain using the Fourier transform. The resulting modified periodograms are averaged to form the smoothed spectral estimate. Data block scan line segments were segmented into three overlapping (50%) Welch subsections. Welch subsections were tested for amplitude nonstationarities and removed from the periodogram average if an amplitude nonstationarity was detected. The method produced spectral estimates for each data block that were unaffected by specular echoes.

The method was applied to simulated and experimental backscatter data containing specular echoes. For example, a reduction of 51% was observed in the standard deviation of effective scatterer diameter (ESD) estimates from a simulated backscatter image containing several specular echoes (with the size of the specular scatterers twice that of the background scatterers). As another example, a reduction of 43% was observed in the standard deviation of ESD estimates measured from the inside of a rodent tumor containing several specular echoes. Results suggest that the described Welch's segment-exclusion method can reduce the effects of specular echoes on QUS estimates, leading to more precise estimation of the ESD parameter. Supported by NIH Grant CA111289.

7.2 **A graphical user interface for quantitative ultrasound data analysis**, Timothy J. Hall,[1] Lindsey Carlson,[1] Andrew Battles,[2] David P. Duncan,[1, 3] James A. Zagzebski[1] and William D. O'Brien Jr.,[2] *[1]Department of Medical Physics, University of Wisconsin, Madison, WI, [2]Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, Urbana, IL and [3]Siemens Healthcare USA Ultrasound Division, Mountain View, CA, tjhall@wisc.edu.*

Objective: Quantitative ultrasound (QUS) imaging techniques are being developed and tested as adjunctive information for medical diagnosis, monitoring disease progression and therapy. Common applications include breast imaging, thyroid imaging and uterine cervical assessment. One of the fundamental steps in many QUS techniques is power-spectral estimation from radiofrequency echo data and it is clear that there is a wide variety of methods for this task. In addition, there are a variety of methods available for estimating 'simple' acoustic properties such as acoustic-attenuation coefficients. To better facilitate application of QUS techniques to different anatomical sites and using various data acquisition systems, tools to aid in common signal selection and processing tasks would be useful. This report describes a graphical user interface to assist in QUS data analysis. The intent is to provide a

common interface for importing echo signal data, selecting regions of interest, computing power spectra and estimating and displaying a variety of QUS parameters.

Method: The GUI in its current form is being shared by two research groups (UW and UIUC). Those groups are jointly developing, testing and enhancing its performance. The tool is being implemented using Matlab as a base signa- processing package. Input data formats include signals from single-element transducer laboratory apparatus as well as from a variety of array-based clinical ultrasound systems, such as the data from the Siemens Axius Direct ultrasound research interface (Siemens ACUSON Antares and S2000), the Ultrasonix RP and the Visualsonics Vevo2100. Selections of analysis conditions such as regions of interest, signal-windowing functions, spectral estimators and computed parameter outputs are provided. The GUI also has software to estimate parameters based on the envelope statistics and the generalized spectrum. Additional parameter-estimate algorithms are currently being implemented and tested. Broad availability of this GUI and associated algorithms is expected in the near future. To test the programming, comparisons are done between attenuation and backscatter coefficients vs. frequency output by the GUI algorithms and results provided by separate programs already implemented by the groups.

Results: The GUI, its source code, algorithm source code and test data from phantoms and *in vivo* scans will be broadly distributed via FTP web access. By making this GUI, the algorithms behind it and sample data sets available to the world-wide 'Tissue Characterization Community,' we expect that users can test these algorithms with the provided data, and compare with published results, to assure proper usage. They can then test their algorithms with the same data or test their data with these algorithms. The anticipated result is a significant advance in the ability to perform and advance QUS technology. Supported by NIH Grants R01CA111289 and R21HD061896.

7.3 **Ultrasonic backscatter coefficient quantitative estimates from Chinese hamster ovary and BALB/3T3 cell pellet biophantoms**, Aiguo Han, Rami Abuhabsah, James P. Blue, Jr., Sandhya Sarwate and William D. O'Brien, Jr., *Bioacoustics Research Laboratory, Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, 405 N. Mathews, Urbana, IL 61801.*

Objective: Model-based quantitative ultrasound (QUS) imaging requires scattering models that match well anatomic microstructure scattering sites. The anatomic model under evaluation is that of a eukaryotic cell. Previous work has demonstrated that backscatter coefficient (BSC) estimates made from low-concentration, Chinese hamster ovary (CHO) cell pellets agree well with the concentric-spheres model. This work has two objectives. First, large concentration CHO cell pellets are studied to observe the effect of coherent scattering. Second, BALB/3T3 fibroblast cell pellets are studied to further validate the applicability of the concentric spheres model for low-cell concentrations.

Methodology: Live cells of known concentration are placed in a mixture of bovine plasma and thrombin to form a clot, what we call a cell pellet. BSC measurements of cell pellet biophantoms containing either CHO (13 μm in diameter) or 3T3 (23 μm in diameter) cells were made with 20, 40 and 80 MHz focused transducers (overall bandwidth: 10-100 MHz). Cell pellets were then histologically processed (H&E) for assessment.

Results: First, 18 - CHO cell pellet samples with six different number densities (1.2, 5.0, 20, 72, 224, 473 Mcells/mL) were evaluated. The results show that the BSC magnitude as a function of number density is nonlinear under the condition of large concentration due to coherent scattering. The estimated cell diameter using concentric spheres model decreases with number density (15.8, 14.6, 15.1, 13.6, 9.6, 7.1 μm for 1.2, 5.0, 20, 72, 224, 473 Mcells/mL cell pellets, respectively), which indicates that the concentric spheres model is not accurate for large cell concentrations. Second, 12 - 3T3 cell pellet samples with 4 differ-

ent number densities (1.2, 4.8, 18, 52 Mcells/mL) were evaluated. The estimated BSC agrees well with the concentric spheres model. Fitting the data to the concentric spheres model yielded average cell diameter estimates of 20 μm and nuclear diameter estimates of 10 μm for 3T3 cells.

Conclusion: At a large cell concentration, coherent scattering appears to affect the magnitude and shape of the BSC vs. frequency curve and consequently the QUS parameter estimates from theoretical models. The concentric spheres model is not adequate for this case. However, for a low cell concentration, the concentric spheres model is applicable to both CHO and 3T3 cells and is able to differentiate CHO and 3T3 cells merely based on cell diameter. Supported by NIH R01CA111289.

