Monday morning

1. IMAGING 1

1.1 ***In vivo* application of short-lag spatial-coherence (SLSC) imaging and harmonic spatial-coherence imaging (HSCI) in the context of fetal ultrasound**, Vaibhav Kakkad[1], Jeremy Dahl[1], Sarah Ellestad[2] and Gregg E. Trahey[1], *[1]Department of Biomedical Engineering, Duke University and [2]Department of Obstetrics and Gynecology, Duke University Medical Center, Durham, NC, v.kakkad@duke.edu.*

Fetal scanning is one of the most common applications of ultrasound imaging and serves as a source of vital information about maternal and fetal health. It is used widely in the first and second trimester of pregnancy to visualize fetal structures like the nuchal translucency, ventricles in the brain, extremities, kidneys and maternal structures like uterine wall and cervix. However, many such exams suffer from the lack of visualization or inadequate visualization of fetal structures due to ultrasonic clutter. Ultrasonic clutter presents itself as a temporally stable haze that reduces contrast and obscures details in ultrasound images. This effect is even more pronounced in overweight and obese patients where approximately 40% of fetal scans suffer from inadequate visualization.

We have developed novel beamforming methods called Short-Lag Spatial-Coherence (SLSC) imaging and Harmonic Spatial-Coherence imaging (HSCI) and applied them to suppress the effects of clutter. This method is used to create images of the spatial-coherence function of the backscattered ultrasound as opposed to images of echo magnitude. In previous work from our group, SLSC and HSCI have been shown to successfully suppress clutter in simulations, phantoms as well as *in-vivo* images of the heart and liver. In this pilot study, we extended the application of this technique to fetal ultrasound imaging. We conducted an IRB-approved study to evaluate the performance of SLSC and HSCI in 10 first-trimester patients at the Duke University Fetal Diagnostic Clinic.

Channel data was collected transabdominally over a 40^0 field of view using the Siemens S2000 system and the 4C1 probe. This data was then processed offline to create matched B-mode, SLSC, harmonic B-mode and HSCI images. The resulting images were separated into “good” and “poor” quality image groups based on the sonographer’s assessment of the B-mode. These were then compared using standard imaging metrics such as SNR, CNR and contrast.

SLSC and HSCI images showed significant improvements across all imaging metrics compared to B-mode and harmonic B-mode, respectively. The improvements in clutter suppression and uterine border delineation were even higher for “bad” images. Clutter levels were calculated in a uniform region of amniotic fluid for a set of 10 “bad” images and were found to have average values of -16 dB for linear B-mode versus -26 dB for SLSC and -16 dB for harmonic B-mode versus -34 dB for HSCI. CNR for the same set of images showed an improvement from 1.4 to 2.5 for linear B-mode versus SLSC and from 1.4 to 3.1 for harmonic B-mode to HSCI. Besides the quantitative improvements, there were also dramatic improvements in the ability to detect fetal structures like the choroid plexus, stomach, bladder and extremities.

These results support the hypothesis that SLSC and HSCI show marked improvements in image quality over the conventional delay-and-sum beamforming, especially in high-noise environments and show promise in terms of adding diagnostic value to fetal ultrasonic imaging. Supported by the Coulter Foundation, NIH Grant R01-EB013661. In-kind and technical support provided by the Ultrasound Division at Siemens Medical Solutions USA, Inc.

1.2 **Real-time spatial coherence imaging using a GPU-based software beamformer**, Dongwoon Hyun, Gregg E. Trahey and Jeremy J. Dahl, *Duke University, Durham, NC, dongwoon.hyun@duke.edu.*

Short-lag spatial-coherence (SLSC) is an advanced ultrasound beamforming technique that images the level of coherence in backscattered waves, rather than imaging the echo magnitude as is done in conventional delay-and-sum (B-mode) beamforming. SLSC imaging has been shown to be less susceptible to clutter than B-mode, with higher contrast and speckle signal-to-noise ratio *in vivo*. However, the SLSC beamforming algorithm is heavily computationally intensive and requires real-time access to the raw-channel rf data and is challenging to realize at rates suitable for real-time imaging.

We have engineered a real-time SLSC imaging system capable of rates up to 6 frames per second by utilizing the parallel computing power of an NVIDIA Quadro 5000 graphics processing unit (GPU) in tandem with a Verasonics ultrasound research scanner. The GPU was used to perform simultaneous conventional delay-and-sum and SLSC beamforming. This system provides a 60-fold increase in computational throughput over previous optimized CPU implementations of SLSC imaging. The imaging system was used to display and compare live side-by-side B-mode and SLSC video of *in vivo* targets. We demonstrate this device applied to thyroid, carotid and liver imaging. Supported by the NIH grant R01-EB013661 from the National Institute of Biomedical Imaging and Bioengineering.

1.3 **Synthetic-aperture image quality study of short-lag spatial-coherence imaging**, Nick Bottenus[1], Brett C. Byram[1], Jeremy J. Dahl[1] and Gregg E. Trahey,[1, 2] *Departments of [1]Biomedical Engineering and [2]Radiology, Duke University, Durham, NC, nick.bottenus@duke.edu.*

Short-lag spatial-coherence (SLSC) imaging takes advantage of the coherence of imaging targets to produce images with reduced clutter compared to conventional B-mode images. It has been previously shown that SLSC images exhibit distinct changes with varying transmit aperture properties not seen in B-mode imaging. Until this point, such observations have been limited by the computational burden associated with individually simulating each transmit aperture case. We propose the use of synthetic-aperture techniques

to vary transmit and receive aperture characteristics in postprocessing, allowing a more extensive study of SLSC image quality using matched data sets.

Complete channel data sets were acquired using the Verasonics research scanner, simultaneously recording 128 receive channels for individual-element diverging wave-transmit events. Treating each transmit event as a virtual source point, we use synthetic-aperture beamforming to focus each reconstructed point in the image in both transmit and receive. The speed of this sequence allows for *in vivo* studies even in the presence of motion as well as simulation and phantom studies. We show image sets from *in vivo* targets in the liver, thyroid and breast.

We present matched B-mode and SLSC images over a range of parameters to directly compare image quality and properties. Varying aperture sizes demonstrate the dependence of the coherence function on transmit aperture size and the resulting image quality differences due to the relationship to either the point-spread function or the coherence function. We also vary transmit and receive aperture sizes individually, demonstrating the dependence of coherence only on the transmit aperture. We explore the potential for adaptive imaging in SLSC using the synthetic-aperture data set to vary both apodization and phasing of the recorded channel data. Supported by the NIH grants T32-EB001040 and R01-EB013661 from the National Institute of Biomedical Imaging and Bioengineering.

1.4 **Comparison of delay-and-sum and coherence beamforming methods**, Gregg E. Trahey, Muyinatu A. Lediju Bell, Marko Jakovljevic, Dongwoon Hyun and Jeremy Dahl, *Department of Biomedical Engineering, Duke University, Durham, NC, gregg.trahey@duke.edu.*

We have recently introduced two spatial coherence-based imaging methods, Short-Lag Spatial Coherence (SLSC) and Harmonic Spatial-Coherence (HSC). These methods form images qualitatively similar to their conventional B-mode counterparts; however, their speckle statistics, transfer functions and response to random noise and clutter differ significantly. Coherence-based methods are shown to be more robust in the presence of bright off-axis scatterers, reverberation and random acoustical noise. We review the mathematical bases for these differing image characteristics and present simulations, phantoms and clinical examples demonstrating these differences. We discuss clinical scenarios in which coherence methods appear to outperform B-mode and harmonic imaging.

1.5 **Synthetic-aperture ultrasound tomography using both transmission and reflection data simultaneously,** Lianjie Huang, Youzuo Lin, Zhigang Zhang, Nghia Nguyen and Yassin Labyed**,** *Los Alamos National Laboratory, Los Alamos, NM, ljh@lanl.gov.*

Ultrasound tomography has great potential to provide quantitative estimation of mechanical properties of breast tumors for breast-cancer detection and characterization. It is difficult for breast ultrasound-tomography systems with a circular transducer array or two rotating-transducer arrays to image the axillary region. In addition, the circular or rotating-transducer arrays cannot be adjusted to optimally fit different sizes of the breast.

We design and construct a new synthetic-aperture ultrasound tomography system with two parallel phased-transducer arrays. The distance of the two phased-transducer arrays can be adjusted to fit different sizes of the breast, like breast MRI. One of the parallel phased arrays can be positioned near the armpit for imaging the axillary region. The two parallel phased arrays are translated vertically to scan the breast from the chest wall/axillary region to the nipple region to acquire ultrasound transmission and reflection data for whole-breast tomographic imaging. The data acquisition time to scan 100 slices for one breast is approximately two minutes. Our system is undergoing integration and testing for patient data acquisition at the University of New Mexico Hospital. Approximately 200 patients will be recruited to scan using our breast ultrasound-tomography system.

We develop several new ultrasound waveform tomography methods for high-resolution and high-fidelity reconstructions of the breast sound speed. We apply these methods to phantom data to investigate the capability of our synthetic-aperture breast ultrasound tomography system for detecting and characterizing small breast tumors. Our results demonstrate that ultrasound waveform tomography using both transmission and reflection data simultaneously greatly improves tomographic reconstructions compared to those obtained using only transmission data or only reflection data. Supported by the Breast Cancer Research Program of the U.S. DoD Congressionally Directed Medical Research Programs.

1.6 **Towards reconfigurable arrays for ultrasound,** Kai E Thomenius, Robert Wodnicki and Rayette Fisher, *GE Global Research, Niskayuna, NY, thomeniu@ge.com.*

Reconfigurable arrays (RAs) can be defined as 2D ultrasound arrays in which the individual array elements (cells or pixels) can be connected into larger groupings as required by one's clinical needs. This can be accomplished using Application Specific Integrated Circuits (ASICs) positioned immediately below the array. These larger groupings can then be connected directly to the transmit and receive electronics of a scanner. A particularly attractive grouping of elements is that of an annular array (AA); this aperture configuration can be moved along the 2D array surface, thereby enabling an electronically-steerable AA. As a consequence, the advantages of systems using RA devices include excellent beam quality and depth of field due to superior elevational focus as compared to 1D linear arrays as well as reduced cost, size and power consumption resulting from the far smaller number of beamforming channels needed with this configuration. This review will relate these benefits.

The challenges with the construction of the RA-integrated assembly including 3D packaging and the associated results will be described in the context of a breast-screening prototype application. The prototype architecture was for an array based on 2D capacitive Micro-machined Ultrasound Transducer (cMUT) chips with backside trench-frame pillar interconnects as well as RA ASICs for interfacing with the ultrasound system. Standard electronic assembly techniques such as flip-chip and Ball Grid Array (BGA) attach along with organic laminate substrate carriers were investigated for building large area arrays composed of tileable modules of cMUT chips and RA ASICs. Imaging results with a completed linear array test vehicle demonstrate a functioning device based on the modular assembly architecture. Future work would bring together the new assembly techniques with RA ASICs in order to realize a truly tileable and modular transducer array for large-area applications.

1.7 **Accelerating medical ultrasound simulations in FOCUS: hardware and software strategies**, Peter B. Beard and Robert J. McGough, *Electrical and Computer Engineering, Michigan State University, East Lansing, MI, mcgough@egr.msu.edu.*

FOCUS, the 'Free Object-oriented C++ Ultrasound Simulator', is a software package for simulating therapeutic and diagnostic ultrasound. FOCUS performs phased-array simulations very quickly within a Matlab environment while achieving superior accuracy in the nearfield region. In part, FOCUS derives computational advantages from algorithms such as the fast nearfield method, time-space decomposition and the angular-spectrum approach. Although further improvements are expected from ongoing algorithm development efforts, the latest performance enhancements are achieved through specialized hardware and software tools that are available on modern desktop and laptop computers. In particular, recent versions of FOCUS employ Single Instruction, Multiple Data instructions through SSE and multithreaded execution using OpenMP. After applying these optimizations, the speed of the code was improved by as much as 42 times in some simulations. Implementation details for each approach will be provided, and results obtained with FOCUS will also be shown. Other new features in FOCUS will also be demonstrated and plans for future enhancements to FOCUS will be discussed. Supported in part by NIH Grant R01 EB012079.

1.8 **Comparison of fast and memory efficient B-mode imaging simulation methods in FOCUS**, Yi Zhu and Robert J. McGough, *Electrical and Computer Engineering, Michigan State University, East Lansing, MI, mcgough@egr.msu.edu.*

In the simulation of B-mode ultrasound imaging, the impulse-response approach requires a relatively high sampling frequency to overcome aliasing problems and achieve an acceptable accuracy. The aliasing problems that are inherent to the impulse approach are avoided in FOCUS (the 'Fast Object-oriented C++ Ultrasound Simulator'), which calculates transient pressures are calculated with the fast nearfield method. B-mode imaging simulations in FOCUS decompose the input signal such that the resulting pulse-echo signal is represented by the convolution of transient outputs produced by transmit and receive apertures. To further optimize the imaging simulations in FOCUS, two algorithms have been developed. The first optimization algorithm calculates the pressure generated by each transducer element at each scatterer. All pairs of signals are convolved and then stored. The rf signal for each A-line is obtained by summing the convolved signal waveforms with appropriate time delays. The second algorithm calculates the total pressure produced by each element at each scatterer and stores the results. To calculate an A-line, the individual pressure signals are delayed and summed and then the total pressure signals are convolved.

These algorithms are evaluated for a simulated linear ultrasound phased array populated with 128 rectangular elements. The simulated array elements are 0.5133 mm wide by 5 mm high, and the kerf is 0.1 mm. In these image simulations, 64 element subapertures are defined for each A-line. The center frequency of the excitation is 3MHz and the sampling frequency is 50 MHz. These parameters are evaluated for 20 point targets with a fixed-focus receive beamformer. The algorithms are implemented in C++ by combining the C/Mex routines in FOCUS with the fftw library. For this combination of parameters, the simulation time for the first algorithm is 2.39 seconds and the simulation time for the second algorithm is 0.34 seconds. The first algorithm calculates a large number of relatively short convolutions and reuses the convolution results in an effort to improve computational efficiency. In contrast, the second algorithm evaluates a smaller number of relatively long FFTs using individual pressure signals that are computed once, stored and reused. Thus, evaluating a larger number of relatively short convolutions increases the calculation time in these simulations. The various trade-offs between these two simulation algorithms will be explained, and efforts to optimize these calculations and further reduce the computation time will also be discussed. Supported in part by NIH Grant R01 EB012079.

2. SHEAR WAVES/ELASTICITY 1

2.1 **Shear-wave speed estimation in the normal nonpregnant cervix**, Lindsey Carlson[1], Helen Feltovich[1, 3], Mark Palmeri[2] and Timothy J. Hall[1], *[1]Medical Physics, University of Wisconsin – Madison, Madison, WI, [2]Biomedical Engineering, Duke University Pratt School of Engineering, Durham, NC and [3]Maternal Fetal Medicine, Intermountain Healthcare, Park City, UT, lcarlson2@wisc.edu.*

Objectives: The cervix plays a critical role during pregnancy and undergoes significant remodeling that is characterized by softening, shortening and dilation for delivery of the fetus at term. This process is necessary for normal pregnancy but premature changes may lead to premature birth. Softening begins soon after conception and gradually progresses throughout pregnancy and yet there is no clinically-established method to quantitatively measure softening. Our objective is to develop a safe, reliable, noninvasive and quantitative method to assess cervical softness. We have shown that shear-wave speed estimation (SWS) is an effective method to measure cervical softness in hysterectomy specimens. The aim of our current work is to assess the sensitivity of SWS estimates for differentiating between normal cervix specimens and those pharmacologically- softened using prostaglandin agents.

Methods: Hysterectomy specimens (n = 14) were collected from non-pregnant women, with six of those subjects given a prostaglandin (misoprostol) to induce softening/ripening. Each specimen was bivalved into anterior and posterior halves, placed in a saline bath and scanned with a 9L4 linear array transducer using a Siemens Acuson S2000 system. The image plane was aligned parallel to the endocervical canal. SWS measurements were obtained at 4-5 non-overlapping positions along the canal with five replicate measures at each location to increase precision. The shear-wave speeds were estimated off-line using an iterative Random Sample Consensus (RANSAC) method. A two-sample t-test was used to compare the SWS estimates for ripened and unripened groups with a $p < 0.05$ criterion for statistical significance.

Results: Specimens from subjects treated with the prostaglandin agent showed lower SWS estimates at the medial location (2.19 ± 0.6 and 2.76 ± 0.66 m/s for anterior and posterior respectively). For the unripened samples, the SWS estimates were higher and had

greater standard deviation (3.61 ± 0.85 and 3.6 ± 0.92 m/s). The SWS estimates were significantly different ($p < 0.001$) between these groups.

Conclusions: These results demonstrate that SWS estimation has the sensitivity to distinguish between normal and ripened cervix specimens. The ability to noninvasively assess the softness of the pregnant cervix provides a quantitative clinical descriptor and a research tool for exploring premature cervical remodeling. Supported by NIH grants R21HD061896 and R21HD063031.

2.2 **Ultrasonic shear-wave imaging of rodent mammary tumors,** Yue Wang and Michael F. Insana, *University of Illinois at Urbana-Champaign, Urbana, IL, mfi@illinois.edu*.

Background: Images of tumor mechanical properties provide important insights into malignant-cell processes manifest by extracellular matrix stiffening and remodeling.

Objectives: This paper presents a pilot study measuring *in vivo* mechanical-property characteristics of rodent mammary tumors using an ultrasonic shear-wave imaging technique. The goal is to relate soft-tissue mechanical behavior to biological characteristics of tumor structures, specifically the collagenous ECM protein content.

Methods: Shear waves are generated by a needle inserted into the tumor of anesthetized rodents that is vibrated harmonically at frequencies between 50 Hz and 450 Hz. Particle motion in the tumor associated with the radiation of cylindrical shear waves is imaged using pulsed-Doppler ultrasound techniques. Shear-speed dispersion curves are estimated from the spatial gradient of shear-wave phase along the direction of propagation. Measured dispersion curves were fit to those predicted by three different rheological models to estimate the elastic and viscous coefficients of the complex shear modulus. The investigation was performed *in vivo* on four rat-mammary fibroadenoma tumors and five xenograph mouse-mammary carcinoma tumors. Each tumor was subsequently excised for histological imaging and composition analysis. Collagen composition was measured using hydroxyproline assays that were then correlated with mechanical measurements.

Results: (1) Rat mammary tumors are representative of the mechanical environment in human fibroadenoma tumors and thus may be used to study viscoelastic contrast in tumors. (2) Shear-wave-based measurements of elastic and viscous coefficients yield consistent values with breast tumors reported by other groups regardless of species or imaging technique. (3) Large within-class variability should be subclassified into histologically-specified grades when possible to improve lesion classification. 4) Small tumor sizes can bias measurements of shear-wave velocity. In tissue applications, the distance between the source and tumor boundary is recommended to be at least one wavelength when harmonic forces are applied.

Discussion: The relative merits of impulse and harmonic stimuli are discussed as well as the merits of direct mechanical and acoustic radiation force stimuli. These data also provide new perspectives on uses of rheological models to estimate the complex moduli when searching for biological sources of diagnostic elasticity contrast.