7.4 **A simulation study on the photoacoustic signals from nonaggregating and aggregating erythrocytes**, Ratan K. Saha, Eno Hysi and Michael C. Kolios, *Department of Physics, Ryerson University, 350 Victoria Street, Toronto, Canada, M5B2K3, ratank.saha/ eno.hysi/mkolios@ryerson.ca.*

Background: Photoacoustic (PA) imaging combines the molecular specificity provided by optical imaging and the resolution provided by clinical ultrasound to probe the optical and thermoelastic properties of tissue. By exploiting the large optical absorption of oxygenated and deoxygenated blood at the appropriate wavelengths, it can differentiate the oxygenation states of erythrocytes. Erythrocyte aggregation is observed in a wide range of circulatory disorders. Since the aggregation of erythrocytes alters their spatial organization, we hypothesize that this erythrocyte aggregation would alter the photoacoustic signal produced and could be detectable using PA spectral analysis. The technique presented here demonstrates the potential of PA imaging as a diagnostic modality for detecting erythrocyte aggregation based theoretical calculations of the PA signal as a function of aggregate size.

Method: Two-dimensional blood tissue realizations simulating nonaggregating erythrocytes were generated using a Monte Carlo method known as Random Sequential Adsorption. Coordinates of nonaggregating erythrocytes were randomly chosen with the restriction that they would not overlap with existing particles under periodic boundary conditions. A hexagonal-packing scheme was used to arrange individual erythrocytes forming an aggregate. Such an aggregate was then placed randomly and repeatedly within the region of interest to generate an aggregated blood sample. The PA signal from a collection of cells emulating a tissue realization was simulated by using the linear-superposition principle for the spherical waves generated by the erythrocytes. For each erythrocyte (approximated as a homogeneous sphere), the PA pressure due to the exposure to a delta-function laser pulse was computed by employing a frequency-domain approach. The PA signal properties, such as envelope statistics and frequency-dependent power spectra, were investigated by varying the hematocrit and aggregate size for 250 tissue realizations for each erythrocyte hematocrit/aggregate size condition examined.

Results: A monotonic increase in the PA signal amplitude was observed with increasing hematocrit (for nonaggregating erythrocytes) and the corresponding signal envelope histograms followed the Rayleigh distribution. The dominant frequency content of the signal appeared at approximately 200 MHz. For aggregated erythrocytes, the PA signal amplitude increased as the mean radius of gyration of aggregates increased. The Rayleigh fit parameter, associated with the best fit curves of the PA signal envelop histograms, also increased as the aggregate size increased. The spectral intensity in the low frequency regime increased significantly as the mean size of clusters increased compared to the nonaggregating case. For example, at 15.6 MHz for cluster sizes of 9.79 μm and 15.39 μm, we found 8 dB and 11 dB enhancements, respectively, in the PA spectral intensity compared to the nonaggregated tissue sample.

Conclusion: To the best of our knowledge, the PA method discussed here has never been applied to the investigation of erythrocyte aggregation. Our simulation results show a large increase in spectral intensity of the PA signals, specifically 11 dB for the largest aggregate size compared to the nonaggregated sample near diagnostic ultrasound frequencies. This suggests that aggregated samples of blood could be assessed using PA spectroscopy. The simulation method developed here can easily be extended to generate more realistic tissue realizations (such as erythrocyte rouleaux) in 3D. This study demonstrates the feasibility of PA imaging for the clinical detection and assessment of erythrocyte aggregation.

7.5 **Estimations of acoustic attenuation and backscatter coefficient of rodent tumor-mimicking structures**, Ivan M. Rosado-Mendez,[1] Kibo Nam,[1] Lauren A. Wirtzfeld,[2] Goutam Ghoshal,[2] Alexander D. Pawlicki,[2] Viksit Kumar,[3] Ernest L. Madsen,[1] 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, WI, [2]Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, Urbana, IL and Department of Mechanical Engineering, Iowa State University, Ames, IA, rosadomendez@wisc.edu.*

Objective: The attenuation ( ) and backscatter coefficients (BSCs) of tissue are inherent characteristics and, as such, their estimations are expected to be independent of the probing system and the data-processing technique. A recent characterization of spontaneous fibroadenomas and implanted carcinomas in live rodents was conducted with several different imaging systems. Fibroadenomas exhibited unexpectedly high attenuation coefficients and estimated BSCs within and among these tumors exhibited large variability.[1] Thus, it is imperative to evaluate the experimental methodology using well-characterized phantoms where agreement between systems can be compared to each other and to ground truth. The current work is a multisystem, phantom-based comparison of   and BSC estimates under conditions emulating *in vivo* rodent-tumor scanning.

Method: A phantom with a homogeneous background containing two lesion-mimicking, 1.5 cm diameter spherical inclusions with different attenuation and backscattering properties (1.0 and 1.5 dB/cm-MHz with 25-43 and 75-90 m glass beads, respectively) was constructed. The inclusions protruded from the surface of the phantom, mimicking conditions under which live animal tumors were studied. Inclusions were scanned with four different ultrasound systems: an Ultrasonix RP, a VisualSonics Vevo2100, a Zonare Z.one, and a Siemens Acuson S2000, each using linear array transducers and each providing radiofrequency (rf) echo data. Estimates of   for the inclusions were computed from the rf data either by a reference phantom method[2] or by a hybrid method.[3] BSCs were estimated using the reference-phantom method.   and BSC estimates made with the clinical systems were compared with laboratory measurements from test cylinders of the phantom contents, obtained during phantom construction. The latter measurements applied a substitution technique and single element transducers. Faran theory predictions, based on the known phantom composition, were also included in the BSC comparisons.

Results: Laboratory-based estimates of   were 1.0 dB/cm-MHz (sphere 1) and 1.58 dB/cm-MHz (sphere 2). Fractional differences of clinical-based estimates from these values ranged from 0 to 26% (sphere 1) and from 0.6 to 25% (sphere 2). Preliminary results of BSCs were comparable to laboratory-system estimations and Faran-theory predictions. Intersystem variability was larger in the case of the highly attenuating sphere. Supported by NIH Grant R01CA111289.

(1) Wirtzfeld et al. *J Ultrasound Med 29,* 1117-1123 (2010). (2) Yao et al. *Ultrasonic Imaging 12,* 58-70 (1990). (3) Kim and Varghese. *Ultrasound Med Biol 34,* 1808-1819 (2008).

7.6 **Attenuation and backscatter coefficient estimates in layered tissue-mimicking phantoms**, Kibo Nam,[1] Ivan M. Rosado-Mendez,[1] Lauren A. Wirtzfeld,[2] Goutam Ghoshal,[2] Alexander D. Pawlicki,[2] Viksit Kumar,[3] Ernest L. Madsen,[1] 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, WI, [2]Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, Urbana, IL and [3]Department of Mechanical Engineering, Iowa State University, Ames, IA, kibonam@wisc.edu.*

Backscatter and attenuation coefficient estimates are essential elements in many Quantitative Ultrasound Imaging modes. In clinical applications, some of these parameters are not easily obtained because of inhomogeneities of overlying tissue above a region of interest. In a previous study,[1] using rf echo signal data acquired by a Siemens Antares imaging system and applying a reference phantom method[2] to account for system dependencies, excellent agreement was obtained among backscatter coefficients and attenuation estimations from well-controlled laboratory experiments with layered phantoms and theoretical values. The goal of the current study is to assess the reproducibility of backscatter and attenuation estimates of layered phantoms scanned with a variety of clinical ultrasound systems.

Two phantoms were scanned using linear-array transducers. Both phantoms have three layers. One phantom has a uniform attenuation coefficient in all layers but the middle layer has 6 dB higher backscatter. The other phantom has uniform backscatter in all layers but the middle layer has a 0.2dB/cm-MHz higher attenuation coefficient. These properties were verified using substitution measurements applied to cylindrical test samples formed during phantom construction. The layered phantoms were scanned with four clinical ultrasound imaging systems: a Siemens Acuson S2000, an Ultrasonix RP, a Zonare Z.one and a VisualSonics Vevo2100, and rf echo data were stored for offline analysis. The attenuation coefficient from each layer was estimated using the reference phantom method[2] independently implemented by each research group, and the backscatter coefficient for each layer was calculated using the attenuation measurements from cylindrical samples of each layer obtained by substitution method measurements in the laboratory.

The attenuation and backscatter coefficients estimates from the Siemens system data showed very good agreement with results from the laboratory measurements and theoretical values for each layer. The attenuation coefficient error varied from 0-15% for the different layers. This study demonstrates that the attenuation and backscatter measurements from layered media can be accurately estimated with a clinical imaging system that provides the appropriate echo data. Supported by NIH Grant R01CA111289.

(1) Nam et al. UITC (2009) (abstract). (2)Yao et al. *Ultrasonic Imaging, 12*, 58-70 (1990).

8.   Quantitative Ultrasound 4

8.1 **Development of artery-mimicking poly(vinyl alcohol) cryogel phantoms**, Benjamin L. Johnson, Joseph J. Hoffman, Jonathan I. Katz, Mark R. Holland and James G. Miller, *Washington University in St. Louis, St. Louis, MO, james.g.miller@wustl.edu..*

Background: Continuing development of very high frequency Intravascular Ultrasound (IVUS) imaging systems has led to a need for stable, accurate arterial tissue-mimicking phantoms. Poly(vinyl alcohol) cryogel has shown considerable promise as an ultrasonic phantom material because of its tissue-like speed of sound, low intrinsic ultrasonic attenuation and scattering properties, high structural rigidity and potential indefinite longevity.

Recent measurements by our laboratory of the ultrasonic properties of human coronary arteries provide the target values for the phantom's ultrasonic characteristics. Values for the

speed of sound, frequency-dependent attenuation coefficient, apparent integrated backscatter and frequency-dependent backscatter coefficient of each layer (intima, media, adventitia) of human coronary arteries were determined from these measurements.

Objective: The objective of this work was to develop a series of individual poly(vinyl alcohol) cryogel phantoms that mimic the acoustic properties of each layer of the coronary arteries and to then construct layered artery-mimicking intravascular ultrasound phantoms.

Methods: The phantom material consisted of an aqueous poly(vinyl alcohol) solution (5–15%) that also contained specific concentrations of polyurethane and graphite nanofibers with the proportions chosen to match the ultrasonic properties of the desired arterial layer. In order to crosslink the phantom solution, the phantoms were put through 2 to 10 freeze/thaw cycles in a chest freezer. Measurements of the speed of sound, attenuation coefficient and backscatter properties of the phantoms were made at 37 C using an acoustic microscope with transducers of nominal center frequencies of 25 MHz, 50 MHz and 100 MHz (covering a bandwidth of approximately 20 MHz to 105 MHz). Artery-mimicking poly(vinyl alcohol) cryogel phantoms were constructed using a custom phantom mold. Intravascular ultrasound images of the phantoms were made with an intravascular ultrasound imaging system (Volcano s5i) with imaging catheters (the 20 MHz Eagle Eye and the 40 MHz Revolution).

Results: The phantom material exhibited a speed of sound of that corresponded well with the measurements made in coronary arteries. The phantom's attenuation properties matched those of the medial coronary artery layer over the bandwidth measured. The frequency dependence of the attenuation coefficient (the slope of attenuation) in the phantoms was linear over the frequency ranges investigated and matched well with the slope of attenuation measured in all three arterial layers. The apparent integrated backscatter values and the backscatter coefficient of the phantoms were both consistent with the measurements made in coronary arteries. The IVUS images made of the artery-mimicking phantoms looked very similar to IVUS images of actual human coronary arteries.

Conclusion: Poly(vinyl alcohol) cryogel phantoms were constructed with ultrasonic speed of sound, frequency dependence of the attenuation coefficient and backscattering properties similar to each layer of the coronary arteries. Additionally, the attenuation coefficient of the poly(vinyl alcohol) cryogel phantoms was increased to a point where it matched the attenuation properties of the medial layer well. Special thanks to Russ Fedewa, Anuja Nair, Stacy Amatangelo, and Amanda McNeeley at Volcano Corporation. This work was supported, in part, by NIH HL40302 and benefited from an equipment loan from Volcano Corp.

8.2 **Ultrasonic propagation properties of fibroadenomas *in vitro***, Ellora Sen-Gupta, Alexander D. Pawlicki, Lauren A. Wirtzfield, Rita J. Miller, Andrew P. Battles and William D. O'Brien, Jr., *Bioacoustics Research Laboratory, Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, 405 N. Mathews, Urbana, IL 61801, esengup2@uiuc.edu .*

Currently, there are no very specific and well-defined ranges of acoustic properties known for fibroadenomas. The purpose of this study was to determine specific ultrasonic propagation properties of rat fibroadenomas *in vitro* in order to better understand these properties relative to quantitative ultrasound techniques. Having a database of values for the attenuation, speed of sound and ultrasonic backscatter provides quantitative information for improved tumor classification. Single-element transducers with center frequencies of 3.5, 7.5, 10 and 13 MHz were used to scan excised rat fibroadenomas with the focal region inside the tissue to obtain backscatter data. The fibroadenomas were then sliced into multiple sections and placed on a reflector for through-attenuation and speed-of-sound measurements.