2.3 **Acoustic radiation force creep-recovery: theory and finite-element modeling**, Carolina Amador, Bo Qiang, Matthew W Urban, Shigao Chen and James F. Greenleaf, *Department of Physiology and Biomedical Engineering, Mayo Clinic College of Medicine, Rochester, MN, amadorcarrascal.carolina@mayo.edu.*

Introduction: Elasticity imaging methods have been used to study tissue mechanical properties and have demonstrated that tissue elasticity changes with disease state. A method to quantify viscoelastic properties in a model-independent way by using the time-dependent creep-recovery response induced by acoustic radiation force push pulse has been proposed to study tissue viscoelasticity.[1, 2] The creep-recovery response can be induced by applying a continuous push or a train of short pushes prior to the release of stress. In this study, a finite-element method is used to model the dynamic response associated with acoustic-radiation-force creep recovery.

Methods: The acoustic intensity fields associated with a creep-recovery excitation were simulated using Field II.[3] A three-dimensional finite-element model (FEM) was constructed in Abaqus/CAE 6.01-EF1 (Dassault Systèmes S.A., Vélizy-Villacoublay, France). The effects of push excitation (continuous push of 500 μs time duration, train of 83 short-time pushes of 6 μs time duration with time between pushes of 38 μs, 70 μs and 140 μs), material properties described by Voigt model, mass density and geometry on the creep-recovery response were analyzed.

Results: It was found that the displacement response was not proportional to the strain response. The creep-recovery displacement response from either a continuous push or a train of short pushes did not recover to the rest position. The strain response resembles a one-dimensional mechanical creep model, where the creep response depends, in addition to the elastic modulus and viscosity, on the density, the geometry and the boundary conditions of the system.

Conclusion: The dynamic displacement and strain response associated with creep-recovery induced by acoustic radiation force were modeled using finite element method. Acoustic-radiation-force excitation (continuous push or train of pushes) as well as factors such as elastic modulus, viscosity, density and geometry appear to affect the creep-recovery response. Supported by NIH grants R01EB002167, R01EB002640 and DK082408.

(1) Amador et al, *Phys Med Biology 57*, 1263-1282 (2012). (2) Amador et al, in *IEEE Ultrason Symp* (2012). (3) Jensen et al. *IEEE Trans UFFC 39*, 262-267(1992).

2.4 **Bayesian shear-wave speed estimation**, Stephen Rosenzweig, Ned Rouze, Brett Byram, Mark Palmeri and Kathy Nightingale, *Department of Biomedical Engineering, Duke University, Durham, NC, stephen.rosenzweig@duke.edu.*

Shear-wave elasticity imaging (SWEI) is a quantitative ultrasound elasticity imaging technique that has shown promise for visualizing structure and pathology.[1, 2] Various reconstruction methods have been proposed to estimate shear-wave speed from SWEI data, with time-of-flight-based methods being the most widely implemented to date. The majority of these methods assume a known direction of shear-wave propagation and that the tissue in the reconstruction kernel is homogeneous and isotropic. Violation of these as-

sumptions can lead to bias in the shear wave speed estimates[3] and image artifacts generated by reflected waves at internal structural boundaries .[4, 5]

In this work, a Bayesian shear-wave speed estimator is investigated to improve the quality of shear-wave speed images. The wave-arrival time at each lateral location is assumed to have white Gaussian noise; thus, the maximum-likelihood estimator (MLE) for the shear-wave speed is maximized by the linear regression of the wave-arrival times versus lateral position. This estimator works well with highly-sampled, low-noise data, but it ignores information about spatially-adjacent velocities, which can be used to improve the shear-wave speed estimate. The maximum *a posteriori* (MAP) estimator is investigated using the MLE likelihood function and a generalized Gaussian prior distribution[6] The goal of this estimator is to reduce the noise and image artifacts in SWEI images in the presence of tissue heterogeneity. A 1D simulation was performed with 20 dB white Gaussian noise added to analytically-computed wave-arrival times assuming a 10 mm stiff (2 m/s) region centered in a 30 mm soft (1m/s) background. Using a regression kernel of 1.5 mm, the MLE estimate had an RMS error of 0.16 m/s and the MAP estimate had an RMS error of 0.03 m/s. We will present parametric analyses investigating the effects of lesion size and stiffness using previously-validated 3D finite element method (FEM) simulations to compare the MLE and MAP estimates for the different cases. This work has been supported by NIH grants EB001040, CA142824, and EB002132. We thank the Ultrasound Division at Siemens Medical Solutions, USA, Inc. for their technical and in-kind support.

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2.5 **Effects of phase aberration on acoustic-radiation-force-based shear-wave generation**, Matthew W. Urban, Carolina Amador, Shigao Chen and James F. Greenleaf, *Department of Physiology and Biomedical Engineering, Mayo Clinic College of Medicine, Rochester, MN, urban.matthew@mayo.edu.*

Objectives: Acoustic radiation force is used in several methods to generate shear waves in order to measure the elasticity of tissue. Strong shear waves are easier to track and lead to more reliable tissue elasticity measurements. The generation of shear waves for *in vivo* applications can be hampered by tissue attenuation and phase aberration effects. In this study, we explored how phase-aberration affects ultrasound focusing for creating shear waves and evaluate the resulting shear-wave amplitude and the shear-wave velocity.

Methods: We conducted various phantom studies to explore how shear waves were affected by phase-aberration effects. For these experiments, we used a Verasonics ultrasound system (Verasonics, Inc., Redmond, WA) equipped with a linear and a curved linear-array transducer (L7-4 and C4-2, Philips Healthcare, Andover, MA). In the first set of experiments, we added random time delay values to the focusing delays to create a random-phase screen. The root-mean-square (rms) time delays of the phase screens were 0.00, 9.00, 18.01, 36.03, 72.06 and 144.11 ns. We varied the ultrasound frequency used for both transducers to evaluate the resulting shear waves after applying these random phase screens. With the linear-array transducer, we used 2.50, 3.00, 3.46, 4.09, 4.50 and 5.00 MHz. With the curved linear array, we used 1.76, 2.00, 2.25, 2.50, 2.73 and 3.00 MHz. Measurements were made in a calibrated elastic phantom (CIRS, Inc., Norfolk, VA) with a shear-wave velocity of 1.48 m/s.

In a second set of experiments, we used an excised piece of swine-belly tissue. This tissue sample consisted of the skin, subcutaneous fat and muscle. We separated the different layers and placed them in different combinations on top of the elastic phantom to evaluate the shear wave produced when transmitting through the different layers. We tested skin alone, fat alone, muscle alone, a double fat layer and a combination of skin, fat and muscle. We evaluated the shear-wave amplitude and shear-wave speed measured with these different layers.

Results: In the experiments with the random-phase screens, the shear-wave amplitudes increased as the ultrasound frequency was decreased. Also, the accuracy of the shear-wave velocity was improved when ultrasound frequency was decreased. In the experiments with the different tissue layers, we found that the shear-wave amplitude decreased with the introduction of the layers. The double-fat layer and the combination of all layers defocused the beam most significantly and led to the largest reductions in shear wave amplitudes.

Conclusions: Shear-wave generation can be impeded by the defocusing of ultrasound beams caused by phase aberration. We found that decreasing the ultrasound frequency was important for maintaining a focused beam for creation of shear waves. Analysis of shear-wave production with real tissue layers showed that large fat layers and combinations of skin, fat, and muscle defocused the ultrasound beam most, thereby decreasing the shear-wave amplitudes. Using lower ultrasound frequencies alleviated aberration effects and allowed for improved shear-wave production. Supported in part by NIH grants DK092255 and DK082408.

2.6 **Optical validation of acoustic-displacement tracking in viscoelastic material**, Tomasz J. Czernuszewicz and Caterina M. Gallippi**,** *Joint Department of Biomedical Engineering, University of North Carolina and North Carolina State University, Chapel Hill, NC, tomekc@unc.edu.*

Background: Recently, our group has proposed a novel imaging technique called Viscoelastic Strain Response (ViSR) ultrasound that uses two acoustic radiation force (ARF) impulses to measure the Voigt-derived relaxation time constant (τ) in tissues. To measure τ, ViSR observes three points along the Voigt viscoelastic creep profile: (1) a measurement directly after the first ARF pulse (d_1), (2) a measurement after the tissue has been allowed to partially recover (d_2) and (3) a measurement directly after the second ARF pulse (d_3). In this method, radiation force pulses are generated by the same transducer that is used to track motion. Hence, the displacements are susceptible to shearing decorrelation and underestimation as in conventional acoustic-radiation-force-impulse (ARFI) imaging. The purpose of this study was to investigate the impact of displacement underestimation on ViSR-measured τ values by validating against an optical gold standard.

Methods: ViSR imaging was performed with a Siemens Antares scanner and VF7-3 linear array with excitation impulses centered at 4.21 MHz with an F/1.5 focal configuration. Tracking pulses were centered at 6.15 MHz with an 11 kHz prf and F/1.5 focal configuration. The ViSR beam sequence was ordered as follows: 2 reference tracking pulses, 2 ARF pulses (300 cycle) separated by 3 tracking lines (0.26 ms) and 3 tracking pulses. Acoustic-displacement measurements were experimentally validated using optical tracking. The optical focus of a microscope fitted with a 10x objective and coupled to a 150 kHz high-speed camera was aligned with the acoustic focus using a needle hydrophone and digital three-axis motion controller. Acoustic and optical data were acquired in a translucent, gelatin-based, tissue-mimicking phantom. Black polystyrene beads (10 µm diameter) were embedded in the phantom and the phantom was translated such that each of 15 unique beads was individually positioned at the confocal optical and acoustic foci to serve as markers for optical tracking. Raw rf and optical data were acquired with three repeated measures on each bead. Motion tracking was performed using zero-mean normalized cross-correlation for both acoustic and optical data sets.

Results: As expected, the d_1 and d_3 displacements measured acoustically were more highly underestimated compared to the d_2 displacement. The d_1 and d_3 values were measured to be 74.19% and 77.55% of the optical displacement on average, respectively while d_2 was measured to be 85.7% of the optical displacement. Acoustically-measured values of τ were 0.168 ± 0.020 ms for F/1.5 while optically-measured τ values were 0.155 ± 0.017 ms. Wilcoxon rank sum tests showed that optical and acoustic τ measurements were statistically significantly different ($p = 0.036$), amounting to a 6.5% acoustic overestimation of the optical τ value.

Conclusions: These results show that acoustic-displacement underestimation impacts ViSR-derived τ measurement and methods for reducing displacement underestimation, including using a larger ARF excitation than tracking F/#, should be evaluated for ViSR imaging.

2.7 **Acute and chronic myocardial infarct differentiation using atrial-kick-induced strain (AKIS) imaging**, *Brett Byram, Pat Wolf and Gregg E. Trahey. Department of Biomedical Engineering, Duke University, Durham, NC, bcb16@duke.edu.*

Every year in the US, there are 470,000 cases of recurrent myocardial infarction (MI). Diagnosis is challenging because diagnostic tools like the ECG and cardiac enzymes have poor outcomes in general but even more so for recurrent MI, which tend to be less severe. For a patient's first MI, ultrasound measures of wall-motion abnormality can be a useful diagnostic tool. However, wall motion has not been shown to differentiate between acute and chronic MI, which is necessary for ultrasound-based diagnosis of recurrent MI.

Differentiation of chronic MI from healthy myocardium has been demonstrated using atrial-kick-induced strain (AKIS) imaging of the ventricles. The ventricles expand quickly during active filling inducing passive strain at the end of ventricular diastole, which is unique because the ventricles are fully relaxed. Strain induced during this period can serve as a proxy for passive mechanical stiffness, allowing for differentiation such as with stiff chronic MI or soft acute MI compared to healthy myocardium. Differentiation of acute and chronic MI based on passive mechanical tissue properties is demonstrated using AKIS.

AKIS images of MI were formed from volumetric IQ data acquired at 100 Hz. The data were acquired using the Siemens SC2000 and 4Z1c matrix array operating at 2.8 MHz (Siemens Healthcare, Ultrasound Business Unit, Mountain View, CA). Chronic MI data were acquired from dogs with infarcts older than one year ($n = 3$), with two dogs yielding sufficient quality data. Acute MI data were acquired from dogs with infarcts less than 15 minutes old caused by left-anterior-descending-artery occlusion ($n = 2$). Cardiac motion was estimated using Bayesian speckle tracking and strain was estimated using a typical regression approach. Images were made of the axial-strain magnitude.

AKIS image metrics were calculated on acute and chronic infarcts. Contrast and contrast-to-noise ratio (CNR) are reported. The healthy myocardium is always used as the background quantity. The chronic infarcts had contrast of 0.81 and 0.87 and CNR of 2.9 and 1.6. The acute infarcts have contrast of -3.3 and -3.9 and CNR of 2.3 and 2.8. The reversal in contrast between acute and chronic infarcts relative to the healthy myocardium demonstrates differentiation between the two pathologies.

Monday afternoon

3. TISSUE PARAMETERS 1

3.1 **Signal-to-noise improvement in ultrasonic thermometry based on the change in backscattered energy**, R. Martin Arthur, Jason W. Trobaugh, Yuzheng Guo and Bowen Zhao, *Electrical & Systems Engineering, Washington University in St. Louis, St. Louis, MO, rma@ese.wustl.edu.*

Thermal therapies from cryosurgery to ablation would benefit from a noninvasive, safe, inexpensive and convenient 3D thermometer to monitor heating patterns. Ultrasound is a modality that meets these requirements. Agreement among predicted, simulated and measured change in the backscattered energy (CBE) from both our *in-vitro* and *in-vivo* experiments has shown that CBE can be used for temperature imaging (TI) in 3D. [1, 2] To optimize temperature accuracy (errors < 0.5 ^{o}C), we have found by both simulation and experiment that the signal-to-noise ratio (SNR) must be > 40 dB. Here, we examine two approaches to imaging temperature within this constraint: (1) by image averaging to achieve this SNR and (2) by using our stochastic-signal framework for improved TI based on CBE.[3]

Our phased-array imaging system is a Terason 3000, which produces SNR values from typical experiments that range from 18 to 28 dB (24 ± 3 dB). We increased SNR by image averaging from the 156 frames typically taken in image loop with the Terason system. As expected, SNR was increased to 40 dB, both in simulation and experimentally, by averaging 40 frames from a typical 24 dB SNR experiment.

We also achieved the performance associated with a >40 dB SNR from a 17 dB simulated measurement by modeling CBE-based temperature imaging as a problem in estimating temperature from temperature-dependent random variables. This approach required characterization of pixel-based CBE as a ratio of random variables. Assuming uniformly-distributed tissue scatterers, the pdf of the ratio was found analytically and used to estimate CBE precisely (effective SNR > 40 dB) even in low signal-to-noise ratio (SNR) conditions. We are determining pdfs appropriate for experimental images to extend these methods to real data, so that we can determine the limits of SNR with this approach.

Whether by using image averaging or the application of a measured pdf, an effective SNR of 40 dB SNR reduces the CBE signal due to noise to about 0.2 dB. At a 24 dB SNR, the spurious CBE signal is about 1 dB. The SNR increase from 24 to 40 dB changes the thermal sensitivity of CBE from 0.30 dB/^{o}C to 0.38 dB/^{o}C, which increase the accuracy of a temperature estimate by about a factor of 5 over the 37 to 45 ^{o}C range. In addition, our stochastic-signal framework formalized the CBE approach to TI, improved temperature accuracy in simulations and can be applied to experimental data. Supported by R21-CA90531, R01-CA107558 and the Wilkinson Trust at Washington University, St. Louis.

(1) Trobaugh et al. UMB 34, 289–298, (2008). (2) Arthur et al. *IEEE Trans UFFC* 57, 1724-1733 (2010). (3) Guo, *PhD Dissertation*, Washington University in St. Louis (2009).

3.2 **Quantitative ultrasound assessment of HIFU therapy *in vivo* in rodent tumors**, Jeremy Kemmerer, Goutam Ghoshal, Chandra Karunakaran and Michael Oelze, *Bioacoustics Research Laboratory, Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, Urbana, IL, kemmere1@illinois.edu.*

High-Intensity Focused Ultrasound (HIFU) is a promising modality for noninvasive cancer therapy but challenges remain for treatment monitoring and assessment that Quantitative Ultrasound (QUS) may address. In this study, 40 rodent tumors (MAT) were exposed to focused ultrasound produced by a 1-MHz single-element transducer (f/1.1) at three intensity (spatial peak temporal average) levels (335, 360 and 502 W/cm^2). The first exposure had a peak pressure of 4.4 MPa and 50% duty cycle, the second exposure had a peak pressure of 3.7 MPa and 75% duty cycle and the third exposure had a peak pressure of 4.4 MPa and a 75% duty cycle. Ultrasound-assessment scans were performed on each tumor before and again after HIFU exposure using clinical (Ultrasonix L14/5, 3-9 MHz) and small-animal high-frequency (VisualSonics MS-200, 8-15 MHz) ultrasound systems. For comparison with QUS assessment, tissue damage from HIFU was also quantified by H&E staining, TTC vital staining and thermocouple data.

Backscatter-coefficient (BSC) and integrate- backscatter-coefficient (IBSC) estimates were generated from each tumor. A statistically-significant (p<0.05) difference was observed in the change in IBSC for the first exposure group (335 W/cm^2) compared to controls. However, no statistically-significant differences were observed in IBSC estimates for exposures two and three compared to controls. TTC staining and histological scoring indicated that the third exposure, which corresponded to the highest spatial-peak temporal-average intensity, produced the highest amount of tissue damage and thermocouple temperature measurements demonstrated that the third exposure condition produced the largest average temperature increases. The results of this study suggest that QUS estimate sensitivity to HIFU therapy depends on exposure conditions and that peak pressure was a better indicator than intensity of this sensitivity. Supported by NIH Grant R01-EB008992.

3.3 **Bayesian analysis of fast and slow wave propagation in cancellous bone to obtain effective mass densities**, Amber M. Nelson, Mark R. Holland, Jonathan Katz, and James G. Miller, *Washington University in St. Louis, St. Louis, MO, nelsonam@wustl.edu.*

Background: Two modes, one fast wave and one slow wave, propagate in cancellous bone. We have previously demonstrated that Bayesian probability theory combined with a simple wave propagation model permits estimation of fast- and slow-wave velocities (SOS), frequency-independent losses A and frequency-dependent losses (which are related to slopes of attenuation (nBUA)) from through-transmission measurements, even under circumstances when the two waves overlap.

Objective: The goal of the present work was to augment the wave propagation model to determine fast-wave and slow-wave effective mass densities, ρ_{fast} and ρ_{slow}. This requires including the functional forms for the fast- and slow-wave transmission coefficients at the interfaces. In the long view, this work represents a step toward improving the utility of bone sonometry for monitoring pharmacological treatment designed to reverse osteoporosis.