The rat's liver was excised and scanned in the same way because liver values are known to within a reasonable range and can validate the methods used to obtain results from the fibroadenoma data. The backscatter data illustrated the heterogeneity of the fibroadenoma tissue with an estimated scatterer diameter range of 50 to 200   m, which was also supported by the attenuation values ranging between 1 and 4 dB/cm-MHz and sound-speed values varying between 1500 and 1600 m/s compared to the sample liver attenuation value of about 0.5 dB/cm-MHz and a sound speed range of 1520 to 1560 m/s. These results show a range of values for the ultrasonic propagation properties that better define the heterogeneous nature of fibroadenomas for improved tumor classification in the future. Supported by NIH Grant R01CA111289.

8.3 **Investigation of cerebral hemodynamic alterations in response to blunt cervical vascular injuries,** Dianna Purvis,[1] Tayseer Aldaghlas,[2] Anne Rizzo[2] and Siddhartha Sikdar,[1] *[1]Departments of Neuroscience and Electrical and Computer Engineering, George Mason University and [2]Department of Trauma Services, Inova Fairfax Hospital.*

Background: Trauma is the leading cause of death in the United States for individuals younger than 45 years of age. Motor vehicle crashes in the United States are the most common cause of blunt trauma injury resulting in nearly five million injuries in 2009. Further, the World Health Organization projects that traffic accidents will be the third leading worldwide health problem by the year 2020. The incidence of blunt cervical vascular injury (BCVI) has been reported as 1-3% of a blunt trauma population, with a 25% mortality incidence from undetected BCVI and a stroke rate of 60%. Undetected BCVI often lead to adverse neurological sequelae in this predominately younger population. Screening for BCVI with computed tomography angiography (CTA) is currently more common than conventional angiography. Although CTA is a validated screening modality, the diagnosis remains imperfect due to high false positive rates. Furthermore, CTA is invasive, requires patient translocation and radiation exposure coupled with contrast risks. Doppler sonography has demonstrated a high specificity in detection of vascular injuries. We are investigating the bedside use of transcranial Doppler (TCD) sonography during initial assessment and evaluation of BCVI in severely-injured trauma patients.

Objective: The goal of this study is to characterize and quantify both local cervical and global cerebrovascular hemodynamic alterations in response to BCVI.

Methods: This is a prospective pilot study conducted at a large level I trauma center. Trauma patients enrolled in the study are screened for BCVI with CTA, followed within 48 hours by a complete TCD examination, following approved procedures. All extracranial cervical and intracranial vascular segments are insonated using a portable multigate power M-mode TCD unit (Spencer Technologies, ST3) with a 2-MHz pencil probe. The insonation scheme is novel in that TCD data is collected for all extracranial cerebral supply vessels, and each segment of the Circle of Willis arterial supply. An inverse damping factor was used to quantify dampened flow due to thrombus-obstructing injured vessels, identification of bilateral asymmetries in mean flow velocity and altered cerebral hemodynamics indicated by waveform morphology. Doppler indices were then derived from the spectral waveform and used to characterize flow alterations.

Results: Ten trauma patients meeting study criteria, some with multiple BCVI, have been studied to date. Four subjects were diagnosed by CTA with BCVIs and another was identified as probable. The remaining five subjects were BCVI negative per CTA. One BCVI subject had contralateral innominate and subclavian artery pseudoaneurysms concurrent with an internal carotid artery (ICA) and vertebral (VA) dissection. Another subject presented twice at another treatment facility and was sent home each time, then presented at our facility and was diagnosed with a cerebellar infarct subsequent to undetected VA dissection. Bilat-

eral VA dissections along with altered middle cerebral artery flow were noted in another subject.

Local cervical TCD spectral waveforms indicate disturbed hemodynamics suggestive of obstruction and correlate with positive CTA results. Specifically, preliminary analysis of one ICA dissection indicated a downstream flow dampened to 23% of the upstream flow. These cervical hemodynamic alterations had a global cerebral effect, extending downstream beyond the local-injury site. Global cerebral-flow alterations were noted on TCD spectral waveforms; specifically, the subject described above with multiple ICA, VA, innominate and subclavian vascular injuries demonstrated a basilar artery steal phenomena and local cervical spectral waveform alterations that include tardus-parvus and to-and-fro waveforms. Our data findings show cerebral spectral waveform anomalies that include: bruits, high resistance flow, absent antegrade diastolic flow, reverse flow and reversed ipsilateral ophthalmic artery flow. Bilateral mean flow velocity asymmetries greater than 25% were also noted between left and right middle cerebral arteries.

Discussion: Preliminary results indicate that TCD is able to detect altered local- and global-flow signatures associated with BCVI confirmed by CTA. Whereas CTA provides definitive anatomical assessment of vascular injury, TCD provides rich flow data regarding hemodynamic abnormalities and vessel wall integrity without contrast and patient risk. Local and global neurovascular changes in the BCVI injured patient are not well studied. Indices derived from TCD spectral waveforms can be analyzed to assess severity of injury. Studies have shown that the stroke rate is higher when thrombus obstructs 25% or more of the injured vessel. Subsequent analyses will use a network analysis approach to further elucidate hemodynamic alterations and consequent autoregulation in response to BCVI. This methodology will assess system behavior in response to a local perturbation. Methods will include modeling each Circle of Willis arterial segment with an appropriate surrogate such as a resistor-capacitor (RC) circuit representation and quantification of pressure-flow relationships to identify hemodynamic flow alterations. In addition, a means cluster analysis of Doppler indices for each arterial segment will be conducted to identify potential signatures associated with BCVI to inform pattern-recognition algorithms and assess cerebral-perfusion status. BCVI assessment and evaluation with portable TCD has huge potential for field and bedside screening of injured patients. We believe the hemodynamic information derived from TCD assessment has the potential to alter the patient care pathway and improve outcomes.

8.4 **Wide-bandwidth measurement (22 MHz–105 MHz) of the ultrasonic attenuation of the coronary artery layers**, Joseph J. Hoffman,[1] Benjamin L. Johnson,[1] Mark R. Holland,[1] Russell J. Fedewa[2] and James G. Miller,[1] *[1]Washington University in St. Louis, St. Louis, MO and [2]Volcano Corporation, San Diego, CA, james.g.miller@wustl.edu.*

Background: The attenuation coefficient plays a significant role in shaping the images created by ultrasonic scans, including those generated by intravascular ultrasound (IVUS) procedures. The effect of attenuation is complicated in IVUS by the layered nature of vascular tissue. Signals received from the deeper layers are influenced by the intervening layers. Furthermore, the properties of the layers can vary substantially from person to person and from site to site within the same individual. Atherosclerotic plaque, if present, presents an additional inhomogeneous layer through which the sound must travel.

Objective: Currently, little is known about the attenuation of the tissues that make up coronary arteries. The goal of this study was to quantify the attenuation of the layers of the coronary arteries at frequencies pertinent to intravascular ultrasound.

Methods: Nineteen human left anterior descending coronary arteries were collected at autopsy. From these 19 vessels, 36 fresh (not chemically fixed) segments were ultrasonically

imaged and measured in the axial orientation with three transducers of nominal center frequencies 25, 50 and 100 MHz. For each segment, a C-scan was performed in a raster pattern with each transducer and at each scan site, the attenuation coefficient was determined by a substitution technique. Comparison of the ultrasonic data with subsequently-generated histology images permitted identification of the adventitia, media and intima/plaque layers.

Results: The measured attenuation coefficients of the constituent coronary-artery tissue layers showed a monotonic increase with frequency over the bandwidth (22-105 MHz). The frequency-dependent attenuation coefficients exhibited continuity across the bandwidth, indicating consistency among the measurements. The attenuation coefficient of each layer was well fit by a single line over the full 22 MHz to 105 MHz bandwidth and from this fit, the slope of attenuation of the adventitia, media and intima/plaque layers were found to be 0.16 dB/mm/MHz, 0.10 db/mm/MHz and 0.20 dB/mm/MHz, respectively. At all frequencies, the media layer demonstrated consistently less attenuation than the intima/plaque and adventitia layers.

Conclusion: The results generated from this study appear to represent the most comprehensive measurements of the axial attenuation coefficient of fresh human coronary-artery tissue and atherosclerotic plaque to date. The axial-attenuation coefficient at the frequencies of current and near future intravascular ultrasound is the lowest in the media and higher in the intima/plaque and adventitia. This result may be useful for future work modeling the ultrasonic and mechanical properties of coronary artery layers and plaques and may be relevant for the design and application of new intravascular ultrasonic imaging devices. Special thanks to Anuja Nair, Amanda McNeeley, and Stacy Amatangelo at Volcano Corporation. Support provided in part by Volcano Corporation and by NIH R01 HL 40302.

8.5 **On-axis evaluations of the power-law impulse response for a circular piston**, Christopher T. Johnson and Robert J. McGough, *Department of Electrical and Computer Engineering, Michigan State University, East Lansing, MI* 48824, *mcgough@egr.msu.edu.*

Ultrasound propagation in biological media often follows a frequency-dependent power-law relationship that increasingly attenuates the pressure as the frequency increases. This power-law relationship is accompanied by dispersion, where higher frequencies travel faster than lower frequencies. This combination of power-law attenuation and dispersion, when evaluated in the time domain as a function of increasing propagation distance, causes temporal spreading in the impulse response as the amplitude decreases. The effects of power-law attenuation and dispersion are modeled in the time-domain with analytical Green's functions that exactly solve the power-law wave equation. These time-domain Green's functions are causal for power-law exponents $0 < y < 1$ and are noncausal for power-law exponents $y \geq 1$.

To demonstrate the effects of diffraction, attenuation and dispersion in the nearfield region, the on-axis impulse response for a circular piston was evaluated in both the time- and frequency-domains for a tendon-like medium with a power-law exponent of 0.763 and an attenuation coefficient of 0.56 Np/cm/MHz$^{0.763}$. The impulse response was computed with the Rayleigh-Sommerfeld integral, which superposes contributions from the power-law Green's function in both space and time. The expressions for the time-domain Green's functions are proportional to scaled stable distributions, which are evaluated with the STA-BLE toolbox. In the frequency-domain, the Green's function is evaluated numerically using the characteristic function for the stable distribution.

The results show that frequency-domain calculations of the impulse response encounter aliasing problems if the spacing between frequency samples is too large. When the impulse response is calculated in the frequency-domain, this aliasing causes wrap-around errors in the time-domain. The aliasing problems, which are a consequence of the slowly-decaying tail of the stable distribution, are diminished when the spacing between adjacent frequency

samples is significantly reduced. Equivalently, the aliasing problems are alleviated when the time window defined for impulse-response calculations is extended until the tail of the stable distribution has decayed to a sufficiently small value. Thus, due to the heavy tail of the stable distribution, the time duration of the impulse response is significantly longer in power-law media than in lossless media. In contrast, impulse response calculations evaluated in the time-domain are independent of the number of time samples and the length of the time window; therefore, the aliasing problems that are inherent to frequency-domain calculations are avoided when the impulse response is computed in the time-domain. These features facilitate accurate time-domain calculations of the impulse response within shorter time windows or with fewer time samples. Despite these differences, numerical evaluations show that the frequency- and time-domain calculations converge to the same result when the frequency-domain representation of the Green's function is sufficiently sampled. Supported in part by NIH grant R01 EB012079.

8.6 **Numerical evaluations of power-law Green's functions,** Donald J. VanderLaan and Robert J. McGough, *Department of Electrical and Computer Engineering, Michigan State University, East Lansing, MI 48824, mcgough@egr.msu.edu.*

The power-law wave equation, which is an extension of the Szabo wave equation, models power-law attenuation and dispersion for power-law exponents $0<y<1$ and $1<y$ 2. Solutions to the power-law wave equation are causal for $0<y<1$ and noncausal for $1<y$ 2. Caputo's fractional wave equation, which was applied to models of biological tissue by Wismer, also models attenuation and dispersion for $1<y$ 2. The Caputo wave equation is causal for all power-law exponents $1<y$ 2. To facilitate comparisons between the Green's function solutions for these two wave equations, a mapping function is defined and the parameters for the power-law wave equation are converted into equivalent values for the Caputo wave equation. The Green's functions for each of these wave equations are evaluated in the time- and frequency-domains at 2 MHz for a phase velocity of 1595 m/s, an attenuation of 77.85 Np/m, and a power-law exponent of $y = 1.4$. In the frequency-domain, the frequency-dependent phase velocities and attenuation coefficients are comparable at distances far from the source but significant differences are observed closer to the source. In the time-domain, the Green's functions demonstrate nearly identical behavior in the farfield region. However, the time-domain Green's function for the power-law wave equation can produce noncausal results in the nearfield region, whereas the Caputo wave equation is causal everywhere for all positive relaxation times and sound speeds. In the time-domain, these Green's function evaluations differentiate between causal and noncausal behavior, which is indicated by the absence or presence of a response that precedes the input. Numerical results demonstrating each of these properties will be presented and the strengths and weaknesses of each wave equation will be discussed.