Methods: The present work accounts for transmission from a water bath into and out of water-immersed cancellous bone specimens, resulting in an explicit dependence of the frequency-independent factors (A_{fast} and A_{slow}) in our propagation model on the complex impedances and . The effective mass densities for the fast-wave (ρ_{fast}) and slow-wave (ρ_{slow}) modes are determined from the frequency-independent factors and speeds of sound for each mode.

Through-transmission data were acquired at 72 sites from 8 specimens of cancellous bone obtained from human cadavers, as well as on a series of test objects of known properties. Anatomical parameters, such as bone volume fraction (BV/TV), of the samples were measured by microCT.

Results: Bayesian analysis of the cancellous bone data yielded effective mass densities ρ_{fast} and ρ_{slow} for the fast- and slow-wave modes that correlate well with microCT parameters such as porosity. The other estimated parameters (velocities, slopes of attenuation and frequency-independent prefactors) were consistent with those obtained with the simpler model.

Discussion: This study may represent the first time that ultrasound has given estimates of the mass densities of cancellous bone samples. Interpretation of these effective densities will require further studies but enhancing our propagation model to include these additional parameters may improve clinical ultrasonic assessment of bone quality. Supported in part by NIH/NIAMS grants R01AR057433 and P30AR057235.

3.4 **Effect of gate choice on apparent integrated-backscatter measurements of bone**, Brent K. Hoffmeister, Joseph A. McPherson and Morgan R. Smathers, *Department of Physics, Rhodes College, Memphis, TN, hoffmeister@rhodes.edu.*

Ultrasonic-backscatter techniques are being developed to detect changes in bone density caused by osteoporosis. One backscatter parameter that has shown promise is apparent integrated backscatter (AIB). AIB measures the frequency-averaged power in a gated portion of the backscatter signal. The goal of this study is to determine how different choices of gate delay τ_d τ_d and gate width τ_w affect AIB. Measurements were performed *in vitro* on 35 cube-shaped specimens of cancellous bone using a 5 MHz transducer. AIB was determined for 13 different choices of gate delay τ_d ranging from 0 to 6 μs relative to the start of the backscatter signal. The analysis was repeated for four different choices of gate width: τ_w = 1, 2, 4 and 6 μs. Increases in the gate delay τ_d caused AIB to decrease. Increases in gate width τ_w caused AIB to increase slightly. AIB correlated positively with bone density for short delays τ_d ≤1.0 μs and negatively for greater delays. These results indicate that the choice of analysis gate delay and width can influence the measured values of AIB and also impact how AIB correlates with bone density.

3.5 **Methods of determining the scatterer source in tissues using quantitative ultrasound**, Muhannad Fadhel and Michael Kolios, *Department of Physics, Ryerson University, Toronto, ON, Canada, mhndfadhel@gmail.com.*

Quantitative ultrasound (QUS) has been used in tissues characterization to differentiate between the healthy and diseased once, such as health and malignant lymph nodes. The scattered radiofrequency (rf) signal from tissues is affected by shape, size, acoustic concentration and mechanical properties of the unknown scatterer. Frequency-based analysis of the rf signal is used to estimate QUS parameters. These parameters are estimated by fitting the experimental backscattering coefficient (BSC) to the theoretical BSC. A reference phantom technique is used to determine the experimental BSC of a tissue-equivalent phantom made of sephadex using the Vevo770 with center frequencies of 20 MHz and 50 MHz. Results were fitted to the theoretical Faran's model to estimate two QUS parameters. The QUS parameters are effective scatterer size and acoustic concentration, which were estimated to be 18.01 ± 9.97 μm and 36.73 ± 25.93 dB/cm^2, respectively, using a 50 MHz transducer, and 41.91 ± 12.57 μm and -1.49 ± 16.87 dB/cm^2 using a 20 MHz transducer. These parameters do not represent a physical size or concentration of the scattering source. Therefore, another method is used to better understand the shape and properties of the anatomical scatterer in tissues and to predict the ability of QUS parameters to differentiate between tissues. This method is called 3D Impedance Map, which can estimate the QUS parameters from the impedance map. The measured acoustic impedance of sephadex is 1.639 ± 0.003 MRayl.

3.6 **High-frequency 3D ultrasound for characterizing overall tumor response to vascular targeting strategies,** 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 and [2]Departments of Radiation Oncology and Medical Biophysics, University of Toronto, Toronto, ON, Canada, Ahmed.ElKaffas@utoronto.ca.*

Introduction: High-frequency spectroscopic ultrasound methods combined with power Doppler ultrasound are ideal for assessing tumor response to various cancer treatments. In this work, we characterize tumor response to novel vascular targeting strategies combined with radiation therapy. Results are confirmed using gold-standard immunohistochemistry assays.

Materials and Methods: Tumor xenografts were treated with single radiation doses in combination with vascular-targeting agents (i.e., Sunitinib). Treatment response was assessed with high frequency three-dimensional ultrasound acquired before, during and after treatment using a VEVO770. The vascularity index (VI) was used to quantify blood flow from power Doppler data while quantitative ultrasound spectroscopy (QUS) was used to monitor tumor cell death and tissue structural changes occurring during vascular-targeting drug delivery. Staining using TUNEL, CA9 and CD31 of tumor sections was used to measure cell death, tumor oxygenation and tumor vasculature distributions.

Results and Discussion: Results demonstrate an acute tumor and tumor vasculature response to combination therapies. Single high doses of radiation caused an acute decrease in the VI by up to 50%, and an average 5 dB mid-band fit increase. In contrast, tumors where the vasculature was pharmacologically protected from radiation effects had no change in the mid-band fit following radiation. Pharmacological vascular targeting agents were used to radiosensitize tumors to radiation therapy. A decrease in the mid-band fit was noted in animals treated with Sunitinib for two weeks. Tumor response to low and high single doses of radiation was enhanced following vascular targeting treatment. Therapies aiming to radiosensitize tumors have been assessed to potentially induce a vascular normalization effect, leading to increased tumor oxygenation and alterations in the tumor microenvironment. Our results indicate that QUS parameters may be sensitive to tumor tissue changes secondary to vasculature changes and that high-frequency spectroscopic methods combined with power Doppler ultrasound may be useful to characterize response to novel vascular targeting strategies. Results from other vascular targeting strategies will also be presented.

3.7 **Feasibility of using high-frequency ultrasound to assess scatterer motion**, Lauren A. Wirtzfeld, Elizabeth S. L. Berndl and Michael C. Kolios, *Department of Physics, Ryerson University, Toronto, ON, Canada, mkolios@ryerson.ca.*

Background: Time-dependent fluctuations light scattering due to the motion of scatterers has been used in optical-coherence tomography (OCT) to assess changes in cell structure associated with cell death. We are investigating the potential of employing the equivalent techniques with high-frequency (55 MHz) ultrasound imaging to provide information related to cellular changes associated with cell death. The ability to use ultrasound increases the depth of analysis compared to OCT and has the potential to provide more detailed information in an *in-vivo* setting.

Objectives: The goal is to use high-frequency (approximately 55 MHz) ultrasound to calculate decorrelation times for models with varied scatterer sizes and sample viscosity to determine the potential application of the technique to detecting changes in spheroids with treatment.

Methods: In order to test the method, polystyrene spheres of varied sizes ranging from 1 to 10 μm were mixed in varied glycerol concentrations (25 to 100%) with PBS to vary the medium viscosity. A VisualSonics Vevo-770 preclinical imaging system (VisualSonics, Toronto, ON) was employed with a nominal 55 MHz transducer. Digital rf data was acquired for 500 consecutive

frames from each sample with 1, 3 and 5 A-scan lines to vary the total length of data acquisition. Transmit power was varied from 10 to 100% to ensure any detected changes in motion were not due to a generated radiation force from the transducer. The rf signal was gated to the region of the glycerol and polystyrene sphere mixture and the autocorrelation function was computed from the Fourier power spectrum. The decorrelation time (DT), defined as the time for the autocorrelation signal to drop to 1/*e* of the zero-lag value, was computed for each data set. A multi-way ANOVA was performed to determine if there were significant differences in DT across the different sphere sizes, glycerol concentrations, power levels or number of acquisition lines, with $p < 0.05$ considered significant. Marginal means were plotted to determine trends with the variables.

Results: The multiway ANOVA indicated there were significant differences in DT due to sphere size, glycerol concentration and number of lines acquired. The transmit power levels did not show significant differences, suggesting that increasing the transmit power does not result in significantly more motion being detected. The marginal means showed an increase in DT with increased sphere size and increased glycerol concentration, with the average DT increasing from 0.06 seconds for the 1 µm diameter sphere up to 1.2 seconds for the 10 µm sphere. Increased DT is expected with increased scattered size and increased velocity, which is consistent with the observations.

Conclusions: Ultrasound measurements of dynamic scattering have adequate sensitivity to detect changes in decorrelation times with varied scatterer size and sample viscosity in a simplified model. This suggests that high-frequency ultrasound could be sensitive to changes in scatterer motion. Such motion is known to occur during cell death as a result of cancer treatment.

4. IMAGE-BASED BIOMARKERS

4.1 **Radiological Society of North America Quantitative Imaging Biomarker Alliance: a paradigm for validating quantitative ultrasound methods,** Timothy J. Hall, *Medical Physics Department, University of Wisconsin - Madison, Madison, WI, tjhall@wisc.edu* (invited overview).

The attendees of the Ultrasonic Imaging and Tissue Characterization Symposium have a long history of contributions to the advancement of medical ultrasound technology. As the Symposium title states, a significant fraction of that effort has been toward quantitative techniques for “tissue characterization.” Numerous novel methods have been first reported at this conference and many of these techniques have been validated in a variety of ways. Some of these techniques are now commercially available as options on clinical ultrasound imaging systems.

Recently, the Radiological Society of North America (RSNA) has created a Quantitative Imaging Biomarker Alliance (QIBA) with pharmaceutical companies, imaging system manufacturers, academics, clinicians and representatives from the federal government (e.g., FDA, NIH, NIST) to advance the concept of converting "imaging systems” to “measurement systems”. The Alliance is organized by Modality Committees and within these committees are Technical Committees whose efforts involve specific classes of biomarkers. Each technical committee is supported by one or more Subcommittees organized for specific tasks. The goal of the Technical Committee efforts is to create QIBA/UPICT (Uniform Protocol for Imaging in Clinical Trials) protocols that specify methods for data acquisition, analysis and interpretation as well as QIBA Profiles that will provide specific claims of what can be accomplished by following the QIBA Protocol. A QIBA Profile will also tell vendors how their system can be compliant with the profile. The intent is to then validate the profile across imaging systems with phantoms and volunteers through work with other organizations such as drug and instrument companies and clinical trials organizations. The validated profile can also be forwarded to the FDA so that they can consider recommendations for use in evaluating clinical trials and approvals/clearances of quantitative measures.

This session is intended to stimulate discussion among the conference attendees regarding the state of the art in many of the areas of quantitative ultrasound techniques currently being developed and tested. The hope is to build consensus in the community for future QIBA efforts by the ultrasound participants.

This presentation will provide an overview of the QIBA structure, strategy of goals with particular emphasis on the Ultrasound Modality Committee efforts. The QIBA effort is funded in part by the RSNA and a contract with the NIBIB (HHSN268201000050C). 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 FDA.

4.2 **Shear-wave speed quantification for staging liver fibrosis**, Mark L. Palmeri, *Departments of Biomedical Engineering and Anesthesiology, Duke University Pratt School of Engineering, Durham, NC, mark.palmeri@duke.edu* (invited).

During the past decade, ultrasonic shear-wave speed quantification methods have been developed, investigated and commercially-released in the context of liver-fibrosis staging. Multiple manufacturers have introduced such systems in Europe and Asia, including: Echosens (Paris, France), Siemens (Mountain View, CA), Super Sonic Imagine (Aix-en-Provence, France), with Philips and GE also developing similar ultrasound products. Clinical studies using these tools have demonstrated a correlation between shear-wave speed and advancing liver fibrosis, with several studies concluding that these tools can be employed for noninvasive staging of advanced hepatic fibrosis and cirrhosis, reducing the need for invasive liver biopsy in some cases. To that end, the National Technology Assessment Centre, which is an advisory body in the United Kingdom, published a document recommending shear-wave speed measurements in the evaluation of liver fibrosis. Although enthusiasm is quite high, some challenges have been identified that are currently being addressed, including differences in the shear-wave-based metrics being reported (e.g., shear-wave speed, Young's modulus or shear modulus) by different commercial systems and absolute differences in these metrics across studies using different imaging systems and different clinical testing sites. The RSNA Quantitative Imaging Biomarker Alliance (QIBA) has started a committee to standardize the shear-wave speed measurements process in the context of liver fibrosis staging and is developing calibration standards

for these systems. A review of the current clinical literature will be presented, along with a discussion of active efforts to address the aforementioned standardization challenges.

4.3 **Quantitative ultrasound of masses in the breast: a multiple parameter approach**, James A. Zagzebski, Ivan M. Rosado-Mendez, Haidy Gerges-Nasief, Kibo Nam and Timothy J. Hall, *Department of Medical Physics, University of Wisconsin-Madison, Madison, WI, jazagzeb@wisc.edu* (invited).

Objectives: There is evidence that ultrasonic backscatter and attenuation features derived from rf echo signals can aid in differentiating benign from malignant breast masses. Previous reports have shown that an effective scatterer size, the acoustic concentration and the integrated backscatter contribute to these successful findings in animal models while recent experiments have demonstrated interlaboratory repeatability of quantitative ultrasound (QUS) estimations in phantoms and in animal models using a variety of clinical instruments. This ongoing study investigates the degree to which these QUS parameters can aid in classifying human breast tumors.

Methods: Radiofrequency echo signals are obtained during prebiopsy scans of subjects with suspicious breast masses under an approved IRB. A Siemens S2000 scanner equipped with the Axius Direct research interface and linear array transducers is employed to obtain data from radial (direction of ducts) and antiradial scanning planes, using beam steered angles ranging up to ± 20°. Reference phantom images are obtained using the same acquisition sequences and scanner settings. Data processing includes estimating total attenuation proximal to masses using a least-squares-method, determining local attenuation by applying either a reference phantom or a hybrid method, estimating backscatter coefficients (BSC) and estimating scatterer size by fitting BSC vs. frequency data to a size-dependent Gaussian-form-factor model. A Bayesian classifier has been implemented by applying 18 data sets for training and 17 for classifying among the first 35 patients, where input data include the above estimates as well as a heterogeneity index for ESD estimations.

Results: In patients studied thus far, the mean slope of the attenuation coefficient vs. frequency was 20% greater for carcinomas than for fibroadenomas, though there was considerable overlap. Most carcinomas exhibited lower values for the average BSC than fibroadenomas. In contrast to published animal tumor model data, the mean ESD alone did not differentiate fibroadenomas from carcinomas; however, the latter had greater variability within lesions. The Bayesian classifier, using attenuation, ESD and heterogeneity index, yielded excellent differentiation between the two classes of tumors. Analogous to subjectively analyzed features on gray scale images, results suggest QUS will also require multiple parameters for classification of breast masses. Supported in part by NIH (grants R01CA111289, R21HD061896, R21HD063031, and R01HD072077) and the Consejo Nacional de Ciencia y Tecnologia of Mexico (Reg. 206414).

4.4 **Quantitative ultrasound as a biomarker for the prostate and lymph nodes**, Ernest J. Feleppa[1], Jonathan Mamou[1] Junji Machi[2], Christopher R. Porter[3] and Alain Coron,[4] *[1]Riverside Research, New York, NY, [2]University of Hawaii and Kuakini Medical Center, [3]Virginia Mason Medical Center, Seattle, WA and [4]UPMC University Paris 06 and CNRS, Paris, France, efeleppa@RiversideResearch.org* (invited).

Cancer of the prostate cannot be imaged reliably by most conventional clinical-imaging modalities and small, but clinically-significant metastases in lymph nodes are easily overlooked by current histopathology procedures. More-reliable imaging of prostate cancer is necessary to improve biopsy guidance (i.e., reduce the rate of false-negative determinations); plan and execute focal therapy (i.e., obviate the need to treat the entire gland); and effectively monitor disease progression and regression (i.e., enable confident surveillance and avoid reliance on surrogate markers such as PSA). More-reliable detection of lymph-node metastases is necessary to improve staging (i.e., to avoid understaging as a result of undetected cancer foci) and to improve treatment (i.e., to provide treatment for systemic disease when metastases are present). Quantitative ultrasound (QUS) offers promise for enabling the needed improvements in prostate-cancer imaging and detecting metastases in lymph nodes.

Prostate-cancer studies utilizing only two spectral parameters combined with the level of serum PSA as inputs to nonlinear classifiers such as artificial neural networks and support-vector machines have produced values for the area under the ROC curve (A_z) of 0.84 using biopsy histology as the gold standard; this result is far superior to the A_z value of 0.64 obtained for corresponding interpretations of conventional B-mode images used to guide the biopsies. Lymph-node studies using spectral parameters, derived scatterer properties and envelope statistics using linear-discriminant methods of classification produced A_z values exceeding 0.95 for lymph nodes of colorectal and gastric cancers and 0.85 for the more-complex axillary lymph nodes of breast cancers.

Ongoing studies are seeking to validate results obtained to date; to improve QUS methods applied to classification (e.g., by integrating QUS with co-registered magnetic-resonance parameters); and to investigate the integration of QUS-based tissue-type-imaging (TTI) methods into HIFU instruments for treating prostate cancer. Similarly, ongoing studies are seeking to validate results obtained to date in detecting lymph-node metastases; to develop means of incorporating the methods into routine pathology workflow and thereby improve the ability of histological procedures to detect cancer foci in dissected nodes; to better understand underlying scattering behavior and to refine associated models; and to extend QUS to lower frequencies for identification of metastatic nodes *in situ*. Supported in part by the following NIH grants: CA053561, CA100183, CA135089, CA140772, EB015856, and EB016117.

4.5 **Cardiac tissue characterization: looking toward the future,** James G. Miller and Mark R. Holland, *Washington University in St. Louis, St. Louis, MO, james.g.miller@wustl.edu* (invited).

A primary goal of ultrasonic tissue characterization as an imaged-based biomarker is to complement and enhance high-resolution ultrasonic imaging by providing physiological and pathophysiological information that supplements the knowledge gained from imaging alone. Efforts to applying tissue characterization methods to enhance echocardiographic imaging predate the founding of this meeting in the mid-1970s.

The goal of this presentation is to identify opportunities for future advances to this potentially-valuable adjunct to echocardiography by reviewing the foundation established from four decades of myocardial tissue characterization as a step toward moving beyond current limitations and by identifying key areas of current interest to the cardiology community. We will very briefly review contributions from our laboratory and other laboratories with an approach that is sensitive to the technological and practical limitations of the time periods at which those contributions were made. Specifically, we will briefly examine the challenges presented by limitations once imposed by cardiac motion, analog-only processing and limited-bandwidth transducers. Areas where ultrasonic tissue characterization can potentially provide adjunct quantitative biomarker information regarding myocardial function, structure, and composition will be described. Armed with that historical perspective and with an awareness of current areas of interest, we will focus on identifying clinical applications as well as current technical challenges.