9. Review, Priorities and Funding of NIH Programs

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

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

9.3 **NIH/CSR**, Lee Rosen, *Scientific Review Administrator for Biomedical Imaging Technology, Center for Scientific Review, NIH* (invited)

10. ARFI/Elasticity

10.1 **Recent results and advances in transthoracic cardiac acoustic radiation force impulse imaging**, David P. Bradway, Stephen J. Rosenzweig, Joshua R. Doherty, Dongwoon Hyun and Gregg E. Trahey, *Duke University, Durham, NC, david.bradway@duke.edu.*

We have previously shown feasibility of transthoracic cardiac acoustic radiation force impulse (ARFI) imaging in animal studies, despite known limitations in the system hardware specifications, receive-beam parallelism and data processing and display rates. Several concurrent projects carried out by the authors of this work have sought to address these limitations while further developing ARFI imaging methods. Firstly, we are currently working to implement next-generation ARFI imaging on the Siemens ACUSON SC2000 system. We are utilizing its robust power supply and high parallel-receive channel count for sustained excitations and fast off-axis tracking. Transthoracic cardiac ARFI images from this new system will be presented. Secondly, we have worked to improve computation and display speeds for use with our current ARFI imaging systems, the Siemens ACUSON Antares and S2000. The real-time processing code implemented by the authors utilizes NVIDIA's CUDA parallel computing architecture on a graphics processing unit (GPU) for calculating the displacement estimation between tracking lines. In previous transthoracic cardiac ARFI tools, relatively long processing and display times made it difficult to do real-time ROI selection, to get quick, high-quality feedback and to further develop the method into a clinically-viable tool. Early studies either relied on simple filtering and processing of only a small subset of the acquired data, or were completed while 'flying blind' with delayed off-line analysis. In this work, we will show results from animal studies which were acquired with real-time guidance. We will discuss future work to combine these two projects and to utilize powerful instrumentation, fast processing and near-real time display in the clinic. Supported by NSF Graduate Research Fellowship and NIH grant #5R37HL 096023. The authors thank the Ultrasound Division at Siemens Medical Solutions, USA, Inc. for technical and in-kind support.

10.2 **Intracardiac ARFI imaging: applications, advancements and results**, Peter J. Hollender,[1] Stephanie A. Eyerly,[1] Stephen J. Hsu,[2] Patrick D. Wolf[1] and Gregg E. Trahey,[1] *[1]Duke University, Durham, NC and [2]Siemens Medical Systems, Issaquah, WA, peter.hollender @duke.edu*

Acoustic Radiation Force Impulse (ARFI) Imaging techniques are being increasingly used to characterize tissue elastic properties. Intracardiac Echocardiography (ICE) is a commonly-used imaging technique and ICE transducers hold promise for measuring myocardial stiffness with the application of ARFI methods. With advances like cardiac-optimized beam sequencing and 3D registration of transducer location, ICE ARFI is overcoming many of the hurdles faced when attempting to image the heart and asses its function. The current state-of-the-art will be reviewed and *in vivo* data from four canine radiofrequency ablation procedures evaluating lesion continuity will be presented. Supported by NIH Medical Imaging Training Grant EB001040, NIH 5R37HL096023 and NIHR01EB01248.

10.3 **Demonstration of a freehand B-mode/ARFI imaging system as a real-time clinical tool**, Joshua R. Doherty,[1] Douglas M. Dumont[1] and Gregg E. Trahey,[1,2] *[1]Department of Biomedical Engineering, Duke University, Durham, NC and [2]Department of Radiology, Duke University, Durham, NC , joshua.doherty@duke.edu.*

Acoustic Radiation Force Impulse (ARFI) imaging techniques have demonstrated the ability to evaluate the mechanical properties of tissue by providing a relative measure of stiffness of structures compared to surrounding tissue. These techniques have been applied

by clinicians in several areas of study, including liver, breast, prostate, thyroid, cardiac and cardiovascular imaging. With slow data-processing times and typically only single frame images, the clinical success of ARFI has been limited in part due to the inability of the method to provide real-time feedback and multiple viewing angles to a clinician.

Recent advancements in pulse sequencing techniques have allowed for the rapid acquisition of multiple frames of combined B-mode and ARFI images at frame rates of 10 to 20 fps for multiple seconds while meeting the FDA acoustic-exposure safety limits. Studies on the use of freehand scanning in which the transducer is swept across regions of interest have shown there is little loss in the overall quality of the formed images compared to steady non-swept acquisition scans. We have also developed new methods that limit the size of the data to be processed by using only the time samples needed to motion-filter and display an ARFI image. Combined with the use of GPU cards for processing the data, real-time processing techniques are becoming possible.

The approach taken in this work is to demonstrate the feasibility of these real-time ARFI imaging techniques as a viable clinical tool. Implemented on a Siemens S2000 Acuson ultrasound system with the 9L4 linear array transducer, we collected high frame rate combined 2D B-mode and ARFI images of the breast, thyroid, and carotid artery *in vivo* using freehand-sweeping techniques. In-phase (I) and quadrature (Q) radiofrequency data was processed off-line using GPU processors on a laptop connected to the scanner. The consistency of the depicted ARFI displacements and artifacts within the field of view were investigated to evaluate the use freehand scanning in an *in vivo* environment with motion.

We have demonstrated ARFI as a real-time imaging tool capable of acquiring multiple frames of data with the ability to process and display these images quickly. We believe this system could provide a clinician with an improved method for identifying specific structures of interest such as cancer that may be undetected with conventional B-mode ultrasound. Supported by NIH grant R01-HL075485 and R37-HL096023. We would like to thank the Ultrasound Division at Siemens Medical Solutions USA, Inc. for their technical and in-kind support.

10.4 **Photoacoustic detection of acoustic-radiation-force-induced displacements in ocular tissues**, Ronald H. Silverman,[1, 2] Raksha Urs,[1] Harriet O. Lloyd,[1] Jeffrey A. Ketterling,[2] Fanting Kong[3] and Y-C Chen,[3] *[1]Department of Ophthalmology, Columbia University Medical Center, New York, NY, [2]Lizzi Center for Biomedical Engineering, Riverside Research, New York, NY and [3]Department of Physics and Astronomy, Hunter College, New York, NY, rs3072@columbia.edu.*

Absorption of acoustic radiation generates a force that can induce tissue compression that can be used to assess tissue stiffness, generally by detecting displacements in the phase-resolved pulse/echo ultrasound waveform. In this report, we describe use of photoacoustics for tracking displacements produced by acoustic-radiation force in the iris and retina.

The probe consisted of a 20-MHz ring transducer of 12-mm aperture and 30-mm focal length. The transducer had a 5-mm diameter central aperture through which 532 nm laser pulses were introduced and brought to a common focus (10 µm laser-spot diameter) with the ultrasound focal point. Laser pulses were 5 ns in duration, 1 µJ in intensity, and emitted simultaneously with excitation of the transducer by a 20-MHz monocycle. The pulse repetition frequency was 500 Hz. After establishing baseline conditions for 100 consecutive pulses along one line-of-sight, we interleaved force-generating 20-MHz tone bursts 1.8 ms in duration (90% duty cycle) between successive laser pulses/monocycles over a total period of 12 ms (6 cycles). The interleaving process allowed sufficient time between successive tone bursts to obtain pulse/echo and photoacoustic data. The system then reverted to laser-pulse/monocycle excitation to record the recovery. Ultrasound intensity at the focal

point during tone bursts was determined by calibrated needle hydrophone measurements. Radiofrequency echo and photoacoustic data were digitized at 400 MS/s (12-bit resolution). Because photoacoustic signals travel only one-way, photoacoustic and pulse/echo data could be recorded simultaneously. A spline-based algorithm was used to process the digitized photoacoustic and pulse/echo data to determine the magnitude and time course of displacements in the iris and retina in a fresh *ex vivo* rabbit eye.

Iris displacements averaged 26.5 and 76.7 μm photoacoustically versus 24.9 and 71.3 μm by pulse/echo at 60 and 100 Wcm^{-2}, respectively. For the retina, the displacements were 14.6 and 25.3 μm photoacoustically versus 12.4 and 25.8 μm by pulse/echo. Pulse/echo displacements were more difficult to measure precisely because of their relative broadness and because reflections are generated from all anatomic structures producing acoustic impedance discontinuities rather than just pigmented tissue layers.

In the *ex vivo* case examined here, the photoacoustic signal was produced by absorption of 532-nm light pulses by melanin, because light-absorbing hemoglobin was largely absent. The photoacoustic signal is advantageous for measuring displacement because of its highly broadband character, which offers the potential for detecting smaller displacements than is possible using pulse/echo, and because the photoacoustic signal is only generated by specific tissue layers containing molecules that strongly absorb at the wavelength of the incident light. Supported in part by NIH grant 3G1 2RR3037-25S, the Riverside Research Biomedical Engineering Research Fund and an unrestricted grant to the Department of Ophthalmology of the Columbia University Medical Center from Research to Prevent Blindness.

10.5 **Prostate-deformation modeling for elastography using finite-element analysis**, Zhennan Yan,[2] S. Kaisar Alam,[1] Shaoting Zhang,[2] Dimitris Metaxas[2] and Ernest J. Feleppa,[1] [1]*Riverside Research, New York, NY and Rutgers University, New Brunswick, NJ.*

Elastography models generally assume a planar compression device for deformation of tissue surfaces. When the deformation force is applied to an externally-accessible organ using a large, flat compressor, the stress distribution is essentially uniform close to the surface and diverges gradually with increasing tissue depth. However, the transrectal probes used for scanning and compression in prostate elastography are cylindrical side-fire or rounded end-fire probes. When the force is applied over such a small area, the stress concentration decreases rapidly over distance. The rounded contact surfaces exaggerate the nonuniformity of the applied stress and the applied stress rapidly decreases away from the center of the application area, which worsens the nonuniform nature of the stress distribution.

We have developed a preliminary finite-element model (FEM) to simulate prostate motion in elastography. The prostate is modeled using a homogeneous Young's modulus of 20 kPa. A stiffer tumor is modeled in the anterior region of the gland with a Young's modulus of 80 kPa. A simulated force is applied on the rectal wall to deform the prostate, and strain is computed from the resultant displacements.

The FEM model showed that strain and strain contrast were maximal directly beneath the probe and deceased very rapidly with increasing depth and lateral distance. Therefore, lesions that located directly adjacent to the probe would be the most clearly visible. We also evaluated modulus reconstruction methods (inverse problem) to assess the ability of modulus images to depict relatively stiff (80 kPa) lesions in the uniformly less-stiff (20 kPa) prostate, including lesions located in the lower-strain regions, e.g., at greater depths and laterally more distant from the probe center. Initial results indicated that modulus images were superior for depicting tumors in the low-strain regions.

10.6 **Monitoring the physiological-level electric-field-induced mechanical changes (PLEFIMC) in general soft biological tissues with ultrasound,** Ozkan Doganay and Yuan Xu, *Department of Physics, Ryerson University, Toronto, ON, M5B 2K3, Canada.*

Objectives: When biological tissues were subjected to a physiological-level (about 1 V/cm) external electric field, changes in the amplitude and arrival time of the ultrasound echoes from the bulk tissues were observed.[1] Our objectives are to (1) quantify the electric-field-induced changes in ultrasound echoes, (2) understand the mechanisms underlying these changes and (3) investigate the potential of using this effect to differentiate various types of tissues for medical application.

Methods: We applied dc and ac voltage sources to various types of tissues from grocery stores and gelatin phantoms for minutes. Ultrasound echoes were acquired continuously with a single-element transducer or a phased array. The rf signals were divided into windows with a size of about one wavelength. The amplitude of the ultrasound signal in a window was represented by the peak-to-peak value in the window. The shifting between the corresponding windows of the rf signals at two slow-time instants was analyzed with a cross-correlation-based method. The shifting of the echoes versus fast time (or distance to the transducer) was decomposed into a trend component and a fluctuation (feature) component.

*Results and conclusions***:** We found that a physiological-level direct-current electrical field-induced time-varying mechanical strain in biological tissues.[2] The physiological-level electric-field-induced mechanical changes (PLEFIMC) in general soft biological tissues cannot be explained by the piezoelectric effect, tissue contraction, temperature changes and electrorestriction. The new effect might be related to electrokinetic phenomena due to the fixed electric charges[3] existing on the surfaces of cells and in the extracellular matrix in biological tissues. PLEFIMC depended on the polarity of the applied electric field. The fluctuation component of the time shift and the amplitude change, but not the trend component of the time shift, were reversed after we reversed the polarity of the applied voltage. The polarity dependence study reveals two different mechanisms underlying PLEFIMC. We will also show the results of PLEFIMC in various tissues and gelatin phantoms.

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11. Insulin Resistance and Diabetes

11.1 **Opportunities for ultrasonic tissue characterization: relationships between obesity, insulin resistance and Type 2 Diabetes Mellitus and the potential effects on cardiac structure and function**, Gautam K. Singh, *Washington University School of Medicine, St. Louis, MO, Singh_G@kids.wustl.edu* (overview).