This presentation will attempt to draw the audience into an active discussion and debate regarding hurdles and opportunities for quantitative ultrasonic tissue characterization as a useful imaged-based biomarker. Supported in part by NIH/NHLBI grants R21HL10641 and R01HL40302.

4.6 **From biparietal diameters to shear waves: five decades of quantitative imaging in obstetrics**, Helen Feltovich, *Medical Physics Department, University of Wisconsin - Madison, Madison, WI, and Intermountain Healthcare, Provo UT, hfeltovich@gmail.com* (invited).

The first CT scan on a human was performed in 1971, the first MRI in 1977, both for cancer diagnosis. Not long after these techniques were implemented clinically, quantification of images and biomarkers for cancer detection were introduced. The Radiological Society of North America's Quantitative Imaging Biomarker Alliance was established in 2007, and its Ultrasound modality in March 2012. Quantitative imaging in ultrasound, however, has its roots in obstetrics in the 1950s. In 1959, a Scottish obstetrician, Ian Donald, first noted that ultrasound echoes could be obtained from the fetal head. He published on the first metric to be used in obstetrics to accurately date pregnancies, the biparietal diameter, in 1962. Fetal biometric measurements to monitor fetal growth (biparietal diameter, head circumference, abdominal circumference and femur length) were in wide clinical use by the time the first CT and MR were performed and remain a fundamental component of both basic and advanced obstetrical care today. For the past five decades, obstetrics has continued at the forefront of quantitative imaging. Many ultrasound and some MR techniques have moved far beyond biometry and are used in the fetal brain, heart, skeleton, face and lungs for diagnosis and monitoring of the fetal condition during pregnancy. Quantitative ultrasound techniques have also been very recently applied to the placenta, uterus and cervix. This presentation will review the history of quantitative imaging in obstetrics and discuss its future challenges. Supported in part by NIH (NICHD) R21HD061896, R21HD063031 and R01HD072077.

Tuesday morning

5. LIGHT PLUS ULTRASOUND

5.1 **Sound from light: application of photoacoustics for tissue characterization,** Ashwin Sampathkumar[1], Parag V. Chitnis[1], Jeffrey A. Ketterling[1], Jonathan Mamou[1], Ronald H. Silverman[2] and Ernest J. Feleppa[1] [1]*Lizzi Center for Biomedical Engineering, Riverside Research, New York, NY and* [2]*Department of Ophthalmology, Columbia University, New York, NY, ashwin@riversideresearch.org* (invited overview).

Photoacoustic imaging (PAI) and photoacoustic microscopy (PAM) for biomedical applications are rapidly growing areas of research. Purely optical techniques like confocal and two-photon microscopy, as well as optical-coherence tomography, employ low-intensity nonionizing radiation as a tool to investigate molecular optical contrast for tissue characterization. Unfortunately, optical waves do not penetrate biological tissue beyond a few millimeters because of scattering of light and thereby purely optical methods have limits on available spatial resolution and sensing depth. In comparison, ultrasonic imaging provides good image resolution at deeper sensing depths but has strong speckle artifacts as well as poor mechanical contrast in early staging of tissue (e.g., tumors). The goal of PAI and PAM is to achieve high contrast and high spatial definition in a single hybrid modality. An overview of photoacoustic projects will be presented. These include PAI of mouse embryos and porcine retinas for disease modeling, PAI as a tool for therapy monitoring, quantitative photoacoustic analysis of lymph nodes for early staging of cancer and the development of an all-optical PAI/PAM system as an emerging tool for remote tissue characterization.

5.2 **Near-field photoacoustic imaging of subsurface optical absorption using a plasmonic nanofocusing probe,** Oluwaseyi Balogun and Phillip Ahn, *Mechanical Engineering Department, Northwestern University, Evanston IL, seyi.balogun@gmail.com* (invited).

Photoacoustic techniques use pulsed lasers for thermoelastic generation of high-frequency ultrasound, which are detected after propagating through a material with a transducer. The technique has enabled quantitative mapping of local optical absorption in biological media, in a noninvasive fashion with high contrast and spatial resolution. Spatial resolution is one of the important characteristics of photoacoustic-imaging applications. The spatial resolution depends on the numerical aperture, bandwidth and aperture size of the receiving ultrasound transducer. Using high-frequency ultrasound transducer arrays and robust image reconstruction algorithms, the spatial resolution of the state-of-the-art photoacoustic techniques is limited to fractions of the ultrasound bandwidth. We present a new approach to photoacoustic imaging that relies on spatial and temporally-resolved measurement of laser-generated ultrasound within the near-field of the optical absorber. In the approach, a plasmonic nanofocusing probe is used to provide a nanoscale optical

transducer for measurement of ultrasound on a sample surface. Experimental results are presented that show the capability of the technique to map the presence of nanoscale subsurface optical absorbers in soft tissue-mimicking samples. The penetration depth of the technique is addressed. The technique may find application in the photoacoustic imaging of nanoscale optical absorbers in single cells.

5.3 **Optical coherence tomography: overview and biomedical imaging applications**, Gopi Maguluri, *Thorlabs Inc., Newton, NJ, gopi.maguluri@gmail.com* (invited).

Optical Coherence Tomography (OCT) is emerging as a preferred technique for subsurface, depth-resolved, high-resolution imaging of tissue on a micron scale. It is an all-optical technique that is analogous to ultrasonic imaging except that it uses light instead of sound. This talk gives a brief overview of OCT from studies involving various researchers and applications. Introducing the basic principles of OCT, diagnostic capabilities of commonly-used noninvasive biomedical imaging modalities are compared. Advances in OCT technology has led to Fourier-domain techniques, such as Spectral Domain (SD) and Swept Source (SS) OCT, with improved sensitivity and speed when compared to the original Time-domain (TD) OCT methods. A brief introduction of those techniques and a multitude of biomedical and clinical applications exploring the structural and functional information they provide are discussed.

Applications that will be presented include ophthalmic imaging that uses mostly the structural information of the tissue with a potential to diagnose ocular diseases. Optical sectioning and biopsy comparisons to OCT images are explained showing retinal degeneration studies on a mouse. Functional information exploring the birefringent properties of the tissue is analyzed using polarization sensitive OCT (PSOCT) imaging techniques. A brief introduction of PSOCT and studies including vocal fold and burn imaging are discussed. Doppler imaging is briefly mentioned, showing the capabilities of imaging blood flow in arteries. Probes used as catheters for endoscopic imaging applications are also discussed. A compiled list of products that Thorlabs offers for researchers interested in OCT technology will be provided at the end.

5.4 **Imaging the effects of ultrasound radiation force in the retina and choroid,** Ronald H. Silverman[1, 2], Qifa F. Zhou[3] and Zhongping Chen[4], *[1]Department of Ophthalmology, Columbia University Medical Center, New York, NY, [2]F.L. Lizzi Center for Biomedical Engineering, Riverside Research, New York, NY, [3]NIH Resource Center for Medical Ultrasonic Transducer Technology, University of Southern California, Los Angeles, CA and [4]Beckman Laser Institute, University of California at Irvine, Irvine, CA, rs3072@columbia.edu* (invited).

The posterior coats of the eye comprise the retina (with about 10 layers), the underlying choroid (a vascular layer with a fine capillary network and underlying larger venules and arterioles) and finally the sclera (the connective tissue forming the wall of the eyeball). Because the retina and choroid are only about 0.25 mm in thickness, and because the eye offers an optical window, optical-coherence tomography (OCT), offering resolution better than 10 µm, has become the most widely used means for cross-sectional imaging of these tissues.

We have investigated the effect of ultrasound radiation force (ARF) on the retina, choroid and orbital tissues in the *in vivo* rabbit eye using focused 20 MHz transducers emitting tracking pulses interleaved with 'push' tone bursts. In the normotensive eye (intraocular pressure about 10 mmHg), we demonstrated displacements on the order of 10 µm and readily visualized perfusion in the orbit and choroid. In proptosed eyes, where intraocular pressure was elevated to about 30 mmHg, choroidal blood flow was not seen and exposure to ARF often resulted in a transient increase in choroidal backscatter lasting about one second. We attribute this either to transient influx of blood, or to alteration of spacing within the choroidal capillary network.

ARF thus offers the unique potential for 'palpating' the retina/choroid. The relatively modest resolution provided by ultrasound compared to OCT, however, motivates combination of OCT with ARF. Phase-resolved OCT images will allow measurement of displacements and identification of such displacements within the layers of the retina. OCT systems also now allow depiction of the choroidal vasculature.

When ARF push and tracking pulses are generated from a single transducer, co-registration is inherent. This is not the case for combined ARF and OCT. In OCT, the low-coherence light-beam must pass through the pupil and lens. If the ultrasound beam is coaxial, the lens will both strongly absorb and refract the ultrasound beam in the opposite direction to that of the optical beam. Thus, the solution will be to introduce ARF into the eye via the pars plana (avoiding the lens) and to have a sufficiently large spot size to facilitate co-registration. We are now exploring a number of approaches, including unfocused and ring transducers, to address this requirement.

The capacity to induce displacements in the retina and choroid and to identify within high-resolution OCT images will offer a new means for assessment of development and pathology of diseases such as age-related macular degeneration. Supported in part by NIH grant R01 EY021529 and an unrestricted grant to the Department of Ophthalmology of the Columbia University Medical Center from Research to Prevent Blindness.

5.5 **Coherence-weighted beamforming and automated vessel segmentation for improving photoacoustic imaging using annular arrays**, Parag V. Chitnis[1], Orlando Aristizabal[2], Ashwin Sampathkumar[1], Erwin Filoux[1], Jonathan Mamou[1], and Jeffrey A. Ketterling[1], *[1]F. L. Lizzi, Center for Biomedical Engineering, Riverside Research, New York, NY and [2]Skirball Institute of Biomolecular Medicine, New York University School of Medicine, New York, NY, pchitnis@RiversideResearch.org* (invited).

In vivo imaging of embryonic vasculature is crucial to the study of development of mammalian physiology and congenital diseases. Mouse embryos are the preferred animal models for such studies but require an imaging depth of several mm while maintaining micron-scale resolution. Photoacoustic (PA) imaging using high-frequency ultrasonic transducers is a viable technique for depicting microvasculature. Mechanically-scanned annular arrays, in conjunction with delay-and-sum (DAS) beamforming at multiple depths, have the potential to provide fine resolution at relatively large imaging depths. This work applies adaptive DAS beamforming and automated vessel segmentation algorithms to 3D PA data acquired from an *in vivo* mouse using a high-frequency annular array. A 5-

element, 40-MHz annular array was modified to accommodate coaxial illumination using a 532-nm pulsed laser and was raster scanned to facilitate acquisition of 3D PA-image data. At each scan location, one laser pulse was fired and the resulting PA signals received by the 5 elements were simultaneously digitized and recorded. The 5-channel PA data were processed using a conventional DAS algorithm and the coherence factor (CF), defined as the ratio of coherent energy to the total energy, was computed at all depths. The depth-dependent CF obtained at each scan location was then employed as a weighting function for the corresponding DAS-processed A-line. The performance of the conventional DAS and CF-based DAS were quantitatively compared using log-compressed B-mode images of a phantom containing an 80-µm diameter hair. 3D PA data were then obtained from a 12-day old mouse embryo in an externalized, intact uterus. After CF-DAS-processing, the 3D data, an automated vessel segmentation algorithm involving multiscale Gaussian diffusion and second-order spatial derivatives was employed to visualize microvasculature. The CF-based DAS scheme applied to the hair phantom improved SNR by more than 10 dB in comparison to conventional DAS. B-mode images of the hair with a 20-dB dynamic range obtained from CF-based DAS of PA data resulted in a lateral dimension of less than 200 µm at depths ranging from 8-20 mm, whereas the conventional DAS resulted in lateral dimension exceeding 1 mm at locations away from the geometric focus. A similar improvement in SNR was observed for the processed embryonic data as was a qualitative improvement in sharpness of vasculature. In addition, the vessel-segmentation algorithm suppressed speckle and connected vascular structures together, which enhanced depiction of major blood vessels in the mouse embryo.

5.6 **Multispectral Optoacoustic Tomography (MSOT) – a versatile new imaging modality for biomedical research**, Wouter Driessen[1, 2], Neal C. Burton[1, 2], Stefan Morscher[1-3], Jing Claussen[1, 2], Thomas Sardella[1], Daniel Razansky[2, 3] and Vasilis Ntziachristos[2, 3], *[1]iThera Medical GmbH, [2]Helmholtz Zentrum München and [3]Technische Universität München, wouter.driessen@ithera-medical.com* (invited).

Multispectral Optoacoustic Tomography (MSOT) is a powerful new imaging modality that visualizes the spectral response of chromophores *in vivo*, with high resolution and at depths of up to several centimeters. Uniquely, it provides the capacity to separate endogenous signals of interest, such as melanin and oxy-/deoxy-hemoglobin and tissue contras, from extrinsically-administered agents, including nanoparticles and fluorescent dyes or proteins.

By simultaneously delivering functional, anatomical and molecular imaging within one unique platform, a range of disease models, including cancer, cardiovascular, infection and inflammation, can be characterized. The high temporal resolution of the technology allows for the monitoring of pharmacokinetic and pharmacodynamic processes in real-time. In summary, MSOT offers a new and unique imaging modality that (1) has a resolution at least ten-fold higher than nuclear and optical imaging, (2) allows for real-time imaging with molecular specificity through several centimeters of tissue and (3) is safe (i.e., no ionizing radiation) and cost-efficient.

5.7 **Transrectal photoacoustic-ultrasonic imaging for cancer diagnosis and therapy guidance in the prostate**, Trevor Mitcham,[1] Tatiana Marques,[2] Dev Chatterjee,[2] Sunil Krishnan,[2] Thomas Pugh[2] and Richard Bouchard,[1] *Departments of [1]Imaging Physics and [2]Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, rrbouchard@mdanderson.org.*

Background: Prostate cancer is the second leading cause of cancer deaths in the US. Improved imaging contrast and sensitivity could enhance diagnostic and therapeutic options in the prostate. Transrectal photoacoustic-ultrasonic (TR-PAUS) imaging has the ability to probe the molecular composition of tissue with high sensitivity and to image metallic implants with increased contrast. A TR-PAUS imaging solution has potential to improve visualization of implanted seeds during prostatic brachytherapy or to allow for local tissue assessment (i.e., oxygen saturation or presence of targeted nanoparticles) during needle biopsy of the prostate.

Objectives: The goal of this study was to demonstrate feasibility of using TR-PAUS imaging in conjunction with local interstitial irradiation and targeted plasmonic nanoparticles for the purpose of improved prostatic cancer diagnosis and therapy monitoring.

Methods: A BPL9-5/55 transrectal probe connected to a Sonix RP ultrasound system was modified to include seven 800-µm optical fibers that were coupled to a Pro-270-10 Nd:YAG tunable laser. In addition to a transrectal irradiation source, the use of an interstitial single-fiber (800-nm) irradiation source was also demonstrated. TR-PAUS imaging acquisitions were conducted in a tissue-mimicking phantom or excised bovine prostate. PA imaging of gold nanorods (AuNRs; absorption peak 810 nm) targeting the LHRH receptor in PC-3 human prostate cancer in a subcutaneous murine tumor model was achieved with a Vevo LAZR small-animal PAUS imaging system operating in a multi-wavelength (680, 734 758, 875 and 950 nm) imaging mode.

Results: A clinical-imaging system was integrated with a TR-PAUS probe that is capable of delivery >100 mJ (@ 1064 nm) per pulse. PAUS imaging is able to provide contrast improvements over diagnostic ultrasound in excess of 25 dB when imaging brachytherapy seeds in prostate tissue. Use of an interstitial irradiation source was demonstrated to provide >15 mJ (@ 1064 nm) of local irradiation, which could facilitate local assessment of oxygenation saturation during a needle-biopsy procedure. In a small-animal model of PC-3 human prostate cancer, LHRH-targeted AuNRs were successfully imaged and spectrally unmixed using correlation-based methods.

Conclusions: With its potential for enhanced imaging contrast and sensitivity, TR-PAUS imaging shows tremendous potential in assisting in diagnostic procedures (e.g., needle biopsy) and during therapy guidance (e.g., visualization of brachytherapy seeds). The continued development of targeted plasmonic nanoparticles is expected to further improve the clinical translatability of these technologies. Supported by NIH P50 CA140388.

5.8 **Prototype system and preliminary comparison of beamforming algorithms for photoacoustic imaging of prostate brachytherapy seeds**, Nathanael Kuo,[1] Muyinatu A. Lediju Bell[2] and Emad M. Boctor,[3] *Departments of [1]Biomedical Engineering, [2]Computer Science, and [3]Radiology, Johns Hopkins University, Baltimore, MD, nkuo8@jhmi.edu.*

Background: Prostate cancer is the most diagnosed cancer among men in the United States. Permanent prostate brachytherapy, a minimally-invasive surgery involving the implantation of approximately 100 grain-sized radioactive seeds, is one of the most popular

treatments today. Traditionally guided by ultrasound, it has become widely accepted that ultrasound imaging alone is insufficient to detect seeds. Photoacoustic imaging is an innovative way to detect seeds while minimizing changes to current surgery workflow.

Objectives: The goals of this study were to develop the photoacoustic imaging hardware and software necessary for prostate brachytherapy and to compare various beamforming algorithms for localizing brachytherapy seeds.

Methods: A photoacoustic imaging system for prostate brachytherapy was integrated using a Quantel 1064nm Nd:YAG Q-switch Brilliant pulsed laser system, an Ultrasonix SonixTouch ultrasound scanner and an Ultrasonix SonixDAQ data acquisition device. An optical fiber was coupled to the laser and an Ultrasonix BPC8-4/10 & BPL9-5/55 transrectal ultrasound probe was used to acquire raw radiofrequency acoustic echoes from decayed palladium brachytherapy seeds embedded in gelatin phantoms. Various beamforming algorithms were tested to reconstruct photoacoustic images, including a standard delay-and-sum (DAS) algorithm, Fast Fourier Transform (FFT)-based reconstruction using the k-Wave toolbox for MATLAB and a short-lag spatial coherence (SLSC) beamformer. The contrast and contrast-to-noise ratio (CNR) of brachytherapy seeds were measured in the reconstructed images.

Results: Our prototype system successfully produced raw prebeamformed photoacoustic data. The measured contrast and CNR were: 45 dB and 92, respectively, with the DAS beamformer; 61 dB and 93, respectively, with the FFT-based reconstruction and 6 dB and 4, respectively, with the SLSC beamformer. Contrast and CNR were increased when the SLSC images were multiplied by images created with the DAS and FFT-based beamformers, measuring 49 dB and 144, respectively, in the combined SLSC-DAS image, and 66 dB and 147, respectively, in the combined SLSC-FFT-based image. Clutter-noise artifacts were also reduced with the combined approach.

Conclusion: We developed a working prototype for photoacoustic imaging of brachytherapy seeds. Although images reconstructed with the SLSC beamformer were poor, when combined with the DAS or FFT-based beamforming method, contrast and CNR were enhanced compared to either method individually. Thus, a beamforming approach that incorporates spatial coherence information appears to be more ideal when detecting brachytherapy seeds in photoacoustic images.

5.9 **Freehand spatial-angular compounding of photoacoustic images,** Hyun-Jae Kang[1], Muyinatu A. Lediju Bell[1], Xiaoyu Guo[2], Russell H. Taylor[1] and Emad M. Boctor[1, 3]**,** *Departments of [1]Computer Science, [2]Electrical and Computer Engineering and [3]Radiology, Johns Hopkins University, Baltimore, MD, eboctor1@jhmi.edu.*

Photoacoustic (PA) imaging is an emerging medical imaging modality that relies on the absorption of optical energy and the subsequent emission of an acoustic wave. PA images are susceptible to background noise artifacts that reduce the Signal-to-Noise ratio (SNR) and Contrast-to-Noise ratio (CNR). We implemented freehand spatial-angular compounding of photoacoustic images to enhance SNR and CNR.

A two-layer black and transparent plastic phantom was irradiated with a Q-switched Nd:YAG laser (QUANTEL, Les Ulis, France) operated at a wavelength of 1064 nm. A SONIX-DAQ (Ultrasonix Co., Vancouver, Canada) device connected to a Sonix-CEP ultrasound system and a hand-held L14-5W/38 ultrasound probe was used to acquire the resulting radiofrequency PA data. Position information of the ultrasound probe was recorded with a medSAFE electromagnetic tracker (Ascension Technology Co., Milton, USA), as the hand-held probe was rotated about the elevational axis during image acquisitions. A custom-built controller board was used to synchronize the acquisitions of PA data and probe position information. Based on the probe's position information, a *frame-selection process* was applied to pre-beamformed rf data to identify frames that were in the same elevation plane. These selected frames were averaged to generate a *spatial-angular* compounded PA image. CNR and SNR values were measured in single and spatial-angular compounded PA images. A total of 420 compounded images and 262 single images were compared.

The mean CNR and SNR were 0.96 and 1.03, respectively, in single PA images, and 1.26 and 1.31, respectively, in compounded images. The ranges were 0.73-1.23 and 0.83-1.26, respectively, in single PA images and 0.86-1.43 and 0.92-1.50, respectively, in compounded images. Thus, CNR and SNR were generally increased with spatial-angular compounding of PA images. We also report on the optimal frame-selection thresholds required to generate high-quality spatial-angular compounded PA images.

6. TISSUE PARAMETERS 2

6.1 **Quantitative ultrasound monitoring of cell death response to chemotherapy in locally-advanced breast cancer patients using frequency-dependent backscatter model**, Lakshmanan Sannachi[1, 2], Hadi Tadayyon[1, 2], Ali Sadeghi-Naini[1, 2], Omar Falou[1, 2], Michael Oelze[3] and Gregory Czarnota[1, 2], *[1]Department of Radiation Oncology and Imaging Research – Physical Sciences, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [2]Department of Radiation Oncology and Medical Biophysics, University of Toronto, Toronto, ON, Canada and [3]Bioacoustics Research Laboratory, Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, Urbana, IL, Lakshmanan.Sannachi@sunnybrook.ca.*

Introduction: In previous studies, imaging techniques based on analysis of ultrasonic backscatter have been successfully used to characterize different types of tissue. The goal of this study was to monitor changes in the histological features of breast tumors after chemotherapy in order to distinguish between treatment responders and nonresponding patients, using estimates of ultrasound-backscatter characteristics.

Methods: Tumor responses of 29 breast-cancer patients to chemotherapy were examined using quantitative ultrasound with two center frequencies, ~5 MHz (bandwidth range: 3.6 – 6.6 MHz) and ~7 MHz (bandwidth range: 4.5 – 9 MHz). Patients were classified as responders or nonresponders based on their ultimate clinical and pathological response. Ultrasound backscatter parameters, such as average scatterer diameter (ASD) and average acoustic concentration (AAC), were estimated from regions-of-interest in tumors prior to treatment onset and at four times during neo-adjuvant chemotherapy treatment (weeks 1, 4, 8 and prior to surgery). The Anderson model was used over analysis bandwidths to obtain backscatter parameter estimates.

Results: The ASDs calculated from 5 MHz data were significantly higher than those obtained from 7 MHz data. The AACs estimated from both frequency ranges showed significant changes during treatment period, compared to pre-treatment, for treatment responding patients. The data indicated maximum increases of approximately 7.1 and 6.6 dB/cm^3 in acoustic concentration calculated from 5 and 7 MHz ultrasound data at week 8 in responders, respectively. Nonresponders did not show any significant changes in any of the backscatter parameters over treatment times. The range of ASD estimates obtained from both frequency ranges were comparable with the size of microstructures observed in microscopic images of the histological samples corresponding to the nonresponders. However, such an agreement was not observed in the case of responding patients. The acoustic concentration showed clear separation between two treated populations one week after treatment initiation.

Conclusions: This study demonstrates that the backscatter parameters have a favorable potential for quantifying histological changes in tumors during treatment noninvasively and consequently, for distinguishing between treatment responders and nonresponders. The backscatter parameter, AAC, can predict treatment response as early as one week after the start of treatment. This is an important insight that can be used to adjust cancer therapies for nonresponding patients early after treatment initiation. However, ASD estimates using a fluid-filled model did not allow corrections with microstructures observed in tumor regions of the responding patients. This indicates that the Anderson model is too simplistic for scattering from breast tumors. Therefore, better models are required for a more accurate estimation of backscatter parameters of breast tissue that can further describe alterations introduced in tissue microstructures as a result of treatment-response development.

6.2 **Quantitative ultrasound spectral and textural biomarkers of tumor cell death response in breast cancer patients undergoing chemotherapy**, Ali Sadeghi-Naini[1, 2], Lakshmanan Sannachi[1, 2], Omar Falou[1, 2], Naum Papanicolau[1, 2], Rebecca Dent[3], Sunil Verma[3], Maureen Trudeau[3], Jean Francois Boileau[4], Jacqueline Spayne[1, 2], Sara Iradji[1], Ervis Sofroni[1], Justin Lee[1, 2], Sharon Lemon-Wong[5], Martin Yaffe[1, 2], Michael Kolios[6] and Gregory J. Czarnota[1, 2], *[1]Department of Radiation Oncology and Imaging Research – Physical Science, 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 Department of Medicine, University of Toronto, [4]Division of Surgical Oncology, Department of Surgery, Sunnybrook Health Sciences Centre and University of Toronto, [5]Department of Nursing, Odette Cancer Centre, Sunnybrook Health Sciences Centre and [6]Department of Physics, Ryerson University, Toronto, ON, Canada, Gregory.Czarnota@sunnybrook.ca.*

Objective: Many cancer therapies are intended 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 the potential to quantify tumor responses to therapy in patients, using quantitative spectral and textural biomarkers extracted from low-frequency ultrasound data (4-10 MHz).

Methods: A clinical study was undertaken investigating the efficacy of ultrasound to quantify cell death in tumor responses with cancer treatment. Patients *(n*=24) with locally-advanced breast cancer received anthracyline and taxane-based chemotherapy treatments over four to six months. 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 with center frequencies of ~5 and ~7 MHz, respectively. The majority of patients went on to have a modified radical mastectomy and correlative whole mount histopathology.

Results: Results obtained from both ~5 and ~7 MHz data indicated considerable increases in ultrasound spectral backscatter power in patients who clinically responded to treatment. This was accompanied by significant increases in quantitative ultrasound spectral parameters such as mid-band-fit (up to 9.1 ± 1.2 dBr) and 0-MHz intercept (up to 10.8 ± 2.4 dBr). Patients categorized as poor responders clinically demonstrated significantly lower increases (1.9 ± 1.1 dBr and 1.4 ± 2.7 dBr for mid-band-fit and 0-MHz intercept, respectively). Textural biomarkers extracted from quantitative ultrasound spectral parametric maps also demonstrated considerable differences in trend between treatment responding and nonresponding patients early after the treatment initiation.

Statistically-significant differences were found between treatment responding and nonresponding patient populations using quantitative ultrasound spectral biomarkers 4 and 8 weeks after treatment initiation. Applying quantitative ultrasound textural biomarkers in order to incorporate response heterogeneities resulted in statistically-significant differences between these two populations only one week after the start of chemotherapy.

Conclusions: 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. This can permit ineffective treatments to be changed to more efficacious ones, potentially leading to improved treatment outcomes.

6.3 **Quantitative ultrasound monitoring of breast cancer cell death *in vivo* using tissue-scattering models – a preclinical study,** Hadi Tadayyon[1, 2], Lakshmanan Sannachi[1, 2], Ali Sadeghi-Naini[1, 2], Omar Falou[1, 2], Michael Oelze[3] and Gregory Czarnota[1, 2], *[1]Department of Radiation Oncology and Imaging Research – Physical Sciences, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [2]Department of Medical Biophysics, University of Toronto, Toronto, Canada and [3]Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, Urbana, Il, hadi.tadayyon@gmail.com.*

Motivation: Locally-advanced breast cancer (LABC) is an aggressive subtype of breast cancer that is commonly treated with chemotherapy prior to surgery. Frequent monitoring of LABC tumors makes early detection of refractory patients and switching to a more aggressive regimen possible, thereby improving survival and reducing morbidity. Previous studies have demonstrated significant increases in the frequency-dependent ultrasound backscatter amplitude associated with cell death. This study assesses the utility of two ultrasound tissue scattering models – the Gaussian and the Anderson form factors, in detecting chemotherapy-induced cell death in mouse models of breast cancer.

Methods: Radiofrequency (rf) data were acquired from xenografted human breast cell line tumors (MDA-MB231) before and after injection of doxorubicin/paclitaxol chemotherapeutic agents, using high-frequency (single-element 25 MHz transducer) and low frequency (linear-array 6 MHz transducer) ultrasound-imaging systems. Four different treatment times were considered – 4h, 12h, 24h and 48h after injection. The control group, which received no treatment, were imaged at 0h and 24h. Rf Spectral analysis involved estimating the backscatter coefficient (BSC) from regions-of-interest in the center of the tumor, to which the form factor models were fitted, resulting in estimates of average-scatterer diameter (ASD) and average acoustic concentration (AAC). The BSCs were corrected for frequency-dependent attenuation using literature values for rat skin (2 dB/cm/MHz) and tumor (0.6 dB/cm/MHz). The changes in the QUS parameters were compared with areas of cell death obtained from tumor histopathology. The two form factor models were compared based on the proximity of high-frequency ASD estimates to mean cell size.

Results: Comparison of the mean cell size of untreated tumors with ASD estimates demonstrated that both models overestimate mean cell size (mean cell size = 18 ± 3μm, Gaussian ASD = 52 ± 4 μm, Anderson ASD = 32 ± 0.1 μm). However, the Anderson ASD estimates provided more proximal values to mean cell size. ESD did not change significantly for any length of time. As early as 24h after treatment onset (time of maximal cell death), both models revealed a 3.8 ± 1 dB/cm^3 increase in AAC ($p < 0.005$) at high frequencies. At low frequencies, only the Gaussian form factor was evaluated as the Anderson model produced excessively large ASD estimates. The low frequency AAC estimate increased by 6.45 ± 2.75 dB/cm^3 ($p = 0.014$). The greatest increases in the EAC were observed at both low and high frequencies at 24 h. In addition, a strong linear correlation was seen between cell death and EAC at the lower frequency range ($R^2 = 0.94$).

Conclusion: The Gaussian form factor model based estimates of EAC can potentially be used to track cell death at clinically-relevant frequencies (< 10 MHz). At higher frequencies, the Anderson model better predicts mean cell size of untreated breast tumors but neither model reflected the changes in cell morphology resulting from cell death. Future work involves further model investigation and spectral-based attenuation estimation that may further improve ESD and EAC correlations to cell death.

6.4 **ViSR discrimination of viscoelastic changes in dystrophic muscle *in vivo***, Mallory R. Scola[1], Joe N. Kornegay[2], James F. Howard[3] and Caterina M. Gallippi[1], [1]*Joint Department of Biomedical Engineering, University of North Carolina, Chapel Hill, NC,* [2]*Deparment of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX and* [3]*Department of Neurology, University of North Carolina, Chapel Hill, NC, cmgallip@bme.unc.edu.*

Background: In Duchenne muscular dystrophy (DMD), an absence of the protein dystrophin causes progressive degeneration of skeletal and cardiac muscle with necrosis and subsequent progressive replacement of muscle by fibrous tissue and fat. Because these changes in muscle composition and structure are associated with changes in muscle viscoelasticity, imaging the viscoelastic properties of muscle may be useful for stratifying degrees of functional muscle degeneration in DMD. Viscoelastic Strain Response (ViSR) ultrasound is a method for quantitatively evaluating the relaxation time constant, τ, defined as the ratio of viscosity to elasticity in the Voigt mechanical model. The objective of this work is to demonstrate ViSR's relevance to delineating progressive dystrophic muscle degeneration in golden retriever muscular dystrophy (GRMD) dogs, a relevant model of human DMD, *in vivo*. We hypothesize that ViSR ultrasound detects differences in τ from early through late stages of disease development.

Methods: ViSR ultrasound was performed *in vivo* on the rectus femoris (RF) muscle of a cross-section of DMD dogs. The dogs were aged 6, 12, 24 and 60 months at the time of imaging, with two dogs of each age ($n = 8$ total dogs). Imaging was performed with a Siemens SONOLINE Antares™ ultrasound system specially equipped for research purposes and a VF7-3 transducer (Siemens Medical Solutions, USA Inc. Ultrasound Division). The acquired ViSR data were processed to calculate τ, and parametric 2D ViSR τ images were rendered. A region-of-interest (ROI) spanning from the central fascia to the bottom muscle boundary was hand-delineated in spatially-matched B-mode images and a median τ within the ROI was computed. Median τ values were averaged within age-matched pairs.

Results: Median ViSR τ values were calculated to be 0.59 ± 0.02 ms for the 6 mo pair, 0.48 ± 0.05 ms for the 12 mo pair, 0.42 ± 0.05 ms for the 24 mo pair and 0.36 ± 0.05 ms for the 60 ms pair. This observed trend of τ decreasing with age suggests an increase in the stiffness of the RF in the progressively-older dogs, consistent with expected progressive fibrous deposition.

Conclusions: These data are consistent with the expected disease development in the RF muscle and suggest the relevance of ViSR ultrasound as a noninvasive biomarker for monitoring dystrophic muscle degeneration.

6.5 ***In vivo* estimation of ultrasonic backscatter and attenuation in subcutaneous breast fat**, Haidy Gerges Nasief, James A. Zagzebski, Sarah Kohn and Timothy J. Hall, *Medical Physics Department, University of Wisconsin, Madison, WI, nasief@wisc.edu.*

Objectives: Interpretation of ultrasound images to diagnose solid breast masses generally includes subjectively comparing B-mode image features of a mass with those of surrounding fat and parenchymal tissue. A mass's echogenicity and ultrasound attenuation are qualitatively described using the US BIRADS lexicon, where subcutaneous fat effectively serves as a standard for comparison. Thus, we are interested in the degree with which backscatter and attenuation within breast fat varies among patients. The aim of this study is to determine acoustic properties of subcutaneous fat in the breast under clinical imaging conditions, at frequencies used in breast ultrasonography.

Methods: 24 human subjects with solid breast masses scheduled for core needle biopsy were selected for this investigation. The study was conducted in accordance with a protocol approved by the UW Madison Health Sciences IRB. Subjects were scanned using a Siemens S2000 system equipped with an 18L6 array transducer. By means of the Axius Direct research interface, rf echo data were acquired from radial and antiradial planes depicting the mass, surrounding subcutaneous fat, and breast parenchyma. Acquisitions applied beam steering angles from -10^o to $+10^o$. Sonographers placed fiducial markers on B-mode images showing the margins of a mass. Echo data were acquired from a reference phantom to account for diffraction and system settings. Offline analysis consisted of estimating attenuation (*Att*) and backscatter coefficients (*BSC*) from fat using the reference phantom method. Effective scatterer diam-

eters (*ESD*) were estimated by applying a Gaussian form factor to backscatter coefficient data. A heterogeneity index (*HI*) was estimated by computing the standard deviation of the *ESD* (ignoring correlations among overlapping windows). Finally, the integrated backscatter coefficient (*IBSC*) was calculated over the 4-9MHz range.

Results: The proximal margin of the parameter estimation region was 0.5 cm below the skin surface for all cases except one, where it was 1.5 cm. A power law fit to the attenuation coefficient for subcutaneous fat among the 24 patients yielded $Att = 1.99\ dB\cdot cm^{-1}\ MHz^{-0.48}$. The mean-attenuation coefficient vs. frequency slope at 7 MHz for these *in vivo* studies is $0.69 \pm 0.34\ dB\cdot cm^{-1}\ MHz^{-1}$. This compares with values of $0.158\pm0.003\ dB\cdot cm^{-1}\ MHz^{-1.7}$ obtained by D'Astous and Foster (1986) for *in vitro* samples, and slope of $0.617\pm0.117\ dB\cdot cm^{-1}\ MHz^{-1}$ at 7MHz.

Semi-log plots of *BSC* versus frequency in breast fat exhibited close agreement among all subjects, both in magnitude and frequency dependence. The mean BSC follows a power law fit of $(0.6\pm0.25)\ x10^{-4}\ sr^{-1}\ cm^{-1}\ MHz^{-2.49}$, in agreement with values reported by D'Astous and Foster. The integrated backscatter, a quantitative surrogate for BIRADS "echogenicity", is $0.004\pm0.0023 cm^{-1}sr^{-1}$. The mean effective scatterer diameter for fat is 60 ± 9.3 µm, and the heterogeneity index, HI is 10± 5.1. Parameter estimates exhibited isotropic behavior in most cases.

Conclusions: The surprisingly narrow range measured illustrates the agreement between acoustical properties of subcutaneous fat for these subjects. Findings support the use of fat echogenicity as a standard for comparison with tumors. Supported, in part, by NIH grant R01CA111289.

6.6 **Automatic thickness measurement of skin melanomas by ultrasonic imaging**, R. Raišutis[1], R. Kažys[1], S. Valiukevičienė[2], R. Kliunkienė[2], G. Linkevičiūtė[2] and K. Andrekutė[1] [1]*Ultrasound Institute, Kaunas University of Technology and* [2]*Department of Skin and Venereal Diseases, Lithuanian University of Health Sciences, Kaunas, Lithuania, renaldas.raisutis@ktu.lt.*

Early stage differentiation of skin tumors into thin (thickness ≤1mm) and thick (thickness ≥1mm) lesions is a very important task of clinical diagnostics. In the case of thick skin melanoma, it requires surgical excision with a sentinel lymph node biopsy in order to avoid the high risk of the metastasis efflorescence. However, it may damage the lymphatic vessels and tumor drainage could occur. Alternatively, ultrasound at a frequency of at least 22 MHz is a noninvasive and safe technique that provides complementary information to clinical examination of various skin lesions and tumors. However, interpretation of ultrasonic images by different investigators often differ. The question of how to improve the quality of ultrasonic image and extract more quantitative features of cancerous tissue is very important during sonography examination, especially for detection of early stage tumors. The objective of this work is to develop a novel ultrasonic technique for automatic thickness measurement of skin melanomas.