Type 2 diabetes mellitus is as much a disease of modern lifestyle as it is a disease of genetic predisposition. The natural history of Type 2 diabetes mellitus in most adults starts with development of abdominal obesity accompanied with insulin resistance, when the body exhibits resistance to multiple biologic actions of insulin. One of the prime manifestations of insulin resistance is impairment in glucose utilization by body organs, the impaired glucose tolerance. With time, the asymptomatic impaired glucose tolerance stage progresses to the prediabetic stage, when some risk factors begin to appear, to symptomatic frank Type 2 diabetes mellitus, when cardiac and noncardiac organs become categorically involved. Prevalence of adult and child obesity has tripled and that of Type 2 diabetes mellitus doubled in the United States in the last three decades. Clinical and experimental studies suggest that diabetes results in functional, biochemical and structural abnormalities of the heart as well as contributes to atherosclerotic disease of vascular system.

In this presentation, we will briefly review what is meant by insulin resistance and impaired glucose tolerance and their impact on metabolic function. We will describe some of the common diagnostic tests and measurements used to assess the degree of impaired glucose tolerance, insulin resistance and Type 2 diabetes mellitus. As a specific example, we will review results of studies that illustrate the impact of insulin resistance and Type 2 diabetes mellitus on cardiac structure and function and explore how echocardiographic imaging and ultrasonic tissue characterization may aid in assessing adverse alterations. We will look at some of the long-term implications this condition could have on public health as well as the potential role of ultrasonic examination in monitoring therapy.

11.2 **Imaging and Diabetes Mellitus: role of ultrasound and other modalities in noncardiac diagnosis and treatment monitoring**, Brian Garra, *Washington DC Veterans Affairs Med. Ctr. and Division of Imaging and Applied Mathematics, CDRH, Food and Drug Administration, 10903 New Hampshire Blvd, Silver Spring, MD, 20993, Brian.Garra @fda.hhs.gov* (invited).

Diabetes Mellitus is one of the major diseases afflicting populations worldwide and especially in developed countries. Early diagnosis and careful control of blood glucose levels is critical for preventing or delaying the onset of the many complications of the disease but most often good control of glucose levels is not achieved and diagnosis of the complications of diabetes then becomes important.

Diffuse vascular disease involving both small and large arteries is one of the most important issues to address. Ultrasound plays an important role because it can reliably detect atheromatous disease and can be performed often enough to permit tracking of disease progression. Plaque measurement and characterization are gradually becoming more widely used and the new technique of elastography may be helpful for identification of 'vulnerable' plaque that may be prone to rupture with consequent vessel thrombosis. Intimal medial thickness (IMT) measurement appears to be a predictor of the onset of atheromatous disease and this sonographic method is becoming more widely available with much easier to use and more accurate measurement systems on the horizon.

Diabetic nephropathy is a major problem in elderly patients because it often leads to renal failure and often prevents the use of radiographic contrast material that hampers the diagnosis of other diseases that the patient might have. Imaging can so far only detect more advanced nephropathy but estimation of glomerular size using ultrasound has the potential of providing much earlier detection of this complication. Imaging, and especially ultrasound, is heavily used in monitoring of renal and pancreatic transplants once the patient reaches the point of renal failure.

Diabetes causes problems for both mother and fetus during pregnancy. Increased problems with hypertension, retinopathy and kidney function occur in the mother. Fetal complications include increased risk of spinal and cardiac defects, Down's syndrome, polyhydramnios and fetal macrosomia, which can cause serious problems during delivery of the fetus. Ultrasound monitoring of the fetus in a diabetic mother is therefore mandatory.

Imaging and ultrasound are also important in the diagnosis of infections to which diabetics are prone and for detection of musculoskeletal damage resulting from diabetic neuropathy. While imaging may not be important for the 'cure' of diabetes, it will continue to be important for the diagnosis and treatment of the many complications of that disease. Because ultrasound is inexpensive and flexible, it will be the primary imaging modality used for diagnosis and management of diabetics around the world for the foreseeable future.

11.3 **Relationship between insulin resistance and cardiac dysfunction in obese children**, Mark R. Holland, B. Seth Goldstein, Deborah Hicks, John Hosie, Diana Hartman and

Gautam K. Singh, *Washington University School of Medicine, St. Louis, MO, james.g.miller @wustl.edu.*

Background: Childhood obesity is associated with increased cardiovascular risk factors and rates of premature death in adults. Animal and human adult studies suggest obesity and insulin resistance cause alterations in myocardial metabolism and efficiency that lead to cardiac dysfunction. We hypothesize that cardiac dysfunction starts with obesity in childhood and insulin resistance is an important determinant.

Objective: The goal of this study was to investigate the potential relationship between the level of insulin resistance and (subclinical) cardiac dysfunction in obese children.

Methods: A cohort of age (13.9±2.6 yrs), gender and developmental stage matched overweight otherwise healthy and lean children were enrolled in this study. This cohort was divided into two groups depending on the degree of insulin resistance: the first group, the *normal group* ($N = 24$, BMI 25.9±6.8 kg/m^2), were those subjects with normal fasting plasma insulin (= 10 µIU/ml) and normal levels of insulin resistance by Homeostasis Model Assessment (HOMA2); the second group, the *insulin resistant group* ($N = 53$, BMI 33.9±7.5 kg/m^2) were those subjects with higher values. Echocardiographic-based measurements of left ventricular global longitudinal strain, strain rate, and torsion were obtained using 2D speckle-tracking analyses of images obtained with a GE Vivid 7™ echocardiographic imaging system and analyzed using a GE EchoPac™ analysis system (General Electric Medical Systems, Waukesha, WI, USA). Cardiac functions between the two groups were compared by t-test and multivariate analyses.

Results: Global longitudinal strain, systolic global longitudinal strain rate and early diastolic global longitudinal strain rate were significantly decreased in *insulin resistant* subjects compared with *normal* subjects (15.6±3.2 vs. 17.5±3.0%, $p = 0.012$; 0.9±0.2 vs. 1.0±0.2%/s, $p = 0.03$; and 1.3±0.3 vs. 1.6±0.3%/s, $p = 0.003$, respectively) notwithstanding BMI > 30.0 kg/m^2 in 25% of *normal* subjects. In those subjects with available torsion measurements, the peak torsion of *insulin resistant* subjects was decreased compared with *normal* subjects. Cardiac function demonstrated negative correlation ($r =$ 0.64 and 0.61, $p < 0.001$) with fasting insulin levels and insulin resistance by multivariate analysis.

Conclusions: Both myocardial longitudinal deformation and circumferential torsion are decreased in children exhibiting insulin resistance, representing an early onset of impaired left ventricular function. This study suggests insulin resistance represents an important determinant of obesity-related altered cardiac function.