An algorithm of automatic parameterization (B-scan contouring, estimation of lateral dimensions and the maximum thickness) of the skin tumors has been developed, assuming that the structure of the tumor is hypoechogenic and the surrounding tissues are hyperechogenic. Signal processing is performed in the following steps: filtering in time and space domains for cancelling of uncorrelated noise; thresholding of the signals at specified levels of the normalized amplitudes for front surface and back surface reflections from the boundaries of the tumor; measurement of the time-of-flight values and recalculation into the penetration depth; correction of measurement artefacts and iterative least-squares polynomial approximations of boundaries of the tumor in order to perform operator-free measurements. The maximum-likelihood-estimator corresponds to the best coincidence between the noncorrected results and the results corrected against the artefacts. Finally, automatic thickness measurement of the tumor as maximal value of difference between the lower edge of the hyperechogenic stratum granulosum and the lower boundary of the hypoechogenic region representing the depth of the tumor was performed. Phantoms are proposed for validation of the technique.

When the operator-free technique was applied to evaluate thin melanomas, sufficient accuracy was obtained. The results are in a good agreement with the reference results of histological examination. The vertical distance from the uppermost level of the stratum granulosum in the epidermis to the lowest point of the tumor (Breslow index, *pT*) was estimated. Assessment of skin melanoma location, margins, thickness and echo pattern by our approach may help to diagnose, plan treatment or detect subclinical recurrence of the tumor after treatment. The algorithm was implemented in the clinical-decision support software.

Tuesday afternoon

7. SHEAR WAVES/ELASTOGRAPHY 2

7.1 **Feasibility of harmonic ARFI tracking for measuring arterial wall thickness**, Joshua R. Doherty, Jeremy J. Dahl and Gregg E. Trahey, *Department of Biomedical Engineering, Duke University, Durham, NC, joshua.doherty@duke.edu.*

Increased arterial wall thickness is correlated with a higher prevalence of clinical cardiovascular events, including stroke and coronary heart failure.(1) Despite its routine use, the poor reproducibility of B-mode intima-media thickness (IMT) measurements across multiple readers and institutions questions their use as a surrogate marker of atherosclerosis.(2) The high contrast difference in stiffness between arteries and surrounding tissues suggests the delineation of arterial boundaries is a potential niche for Acoustic Radiation Force Impulse (ARFI) imaging. Existing ARFI methods, however, are corrupted by clutter mechanisms that can bias displacement estimates and make it particularly difficult to distinguish the vessel-blood interface.

We recently developed a novel pulse-inversion harmonic-tracking method that improves ARFI image quality *in vivo*. Here, the feasibility of this technique for measuring arterial-wall thickness is assessed. We present results comparing the visualization of arterial boundaries in matched fundamental B-mode, harmonic B-mode, fundamental ARFI and harmonic ARFI images of the common carotid artery in six subjects with (n=4) and without (n=2) known atherosclerosis *in vivo*.

Harmonic ARFI imaging demonstrated reduced correlation and increased variance in displacement estimates within the lumen, making it easier to differentiate flowing blood from soft-tissues for improved detection of the vessel-blood interface. In poor quality B-mode images, where the intima-media layer could not be segmented, the matched ARFI images provided improved contrast of the arterial walls. In addition, while observations of arterial structures were typically limited to the distal wall in B-mode imaging, both the proximal and distal walls were visualized with harmonic ARFI imaging. These results suggest that ARFI imaging with harmonic tracking may be useful for improved reliability of arterial thickness measurements. Supported by NIH grant R01-HL075485 from the National Heart, Lung, and Blood Institute.

(1) Lorenz et al. *Circulation 115*, 459–67 (2007). (2) Kanters et al. *Stroke 28*, 665–671 (1997).

7.2 **Technique for quantifying shear-wave velocity and attenuation in tissues for model-free characterization of tissue mechanical properties**, Ivan Z. Nenadic, Bo Qiang, Matthew W. Urban, Shigao Chen and James F. Greenleaf, *Basic Ultrasound Research Laboratory, Mayo Clinic College of Medicine, Rochester, MN, nenadic.ivan@mayo.edu.*

Changes in tissue-mechanical properties are associated with various pathological disorders. Producing a technique capable of quantifying the mechanical properties of the tissue would be beneficial in clinical settings and has been extensively studied in the fields of ultrasound and magnetic-resonance elastography. In order to fully characterize mechanical properties of a tissue at a given frequency, knowledge of both shear-wave elasticity and attenuation is necessary. In this study, we propose such a technique.

A mechanical shaker was used to excite harmonic plane and cylindrical waves in PVA phantoms and excised porcine liver in the frequency range 100–500 Hz. In addition, focused ultrasound radiation force from a linear-array transducer was used to excite impulsive cylindrical waves 600 μs in length. In all three excitation techniques, pulse-echo ultrasound from the linear-array transducer was used to track the motion and calculate the displacement field using cross-correlation. In case of the cylindrical waves, the displacement field was multiplied by square root of the distance vector ($\sqrt{r}$) to correct for the cylindrical diffraction. For all three excitation methods, 2D FFT of the motion as a function time and distance (displacement field) was performed in order to obtain the *k*-space whose coordinates are the frequency (*f*) and the wave number (*k*). Since the velocity $c = f/k$, shear wave velocity at each frequency was obtained by finding the maximum of the given frequency in *k*-space and dividing the frequency coordinate by the wave number coordinate. In order to calculate the attenuation at a given frequency, a *k*-space line along the given frequency was selected and the full-width-half-max (*FWHM*) along the wave number coordinate was measured, since the attenuation $\alpha = FWHM \times \pi / \sqrt{3}$. Finite element analysis of shear-wave propagation was used to validate the mathematical foundation of the approach. This method allowed us to measure both shear-wave velocity and attenuation at each frequency for the three excitation methods. The velocities and attenuations were measured every 1 mm throughout the thickness of the samples and the values were reported as mean and standard deviations.

The values of shear-wave velocity and attenuation at each frequency for the three different excitation methods in both the PVA and excited liver phantom agree within one standard deviation. In addition, the *k*-space estimates of velocity and attenuation were compared to the values obtained using the traditional methods of phase gradient (for velocity) and amplitude decay (for attenuation) and the results were in excellent agreement. These results suggest that the proposed *k*-space-based method can be used to obtain model-free estimates of tissue shear-wave velocity and attenuation at a given frequency and therefore fully characterize mechanical properties of tissue at that frequency. The application of this method was extended to show differences in shear-wave velocity and attenuation in healthy and diseased tissues of several organs.

7.3 **Shear-wave imaging in anisotropic media using a 2D matrix-array transducer**, Michael Wang, Brett Byram, Mark Palmeri, Ned Rouze and Kathryn Nightingale, *Department of Biomedical Engineering, Duke University, Durham, NC, mhw12@duke.edu.*

A system using a 2D matrix array for monitoring shear-wave propagation in 3D is presented. An annular focused HIFU piston transducer (H-101, Sonic Concepts, Bothell, WA) is used for generating shear waves using impulsive radiation force excitation. A 2D matrix array transducer (4Z1C, Siemens Healthcare, Ultrasound Business Unit, Mountain View, CA, USA) inserted in the central opening of the HIFU piston was used for monitoring the resulting shear-wave displacement. In contrast to conventional 1D array transducers, which are capable of measuring the shear-wave speed (SWS) in only one plane of the anatomy, the SWS can be measured in multiple directions using a 2D matrix array. This system allows the mechanical properties of anisotropic tissue, such as muscle, to be characterized with a single shear-wave acquisition without the need to physically reposition the probe.

3D shear wave data was acquired on six excised canine muscle samples with the 2D matrix array in various orientations with respect to the muscle fiber orientation. The 3D fiber orientation and SWS along and across the fibers was estimated from 3D shear-wave data, assuming a transverse isotropic model of elasticity for muscle. The true fiber orientation of the samples were determined using the 3D Radon Transform of high resolution B-mode volumes. The mean error of the 3D fiber orientation estimated from 30 shear-wave acquisitions using various transducer orientations relative to the fibers was 5.4°. Potential anisotropy in the dispersion of shear waves due to viscosity in muscle is being investigated. Supported by NIH grants R01 EB-002132 and R01 CA142824.

7.4 **Reproducibility of tissue deformations with robot-assisted placement of an ultrasound probe,** Muyinatu A. Lediju Bell[1], Tutkun Sen[1], Peter Kazanzides[1], Iulian Iordachita[1], John Wong[2] and Emad Boctor[1,3], *[1]Laboratory for Computational Sensing and Robotics, Department of Computer Science, Johns Hopkins University, [2]Department of Radiation Oncology, Johns Hopkins Medical Institutions, and [3]Department of Radiology, Johns Hopkins Medical Institutions, Baltimore, MD, mledijubell@jhu.edu.*

Tissue deformations naturally occur with transabdominal or transperineal ultrasound imaging of organs such as the liver or prostate. This type of deformation is a limiting factor of clinical applications that require minimal tissue variability after an ultrasound probe has been moved then replaced. For example, in ultrasound-guided radiation therapy, it is necessary to reproduce ultrasound probe placement and the associated tissue deformations to ensure that simulated treatment plans match the administered radiation dosimetry.

An experiment was conducted to determine the reproducibility of tissue deformations when the ultrasound probe is placed with a robotically-controlled arm. A robotic arm was mimicked with a manually-actuated linear stage attached to a passive arm. An Ultrasonix SonixTouch ultrasound system and L14-5W/60 linear array transducer were used to image *ex vivo* bovine liver tissue implanted with spherical metallic markers. The image field of view was limited to 2 cm (axial) x 6 cm (lateral), the transmit frequency was 10 MHz, the axial sampling frequency was 40 MHz, the lateral beam spacing was 0.47 mm and the focus was 1 cm. Images were acquired before and after the transducer was axially translated by 2.5 mm increments. Images were also acquired after the transducer returned to the initial reference position and when there was no transducer translation between acquisitions. Normalized cross-correlation of raw rf and envelope-detected data was implemented to compare the similarity of a 1 cm x 1 cm tissue region of interest (ROI), centered about the focus in acquired images. The ROI was chosen to avoid the implanted metal markers and the associated reverberation artifacts.

For rf and detected data, the peak normalized cross-correlation coefficient was approximately 1.00 when there was no translation between acquisitions, as expected. When the transducer was shifted by 2.5-5.0 mm, peak normalized cross-correlation coefficients ranged from 0.29 to 0.48 and 0.05 to 0.08 for detected and rf data, respectively. When the probe returned to its original reference position, peak normalized cross-correlation coefficients ranged from 0.71 to 0.86 and 0.15 to 0.48 for detected and rf data, respectively. Although images acquired after the probe returned to a specified position were not as highly correlated as images acquired when there was no probe movement, they were more correlated when compared to images acquired with known transduce- position shifts. Higher correlations are expected with the use of a robotically-controlled arm, rather than the mechanically-controlled passive arm used in these experiments. These results indicate that robot-assisted placement of an ultrasound probe may be used to more closely reproduce tissue deformations when compared to deformations that occur after a known axial-transducer shift 2.5 mm or greater.

7.5 **Comparison of shear-wave ultrasound elastography based on external vibration and acoustic radiation force impulse**, Diego Turo,[1] Paul Otto[2] and Siddhartha Sikdar, [1, 2] *Departments of [1]Bioengineering and [2]Electrical and Computer Engineering, George Mason University, Fairfax, VA, ssikdar@gmu.edu.*

Objective: Measurement of mechanical properties of muscle has clinical significance. Our group has been investigating changes in mechanical properties of muscle in patients with chronic neck pain using shear-wave elastography. Shear-wave elastography based on the acoustic radiation force impulse (ARFI) has been used successfully for a range of different tissue types but is not widely available in clinical settings. On the other hand, methods that utilize external vibration can be readily implemented in a clinical setting using commercially-available equipment. In our clinical studies, we therefore utilized external vibration to induce shear waves. Such vibration strategies are widely used for MR elastography as well. Our goal was to investigate how shear-wave velocity estimation based on an external vibration compares against ARFI.

Methods: Shear-wave elastography with external vibration and ARFI were performed on a tissue-mimicking elastic phantom (CIRS, Norfolk, VA) and measured elastic proprieties were compared with the manufacturers' specified value of 24.7 kPa. A Verasonics system with a curvilinear transducer C4-2 (central frequency 3 MHz) was used for the studies. An ARFI push was generated with a focus 3.8 cm from the surface of the phantom. After the push was generated, 50 IQ frames were acquired using plane-wave insonifications at frame rate of 2 kHz and processed using a power Doppler method to visualize the shear wave. The shear-wave front was tracked and the ratio between travelled distance and time-of-flight was used to estimate shear-wave speed. For external vibration elastography, a massager (North Coast Medical, Morgan Hill, CA) was used to generate an external vibration with frequency around 80 Hz and IQ data were acquired at a 2 kHz frame rate. The vibrator head was positioned at around 1 cm from the transducer and along its lateral direction. IQ data were postprocessed to estimate the phase of the instantaneous particle displacement and the spatial gradient of the phase was used to estimate wave speed. The shear-wave speeds estimated using both methods were then converted to shear modulus assuming an isotropic elastic medium.

Results and Discussion: Our experiments showed that elastic modulus measured with ARFI is more precise (23.19±2.66 kPa, mean ± standard deviation) compared to that obtained using an external vibration (23.13±6.01 kPa) but both methods were equally accurate compared to the expected value of 24.7 kPa. We observed that the shear waves generated by the external vibration had a spherical wavefront but in a region close to the surface, i.e., up to 3 cm deep, an approximation of a plane wavefront propagating in the lateral direction does not lead to a significant estimation error. At deeper locations, a 2D wavefront tracking algorithm is required for estimating the true wave speed. In this investigation plane-wave insonification was used for detecting the shear-wave propagation in the medium. However, most ultrasonic systems perform sequential scan-line imaging. For this type of imaging, external vibration elastography requires a further correction to account for the delay between adjacent scan lines.

A major advantage of ARFI is that the locally-induced shear wave is only influenced by the local tissue properties. However, for specific applications, external vibration may be an attractive alternative. Muscle tissue, for instance, has orthotropic mechanical properties and vibrations propagate preferentially along the muscle fibers. Thus, muscles are efficient waveguides when vibrated along their fibers. This property together with the superficial location, make most muscles suitable for shear-wave elastography using an external vibration. Our measurements of the elastic properties of the biceps brachii using external vibration are in agreement with values reported in literature using different methods, including supersonic shear imaging, shear-wave spectroscopy and magnetic-resonance elastography.

One advantage of external vibration over ARFI is that higher frame rates are possible since an external vibration stimulates the entire field of view, whereas ARFI is localized and requires sequential push beams at different spatial locations followed by tracking. This higher frame rate enables more robust temporal averaging to further reduce the variance of the estimate.

In conclusion, we have investigated performance differences between shear-wave elastography with ARFI and external vibration. Measurements performed on an elastic phantom shows that both methods are equally accurate. External vibration elastography presents some limitations but might be attractive for specific applications. Supported by NIH grant 1R01-AR057348.

7.6 **Estimation of shear-modulus ratio using strain ratios in 2D ultrasound elastography**, Congxian Jia[1], S. Kaisar Alam[2], Reza Zahiri Azar[3, 4] and Brian Garra[1, 5] [1]*Food and Drug Administration, Silver Spring, MD,* [2]*Riverside Research, New York, NY,* [3]*Ultrasonix Medical Corp, Vancouver,* [4]*University of British Columbia, Vancouver and* [5]*Washington DC VA Medical Ctr., Washington, DC, congxian.jia@fda.hhs.gov.*

Objective: Ultrasound elastography of breast tissue using external compression can assess the alteration of mechanical properties in breast tissue and has been used to detect and characterize breast lesions. Unfortunately, the application of the resultant strain elastogram has been limited because it can only measure the relative stiffness of the tissue within that image and the strain pattern is also affected by strain-concentration artifacts. Strain-ratio measurement was introduced to alleviate this problem. However, there is a large variation among different research and clinical groups in the selection of a region-of-interest (ROI) in the background breast tissue. The effect of lesion size on strain-ratio calculation also has not been considered. Large variations in reported strain-ratio values have led to a perception that strain ratios may not be reliable in clinical practice. Therefore, the purpose of this study is to find more reliable ways to use properly-measured strain ratios to estimate true relative stiffness in terms of shear-modulus ratios.

Methods: A theoretical model for a small mass lesion with 2 mm diameter was created and analyzed for a 2D plane strain deformation. Both the lesion and the surrounding tissue were assumed to be linear, purely elastic, isotropic and homogenous. Finite-element-method (FEM) simulations also were performed with the same material properties for large lesion size with diameters of 3 mm to 15 mm. In addition, ultrasound radiofrequency (rf) data were also simulated using the location of scatterers calculated by FEM simulation. The corresponding displacement data were estimated using cross-correlation based techniques and the estimated strain ratios were compared to FEM results.

Results: The theoretical model has demonstrated that the lesion to surrounding shear-modulus ratio is linearly proportional to the strain ratio for small lesions when the ROI for the surrounding tissue is at least four diameters away from the lesion. Tracking results using simulated rf data are in an agreement with FEM simulation results for large lesions. Both of them showed that the estimated strain ratio increases with the increase of lesion size. Therefore, a correction factor is needed for large lesions to estimate shear-modulus ratios. In addition, the direction of placement of the background ROI relative to inclusion is of considerable importance.

7.7 **Preclinical evaluation of dose response in ARFI-Monitored Hemostatic Challenge**, Rebecca Geist[1], Timothy C. Nichols[2], Elizabeth P. Merricks[3] and Caterina M. Gallippi[1], [1]*Joint Department of Biomedical Engineering,* [2]*Deparment of Medicine and* [3]*Department of Pathology and Veterinary Medicine, University of North Carolina, Chapel Hill, NC, cmgallip@bme.unc.edu.*

Background: Bleeding is a frequent and deadly complication of inherited hematologic disorders, such as hemophilia A, which result from genetic deficiencies in plasma coagulation proteins. Protein-replacement therapy is associated with continued threat of exposure to infectious agents and is compromised by the development of inhibitory antibodies. Multiple innovative approaches to safely control bleeding in patients with disordered bleeding, especially those with inhibitory antibodies, are in development; however, translating these approaches to clinical trials has been delayed by inadequate *in vivo* hemostasis outcome measures. The objective of this work is to demonstrate a potential *in vivo* outcome measure, ARFI-Monitored Hemostatic Challenge, for sensitivity to therapeutic dose level in a relevant dog model of hemophilia A.

Methods: ARFI-Monitored Hemostatic Challenge was performed in twelve dogs (n = 6 control and n = 6 hemophilia A). The hemophilia A dogs were examined in the naïve state and with prophylactic infusion of c.FVIII to approximately 10% of normal c.FVIII level, a relatively low-dose treatment. Each dog at each treatment level was tested twice with at least two weeks between repeated measures. Dogs were fully anesthetized with isoflurane to effect, with constant monitoring of blood pressure, oxygen saturation and core body temperature. Dogs were placed in a prone position with the hind limb shaved and prepped with an aseptic method and tethered to the table to prevent motion during imaging. The imaging transducer, mounted to a stereotactic clamp, was then positioned above a 1-2 mm diameter vein in the right hind limb, and B-mode guidance was used to puncture the vein with a 12-guage needle in the approximate center of the imaging filed-of-view. Serial ARFI imaging, focusing on the near venous wall, was performed over a 30-minute observation period. Acquired rf data was processed using normalized 1-D cross-correlation to measure ARFI-induced displacement profiles, from which hemorrhagic area was detected in each frame based on displacement variance. Bleeding Rate (BR) and time to hemostasis (TTH) were deduced from the time series of hemorrhagic area measures and compared between cohorts.

Results: TTH was greater than 30 min in 65% and 63% of the studies completed in naïve and treated hemophilia A dogs, respectively, but only 25% of those performed in control dogs. BR was not statistically different between cohorts.

Conclusions: These data suggest that ARFI-Monitored Hemostatic Challenge delineates longer TTH in naïve and 10% treated hemophilia A than in control dogs, which is consistent with the expected bleeding phenotype of hemophilia A (a disorder of primary hemostasis generally associated with prolonged but not accelerated bleeding) and the low-dose treatment administered (which is expected to only minimally impact TTH). Future work will include comparison to hemophilia A dogs treated to 100% c.FVIII level.

8. IMAGING 2

8.1 **Localizing surgical tools with an ultrasound-based active reflector-tracking system**, Xiaoyu Guo[1], Ralph Etienne-Cummings[1], Hyun-Jae Kang[2], Muyinatu A. Lediju Bell[2] and Emad M. Boctor[2, 3], *Departments of* [1]*Electrical and Computer Engineering,* [2]*Computer Science and* [3]*Radiology, Johns Hopkins University, Baltimore, MD, xguo9@jhu.edu.*

Accurate medical tool tracking is a crucial task that directly affects the safety and efficacy of many surgical and interventional procedures. Compared to CT and MRI, ultrasound-based tool tracking has many advantages including low cost, safety, mobility and ease-of-use. However, surgical tools are poorly visualized with conventional ultrasound imaging systems and thus prevents effective tool tracking and guidance. To overcome these challenges, we present the Ultrasound-based Active Reflector-Tracking System (US-ARTS) for interventional surgical tool guidance.

With the US-ARTS, a conventional ultrasound transducer is used to transmit pulses through tissue. The pulses are received by single or multiple piezoelectric elements attached to a surgical tool (e.g., a catheter) and converted to an electrical signal. The signals received by the piezoelectric element are processed with a negligible delay time and then the piezoelectric element transmits an ultrasound pulse to the imaging probe. The signal transmitted by the piezoelectric element acts like an acoustic reflection and this active reflection is used to enhance the visualization of surgical tools with low echogenicity in conventional B-mode images.

To implement this technique, a PZT5H 2-mm cylindrical piezoelectric element with inner and outer diameters of 1.47 mm and 2.08 mm, respectively, was embedded in a plastic 2.4-mm diameter catheter. A Sonix RP ultrasound machine (UltraSonix Co.) connected to an L14-5W linear array probe and a 4DL14-5/38 sweeping linear array 3D probe was used for B-mode image acquisitions. A dedicated electronic system with signal acquisition, data processing and piezo-element driving functions was designed and built. The active echo signal was displayed as a bright spot in the US B-mode image, which blinked at a frequency of 1~10 Hz to indicate the location of the piezoelectric element. The discrepancy between the true element position and the active echo spot in the B-mode image was less than 0.3 mm, as the electronic processing loop delay was approximately 0.6 μs. The active echo frequency, amplitude, duration and temporal modulation can be controlled based on different applications. In addition to being displayed in a B-mode image, the active echo signal can also be extracted by template or wavelet filtering methods for robot-assisted tool guidance.

The US-ARTS is a completely stand-alone system that is capable of operating with most conventional ultrasonic imaging equipment to provide direct tool localization in B-mode images. We also report on the method's effectiveness in the presence of clutter-noise artifacts.

8.2 **Effects of driving signal bandwidth on approximate transient-pressure calculations in viscous media**, Pedro Nariyoshi and Robert J. McGough, *Electrical and Computer Engineering, Michigan State University, East Lansing, MI, mcgough@egr.msu.edu.*

The Stokes wave-equation models ultrasound propagation in viscous media. Although the Stokes wave equation admits an exact closed-form solution for the Green's function in the frequency domain, only approximate far-field expressions are available in closed-form for transient excitations. Approximate solutions are typically obtained by evaluating a Taylor series for the Green's function in the frequency domain and discarding the higher-order terms. This approach produces discrepancies in the high-frequency components. The resulting approximate expressions are accurate in the far field but the errors in the approximate Green's function are much larger in the near-field region. When the approximate Green's function is convolved with an excitation signal, the errors are reduced if a driving signal with limited bandwidth is considered. Two approximate solutions are compared in the time and frequency domains, where one expression is causal, and the other is noncausal. The pressure responses functions are calculated for 1 mm by 1 mm transducer excited by a sinusoidal pulse multiplied by a Hamming window radiating into Dow Corning DC705 pump oil at different distances. Results show that, for this pulse shape, the error is primarily limited by the bandwidth of the excitation. The corresponding implications for power-law models of biological tissue will also be discussed. Supported in part by NIH Grant R01 EB012079.

8.3 **Numerical solutions of Burgers' Equation with the INCS method**, Yiqun Yang and Robert J. McGough, *Electrical and Computer Engineering, Michigan State University, East Lansing, MI, mcgough@egr.msu.edu.*

Burgers' Equation is a partial differential equation that simulates nonlinear plane wave propagation in a viscous medium. Despite the inherent limitations of the plane-wave model, Burgers' equation is commonly employed in simulations of biomedical ultrasound. Plane-wave models are also useful for validating various simulation algorithms that will ultimately be applied to higher-dimensional models. Here, transient numerical solutions to Burgers' equation are computed with the iterative nonlinear contrast source (INCS) method, where the primary advantage of the INCS method for these calculations is the necessary filtering step that eliminates aliasing artifacts. The INCS method also controls the bandwidth of the computed solution through the number of iterations. The INCS method calculates the transient pressure field in viscous media by iteratively convolving the Green's function of the diffusion equation with the contrast source, where the contrast source is obtained from the nonlinear pressure field calculated in the previous iteration. Simulation results obtained with the INCS method are then compared with those obtained with the Cole-Hopf approach, and comparisons between the two results show that, in the absence of shock-wave formation, the INCS method converges to the correct solution in a small number of iterations. Other advantages of the INCS method are also identified in these simulations, including efficient memory utilization and reasonable computation times. These favorable results motivate future plans to evaluate the INCS approach for higher-order models and to combine the INCS approach with FOCUS, the 'Fast Object- oriented C++ Ultrasound Simulator.' Supported in part by NIH Grant R01 EB012079.

8.4 **Numerical simulations of the KZK equation for circular and spherically-focused transducers**, Xiaofeng Zhao, Peter B. Beard, and Robert J. McGough, *Electrical and Computer Engineering, Michigan State University, East Lansing, MI, mcgough@egr.msu.edu.*

The Khokhlov-Zabolotskaya-Kuznetsov (KZK) equation is a parabolic approximation to the Westervelt equation that models the effects of diffraction, attenuation and nonlinearity. The KZK equation decouples propagation in the radial and axial directions, thereby enabling accelerated numerical simulations of nonlinear ultrasound propagation. The KZK equation, which is only valid in the far field of the paraxial region, is commonly applied to simulations of medical ultrasound due to the computational advantages of the parabolic approximation. The KZK equation is often simulated with the finite-difference approach described by Lee and Hamilton[(1)] that

combines the implicit backward finite difference and Crank-Nicolson finite-difference methods with a resampling procedure that modifies the axial step size once a shock wave is fully developed. This approach maintains the accuracy of the solution after a shock wave develops without decreasing the computational efficiency. These two finite difference approaches have recently been implemented in separate routines for FOCUS, the 'Fast Object-oriented C++ Ultrasound Simulator,' to calculate transient nonlinear pressures generated by flat circular and spherically-focused ultrasound transducers. Results obtained from these implementations of the KZK equation without the nonlinear terms are compared to transient linear simulation results calculated with the fast nearfield method in FOCUS. The simulation results are in agreement for farfield paraxial calculations and the results differ elsewhere. The KZK calculation in FOCUS also generates the expected nonlinear distortion when the nonlinear term is included in the calculation. In addition, KZK calculations in FOCUS are evaluated for different values of the nonlinearity parameter and for different spatial and temporal step sizes. These new KZK routines model the transient nonlinear pressure fields produced by these two transducer geometries with the convenient programmable interface in FOCUS. Supported in part by NIH Grant R01 EB012079.

(1) Lee et al. *J Acoust Soc Am 97*, 906-917 (1995).

8.5 **User-friendly system for assessing imaging performance**, Ernest Madsen, Chihwa Song and Gary Frank, *Medical Physics Department, University of Wisconsin, Madison, WI, elmadsen@wisc.edu.*

One indicator of effectiveness of a scanner/transducer configuration to delineate the boundary of an abnormal mass is the level of detectability it affords for small low-echo cyst-like targets. (A scanner/transducer configuration includes make and model of scanner and transducer, focus, image depth, TGC, sector angle, etc.) Phantoms with spatially-random distributions of 2-, 3.2- or 4-mm diameter low-echo spheres and scanning windows allowing use with any shape emitting surface have been reported. Automation software allows quantification of sphere detectability as a function of depth *via* lesion signal-to-noise ratio (LSNR). One objective is to complete refinements in data acquisition and reduction so that the phantoms and software are easily employed by clinical personnel for comparing scanner/transducer configurations.

Current MATLAB software is being converted to a form executable on any PC with user-friendly generalized user interface (GUI). Laboratory data acquisition apparatus will be replaced with a small semiautomatic or automatic one to be part of the phantom. Also, minimal data acquisition will be determined for acceptable reproducibility.

The methods of data acquisition and reduction will be described. A transducer holder and stepper motor system provides for translation of the transducer in steps of 1/4 of the sphere diameter needed for determining the centers of the spheres. The procedure for using the GUI will be demonstrated. Also, reproducibility of mean LSNR-versus-depth curves will be demonstrated. Imaging performance comparisons between scanner/transducer configurations will be shown; one interesting result using a pediatric transducer is that a 4-cm focus resulted in lesser detectability overall than a 3-cm focus.

Comparisons will aid in choosing equipment for a given set of clinical applications, provide a new means of acceptance-testing, and allow optimizing of configurations of installed scanners for specific applications. The phantoms may also be useful for manufacturers to refine their systems.

8.6 **Method for improved consistency of acoustic-output measurements based on deconvolution of hydrophone sensitivity,** K.A. Wear, P.M. Gammell, S. Maruvada, Y. Liu and G.R. Harris, *Food and Drug Administration, Silver Spring, MD, Keith.Wear@fda.hhs.gov.*

Objective: Hydrophones are used to measure pressure waveforms from ultrasound transducers. The standard method for measurement of pressure is to divide the hydrophone output voltage by the hydrophone sensitivity at the "acoustic working frequency" but this approach ignores the frequency dependence of hydrophone sensitivity. A more accurate method is to perform a complex deconvolution between the hydrophone output voltage and hydrophone frequency-dependent complex sensitivity. We previously developed a method for measuring magnitude and phase of hydrophone sensitivity using time delay spectrometry (TDS).[(1)] This method may be applied to assess the effects of deconvolution on consistency of measurements of peak-compressional pressure ($p+$), peak rarefactional pressure ($p-$, related to mechanical bioeffects), and pulse intensity integral (*PII*, related to thermal bioeffects).

Methods: In the first set of experiments, swept-frequency (0–40 MHz) TDS was used to measure complex sensitivities of 8 hydrophones used in medical-ultrasound exposimetry. These included PVDF spot-poled membrane (4), needle (2), capsule (1) and fiber-optic (1) designs. TDS measurements were performed using 5 broadband source transducers (center frequencies: 2, 5, 10, 30, 50 MHz) to obtain complex sensitivities from 1-40 MHz. In the second set of experiments, the 8 hydrophones were used to measure a 4-cycle, 3 MHz pressure waveform representing a pulsed Doppler waveform with significant harmonic content up to 40 MHz. $p+$, $p-$, and *PII* for the 8 hydrophones were measured using 1) the standard approach and 2) deconvolution (using complex sensitivities measured in the first set of experiments). Variability in measurements (across all 8 hydrophones) was described by the coefficient of variation (*COV* = standard deviation/mean).

Results: Average measurements (across all 8 hydrophones) of pulse parameters were 4.0 MPa ($p+$), 2.2 MPa ($p-$), and 0.18 mJ/cm^2 (PII). Compared with the standard method, deconvolution reduced *COV* of $p+$ from 25% to 8% and reduced COV of PII from 36% to 13%. Deconvolution had a small effect on *COV* of $p-$.

Conclusion: Deconvolution significantly improves consistency of acoustic-output measurements.

(1) Wear et al. *IEEE Trans UFFC 58*, 2325-2333 (2011).

Wednesday morning

9. SEGMENTATION AND CO-REGISTRATION

9.1 **Multimodal, multiscale data fusion: fusing ultrasound, MRI and histopathology**, Anant Madabhushi, *Department of Biomedical Engineering, Case Western Reserve University, Cleveland, Ohio, anant.madabhushi@case.edu* (invited overview).

While there has been a surge of interest in the last few years for developing co-registration and multimodal fusion schemes for spatially aligning transrectal ultrasound images with MRI to guide prostate biopsies, most of these methods either involve rigid transformations or require significant manual intervention. In this talk, I will focus on recent developments in my group on a novel, automated, registration method to fuse magnetic-resonance imaging (MRI) and transrectal ultrasound (TRUS). Our methodology consists of: (1) delineating the prostate on MRI, (2) building a probabilistic model of prostate location on TRUS and (3) aligning the MRI prostate segmentation to the TRUS probabilistic model.

TRUS-guided needle biopsy is the current gold standard for prostate cancer (CaP) diagnosis. Up to 40% of CaP lesions appear isoechoic on TRUS; hence, TRUS-guided biopsy cannot reliable target CaP lesions and is associated with a high false-negative rate. MRI is better able to distinguish CaP from benign prostatic tissue, but, requires special equipment and training. MRI-TRUS fusion, whereby MRI is acquired preoperatively and aligned to TRUS during the biopsy procedure, allows information from both modalities to guide the biopsy. Previous work in MRI-TRUS fusion has aligned manually-determined fiducials or prostate surfaces. The accuracy of these methods is dependent on the reader's ability to determine fiducials and/or prostate surfaces with minimal error, which is a difficult and time-consuming task. Our novel, fully-automated MRI-TRUS fusion scheme represents a significant advancement over current state-of-the-art as it does not require any manual intervention after TRUS acquisition. All necessary preprocessing steps (i.e. delineation of the prostate on MRI) can be performed offline prior to the biopsy procedure. We evaluated our method on seven patient studies and found a root-mean-square error (RMSE) for an expertly-selected fiducial of 3.39 ± 0.85 mm.

I will also talk about some of our recent work on co-registering histology and preoperative *in-vivo* MRI for spatially mapping tumor extent from *ex-vivo* histology on *in-vivo* imaging. Qualitative and quantitative results on six patient studies will be shown.

9.2 **Segmentation of ultrasound images and sequences: an overview,** Alain Coron[1, 2] and Thanh Bui Minh,[1, 2] *[1]UPMC Univ Paris 06, Laboratoire d'Imagerie Paramétrique, Paris, France and [2]CNRS, LIP, Paris, France, alain.coron@upmc.fr* (invited).

Segmenting an image or a volume consists in partitioning the data into two or more nonoverlapping regions. Each region should (perceptually) correspond to an object of interest or to the background. Manual segmentation is observer dependent and tedious. So (semi)automatic image segmentation methods have been developed during the last decades and experimented on medical images. However image segmentation remains a challenging problem. We review some of the recent developments with an emphasis on those related to ultrasound images, volume or sequences. We also list some valuable resources available on the web. Supported in part by NIH grant CA100183 and CNRS.

9.3 **Technology for precise registration of interventional tools to ultrasound images**, Francois Vignon, Jay Mung, Douglas Stanton and Ameet Jain, *Philips Research North America, ameet.jain@philips.com* (invited).

In the past decade, ultrasound (US) has become the preferred modality for a number of interventional procedures, offering excellent soft tissue visualization. However, interventional tools are often poorly visualized under ultrasound due to their specular nature that tends to reflect ultrasound away from the imaging probe. Many technologies have been developed to address this problem but with limited clinical success so far. We discuss a new technique for high accuracy and robust tool tracking under US guidance. We present embedding an acoustic sensor at the tip of interventional tool for improved tool localization. These sensors can receive and beamform ultrasound signals coming from the imaging probe as it acquires the pulse-echo image, yielding highly-accurate position information. These coordinates can then be used for 3D surgical navigation. High-frequency PZT material in small sizes were embedded in a functional interventional tool as some test cases. A real-time system was developed and various performance metrics from *in-vitro* and *ex-vivo* experiments will be presented. The technology is nondisruptive in terms of existing clinical workflow, showing high potential for large-scale use. We will discuss the feasibility and utility of this technology.

9.4 **Use of 3D ultrasound imaging in image-guided interventions**, Aaron Fenster, *Robarts Research Institute, The University of Western Ontario, London, ON, Canada, afenster@robarts.ca* (invited).

The last two decades have witnessed unprecedented developments of new image-guided interventional imaging systems making use of 3D visualization. These new technologies provide the clinician with guidance and verification information about the interventional procedure. Although 2D ultrasound (US) has been used for image-guidance, this approach limits our ability to guide therapy because multiple 2D images must be integrated mentally, resulting in an inefficient procedure, which often leads to variability. Investigators have addressed these limitations by developing 3D US techniques. In this paper, we describe our developments of 3D US imaging instrumentation and techniques for use in image-guided interventions. In our approach, the conventional US transducer is scanned mechanically and the 2D US images are digitized and reconstructed in real-time into a 3D image, which can be viewed and manipulated interactively. Examples will be given for use in 3D US-guided prostate biopsy and brachytherapy as well as 3D US-guided focal liver ablation. Supported in part by grants from CIHR, ORF and OICR.

9.5 **Image registration supporting ultrasound-guided interventions in prostate cancer,** Aaron Ward, *Departments of Medical Biophysics, Biomedical Engineering, Oncology, University of Western Ontario, London, ON, Canada, aaron.ward@uwo.ca.*

The development of 3D ultrasound (US) imaging for guidance of prostate-cancer diagnosis and therapy has created the opportunity for accurate and precise guidance of needles for percutaneous interventions. To take full advantage of exciting interventional tools built around 3D US, appropriate interpretation of pre-interventional planning images is important for target definition, as is intraprocedural compensation for target motion. Image registration has been shown to be a valuable tool to address both of these issues. We will discuss our developments in deformable histopathology-imaging registration for the evaluation of the utility of imaging for target definition, as well as our work on 2D and 3D US image registration for patient and prostate motion compensation during 3D US-guided prostate biopsy procedures. Supported in part by grants from the Canadian Institutes of Health Research (CIHR), the Natural Sciences and Engineering Research Council of Canada (NSERC), Cancer Care Ontario (CCO), and the Ontario Institute for Cancer Research (OICR).

9.6 **Nonrigid registration of prostate histology to ARFI and MR image volumes**, Samantha L. Lipman[1], Mark L. Palmeri[1], Stephen J Rosenzweig[1], Kirema Garcia-Reyes[2], Christopher Kauffman[3], Rajan T. Gupta[3], Amy Lark[4], Andrew Buckman[4], Evan Kulbacki[4], John Madden[4], Thomas J. Polascik[5] and Kathryn R. Nightingale,[1 1]*Department of Biomedical Engineering, Duke University, Durham NC, [2]Duke University School of Medicine, [3]Department of Radiology, Duke University Medical Center, [4]Department of Pathology, Duke University Medical Center and [5]Department of Urology, Duke University Medical Center, Durham NC, samantha.lipman@duke.edu.*

Purpose: B-mode ultrasound (US) is currently used to guide needle biopsies for diagnosing prostate cancer (PCa), but the anatomic and pathologic structures within the prostate have poor acoustic contrast. Acoustic Radiation Force Impulse (ARFI) imaging is being developed to differentiate between prostatic tissues of different mechanical properties, and Magnetic Resonance (MR) imaging is also an emerging prostatic imaging modality that can use multiple sequences to delineate structures and characterize regions of disease. We are developing image registration techniques that facilitate correlation of pathology delineated in whole-mount histology data after prostate resection with *in vivo* ARFI, B-mode US and MR images obtained prior to surgery.

Methods: US and ARFI imaging sequences were acquired preoperatively using a side-fire ER7B endorectal US probe on a Siemens ACUSON SC2000 scanner and a custom transducer-rotation stage. Preoperative standard T1 and T2 MR images were also obtained, along with Diffusion Weighted Imaging (DWI), Apparent Diffusion Coefficient (ADC) and perfusion MR imaging sequences. 3D models of the prostate were formed by segmenting pathology and internal prostate structures in each imaging modality using itk-SNAP . Nonrigid 3D registration of the different models was performed using mutual information and cross correlation diffeomorphic methods in the Advanced Normalization Tools (ANTs) software package and the registered images were evaluated for concordance of confirmed pathology with regions of suspicion in all imaging modalities.

Results: In vivo ARFI images delineate anatomic zones of the prostate with higher contrast than the B-mode US images. Additionally, many cancers have been identified as asymmetrical stiffer regions in coronal prostate imaging planes, which have shown concordance with histologic regions of cancer. In many patients, regions identified by radiologists as suspicious for PCa have shown concordance with cancer, especially in large, higher-grade lesions. Gleason scores show correlations with intensity in MR-ADC maps. The multimodality image registration has demonstrated correlations between regions of decreased displacement in ARFI images with prostate cancer, as characterized by whole-mount histology and MR imaging. Atrophy of prostate tissue has also been shown to be a confounding factor for both ARFI and MR images in identifying regions of suspicion for cancer.

Conclusion: Using diffeomorphic image registration methods, confirmed PCa pathology was found to align with similarly suspicious regions in both ARFI and MR images. Improving preoperative localization of PCa using both MR and ARFI imaging facilitates focal therapy treatments. With its improved anatomical visualization over traditional B-mode imaging, ARFI imaging also holds promise for providing targeted image guidance of needle biopsy.

9.7 **Semiautomatic segmentation of carotid-artery atherosclerosis using 3D ultrasound imaging**, Md. Murad Hossain[1], Khalid AlMuhanna[1], Limin Zhao[3], Brajesh Lal[3, 4] and Siddhartha Sikdar[1, 2], *Departments of [1]Electrical and Computer Engineering and [2]Bioengineering, George Mason University, Fairfax, VA, [3]School of Medicine, University of Maryland, Baltimore, MD and [4]Department of Veterans Affairs Maryland Health System, Baltimore, MD, ssikdar@gmu.edu.*

Objectives: Stroke is the third most common cause of death in the world. Carotid atherosclerosis is a major cause of stroke. Clinical diagnosis is currently based on estimation of peak systolic velocities through the stenosis using Doppler ultrasound. Imaging and monitoring carotid plaque progression in 3D can better classify disease severity and plaque burden as well as potentially identify vulnerability to rupture. Several image-based measures of plaque burden have been proposed in the literature: intima-media thickness (IMT), total plaque area (TPA), total plaque volume (TPV) and vessel wall volume (VWV). The VWV is a 3D measurement of arterial wall and plaque, which accounts for complex distributed plaque. VWV is measured by delineating the lumen-intima boundary (LIB) and media-adventitia boundary (MAB) in 3D ultrasound images. Our objectives were to develop and evaluate a new semiautomatic carotid vessel wall segmentation algorithm that can work in the presence of poor boundary contrast and complex 3D geometries of atherosclerotic carotid arteries.

Methods: In this study, we used a distance regularized level set evolution with novel initialization and stopping criteria to segment LIB and MAB. Our proposed method utilizes both longitudinal and transverse slices for initialization to improve robustness. Localization of LIB is first done in the longitudinal slice, which is then reconstructed in the cross sectional slice to place initial boundary points. Manual initialization of the contour is done in a few select slices of the common carotid, bifurcation, and internal and external carotid arteries. Initialization of the other slices is done by eroding (LIB)/ dilating (MAB) segmentation of previous slices. First, the

LIB is segmented using edge-based energies and local and global region based energy. Edge based and local region energies with a constraint contributing minimum separation between LIB and MAB are used to segment MAB. The stopping criteria for the level set evolution are an important consideration. Typically, the iteration number or change in length/area of contours between successive iterations is used as a stopping criterion. These criteria often lead to oversegmentation at boundaries parallel to US beam due to poor contrast. We used a combination of the modified Hausdorff distance (MHD) between contours at successive iterations and a stopping boundary formed by fitting an ellipse through initial points as stopping criteria to stop bleeding through low contrast area.

Results: The proposed algorithm is evaluated against manually-segmented boundaries by calculating dice similarity coefficient (DSC), Hausdorff distance (HD) and MHD in three regions of the carotid artery, the common (C), bulb (B) and internal (I) regions to get a better understanding of performance. Preliminary results from three subject with >50% carotid stenosis showed good agreement with manual segmentation; between algorithm and manuals on whole carotid volume: DSC (algorithm: MAB-82.95±9.3, LIB-82.03+8.8; interobserver: MAB-85.94±8.56, LIB-82±8.83;), MHD (MAB-9.01 ± 3.94, LIB-4.34±1.81; inter observer: MAB-8.79 ± 8.56, LIB-4.34± 2.16), HD (MAB-19.97±7.89, LIB-9.2±3.34; inter observer: MAB-18.8±14.18, LIB-9.95±4.93). In the future, we will also compare our algorithm with conventional stopping criteria on more subjects.

Conclusion: Preliminary validation on three subjects with carotid atherosclerosis showed that the algorithm could accurately localize carotid artery contours. Our algorithm involves initialization of points only, which reduces user interaction. In an ongoing study, we are using this method for longitudinal monitoring of plaque progression in patients with asymptomatic carotid disease.

10. TISSUE PARAMETERS 3

10.1 **Optimization of a multitaper generalized spectrum approach for parametric images of tissue-scatterer ordering**, Ivan M. Rosado-Mendez, Lindsey Carlson, Timothy J. Hall and James A. Zagzebski, *Medical Physics, University of Wisconsin - Madison, Madison, WI, rosadomendez@wisc.edu.*

Objectives: The generalized spectrum (GS) has been used to quantify the contribution of nonrandom scattering sources to backscattered echo signals. The relevance of GS parameters for tissue classification has been previously shown. However, the presence of "speckle noise" can reduce the conspicuity of true GS features sensitive to scatterer ordering in space. Work described in this paper assessed noise suppression of a multitaper GS estimator and optimized the parameter estimation window size to create images of GS features with good spatial resolution. Performance of the multitaper method is compared to the conventional single-taper GS.

Methods: Two tissue-mimicking phantoms were scanned with a Siemens S2000 and an 18L6 linear array transducer. Phantom A was an agarose-based homogenous material with Rayleigh scatterers. Phantom B was similar but included an array of 100 μm-diameter nylon fibers spaced 400 μm apart and spanning 1cm in depth. GS estimates were obtained either by conventional periodogram methods or by first applying a multitaper strategy with Slepian sequences corresponding to $2 \leq NW \leq 20$. The speckle noise was quantified by the integrated off-diagonal terms of the GS Collapsed Average (ICA) computed in Phantom A. Optimization of the GS parameter estimation involved three steps: First, the analysis window length was chosen to minimize bias in the ICA due to spectral broadening. Second, the GS estimator and window width were chosen to minimize speckle noise. Finally, attributes of the GS estimator were chosen to maximize the conspicuity of a GS feature describing nonrandom scatterers. This feature was the SNR of the 1.98MHz peak in the Collapsed Average (CA) corresponding to the fiber spacing in Phantom B. Parametric images displaying the variation of the off-diagonal terms (VOT) of the collapsed average were created using data from Phantom B. Two window-registration methods were tested: one assigned the GS value to the center of the parameter estimation window, the other implemented an adaptive strategy based on a symmetric distribution of the mean and variance of the squared-envelope of signal segments within the window.

Results: The optimum window size was 10 pulse lengths and 7 uncorrelated A-lines. No significant differences in the mean ICA were found among different tapers for the single-taper GS estimator. The multitaper approach reduced the mean ICA by 83% compared to the single taper. An optimum $NW=4$ led to the highest SNR of the fiber-interspacing CA peak. VOT images using conventional registration showed a blurred zone of coherence wider than the fiber region by one window length. This was successfully corrected by the adaptive windowing strategy. These methods are currently being applied in QUS parameter estimation in the breast and the cervix. Supported in part by NIH (grants R01CA111289, R21HD061896, R21HD063031, and R01HD072077) and the Consejo Nacional de Ciencia y Tecnologia of Mexico (Reg. 206414).

10.2 **Modeling volume power spectra for collections of spheres,** Adam C. Luchies and Michael L. Oelze, *Bioacoustics Research Laboratory, Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, Urbana, IL, luchies1@illinois.edu.*

When modeling the power spectrum for a collection of randomly-positioned scatterers, the assumption is usually made that the incoherent component of the spectrum is much larger than the coherent component. With this assumption, scattering form-factor models such as the Gaussian, fluid-filled sphere, etc., can be fitted to the power spectrum of scattered ultrasound signals for the purpose of estimating meaningful parameters such as the estimated scatterer diameter (ESD) or estimated acoustic concentration (EAC). The accuracy of the assumption concerning incoherent and coherent component spectrum magnitudes was studied using simulations of spheres in a finite container.

A collection of spheres with a specific number density was simulated and the volume power spectrum was computed by taking the 3D Fourier Transform and squaring the modulus. Configurations of sphere positions were simulated and the resulting volume power spectra were averaged to study the expected value of the power spectrum versus different number densities of spheres. These results were compared to the volume power spectrum for a single sphere (i.e., the fluid-filled sphere form factor).

For low number densities, the volume power spectrum for a collection of spheres matched the fluid-filled sphere form factor. As number density increased, the volume power spectrum became biased for low values of *ka* compared to the power spectrum for a single sphere. The source of this bias can be attributed to the interaction of sphere positions. As more spheres are placed in the container, their positions become less random, increasing the effect of the coherent component relative to the incoherent component.

The simulations also indicated that the container shape affected the shape of the volume spectrum. When using a cube as the container for the collection of spheres, asymmetry was observed in the volume power spectrum. Specifically, peaks were present on-axis in *k*-space that were not present off-axis nor in the power spectrum for a single sphere. When changing the container to a sphere, the volume power spectrum was symmetric and the on-axis peaks observed for the cube container were not present. The results of this study indicate that when modeling the effects of scattering using single scattering approximations, the shape of the scattering volume must be taken into account. Supported by NIH Grant R01-EB008992.

10.3 **Autocorrelation functions of biologically-inspired simulated scattering media**, Eric P. Nordberg and Timothy J. Hall, *Medical Physics, University of Wisconsin - Madison, WI, epnordberg@wisc.edu.*

Objective: To identify characteristic correlation functions for simple geometries that are comparable to those for biological media containing complex microstructures. The acoustic form factor is proportional to the spatial Fourier transform of the autocorrelation function of the acoustic-impedance distribution within a medium. Our hypothesis is that the impedance distribution can be mapped with various forms of optical microscopy and the autocorrelation function of such image-based data should then correlate with the acoustic-backscatter correlation function via the acoustic form factor. The autocorrelation functions from optical images of tissue can deviate significantly from autocorrelation functions calculated using simple, spherically-symmetric models. Our goal is to develop models that more closely match the autocorrelation functions from optical microscopy images of breast tissues.

Methods: Simulated 2D images comprised of varying number densities of either spatially randomly-distributed circular spots or semi-infinite rods, both with Gaussian cross-sectional profiles, were generated. Gaussian rod-based images were also created with varying degrees of alignment among the rods. Two-dimensional autocorrelation functions of each image were generated by calculating the correlation coefficient of a central image kernel within the larger image area. One-dimensional autocorrelation functions were found by interpolating along both major and minor axes of the 2D autocorrelation function and radially averaging the entire *2D* data set. Qualitative and quantitative properties of these *1D* autocorrelation functions, like characteristic shape and full-width at half-max (FWHM), were tracked while feature density and overall alignment (in the case of the rods) were varied.

Results: When circularly-symmetric Gaussian spots were studied, both the overall shape and the FWHM of the radially-averaged 1D autocorrelation function remained largely unchanged as the feature density went from sparse isolated features to a highly-dense amalgamation. Despite the potentially-complex random systems, the 1D autocorrelation functions retained the shape of analytically-derived 1D autocorrelation functions of an isolated Gaussian. When systems of rods were examined, the full-width-at-half-max and overall shape of the radial average of the 2D autocorrelation function also remained largely independent of both rod density and degree of rod alignment. Despite the similar behavior between the two systems, the prevailing shape of the web-like rod-based system displayed characteristics that were much more similar to the autocorrelation functions computed for second-harmonic generation microscopy images of both breast and cervix tissue and much less similar to simple, spherically-symmetric analytic models.

Conclusions: These findings suggest that when studying biological tissue with a fibrous component that significantly contributes to the overall acoustical scattering, a spherically-symmetric scatterer model may be insufficient to accurately characterize the microstructure of the system. More complex models, taking into account more complicated geometries like networks of rods may more accurately characterize the acoustic correlation functions for fibrous tissues. Supported by the National Institutes of Health grants R21HD061896, R21HD063031, R01CA111289 and T32CA009206.

10.4 **Modeling ultrasonic scattering from high-concentration cell pellet biophantoms using the structure factor,** Aiguo Han, Rami Abuhabsah and William D. O'Brien, Jr, *Bioacoustics Research Laboratory, Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, Urbana, IL, han51@illinois.edu.*

Objective: For a medium containing a sparse concentration of scatterers, the scatterers can be assumed to be spatially randomly distributed and the magnitude of the backscatter coefficient (BSC) is proportional to the scatterer concentration. When the scatterer concentration is high, the assumption of a random distribution of scatterers fails because of the correlation among the scatterers and the BSC are no longer proportional to scatterer concentration. The purpose of this study is to quantify the effect of correlation among cells for high-concentration cell pellet biophantoms in terms of structure factor (defined as the Fourier transform of the spatial distribution of cells) and to compare the calculated structure factor to the widely-used Percus-Yevick approximation.

Methodology: Cell-pellet biophantoms were constructed at two concentrations, a relative low cell concentration (number density: 20 million cells/mL; volume fraction: ~5 %) and a high concentration (closely packed pure cells). This was done for each of the following cell lines: Chinese Hamster Ovary (CHO), MAT (ATCC #CRL-1666) and 4T1 (ATCC #CRL-2539). The biophantoms were scanned using high-frequency single-element transducers (overall frequency range: 9-105 MHz), and the BSC was estimated for each concentration. Assuming that the structure factor is unity for the lower concentration, the structure factor for the higher concentration was then calculated by comparing the estimated BSCs of both concentrations. The calculated structure factor vs. frequency curve was compared to the theoretical prediction by Percus-Yevick approximation.

Results: The results show that the BSC vs. frequency curves have different shapes between the two concentrations for all the three cell lines. The structure factor calculated by comparing the BSCs at two concentrations stays below unity at lower frequencies (<40 MHz) and increases with frequency until it reaches its peak (at around 50- 85 MHz). This general shape of the structure factor is in agreement with the Percus-Yevick prediction. It is also found that the position of the peak in the calculated structure factor curve is related to the cell diameter: the larger the cell diameter, the lower the frequency at which the peak frequency occurs. This finding is

also in agreement with the Percus-Yevick approximation. Fitting the theoretical structure factor to the calculated one yields estimated scatterer diameters that are close to the independently measured cell diameters.

Conclusion: The structure factor is playing a role in the scattering of high concentration cell pellet biophantom. The calculated structure factor is in general agreement with the prediction of Percus-Yevick approximation. Supported by NIH R01CA111289.

10.5 **Comparison between backscatter coefficients of cell pellet biophantoms and tumors *ex vivo***, Aiguo Han[1], Rami Abuhabsah[1], Rita J. Miller[1], Sandhya Sarwate[1] and William D. O'Brien, Jr[1], [1]*Bioacoustics Research Laboratory, Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, Urbana, IL, wdo@illinois.edu.*

Objective: Simple scattering media fit scattering model theories much better than more complex scattering media. Tissue is much more complex as an acoustic-scattering media and, to date, there has not been an adequate scattering model that fits it well. The purpose of this study is to understand the scattering process in tissue and specifically three tumor types, by comparing the ultrasonic backscatter coefficients (BSCs) of tumors *ex vivo* to those of the cell pellets of the same cell lines.

Methodology: Cell pellets and *ex vivo* tumors were scanned using high-frequency single-element transducers (overall frequency range: 9- 105 MHz) and the BSC was estimated for each sample. The cell pellets were formed by centrifugation and composed of densely-packed cells without any supportive background materials. Tumors were grown *in vivo* in mice or rats, as appropriate for the particular cell line and excised when the tumor was about 5 mm in diameter. Cell pellets and tumors were histologically processed (H&E) after ultrasonic scanning. Cell pellets and tumors were evaluated from three cell lines: 4T1 (ATCC #CRL-2539), MAT (ATCC #CRL-1666) and LMTK (ATCC #CCL-1.3).

Results: The BSC vs. frequency curves are similar for 4T1 cell pellets and 4T1 tumors whereas the BSC curves are significantly different between MAT cell pellets and MAT tumors and between LMTK cell pellets and LMTK tumors. These findings suggest that the ultrasonic scattering behavior from the pure cells (the cell pellets) of the same type as that from tumors can be quite different. It is also found that the scattering behavior is related to histologic features. For example, histological evaluation shows that the 4T1 cell pellets and tumors have similar anatomic structures; hence, similar BSC curves are observed. In contrast, the MAT cell pellets and tumors have different anatomic features in the sense that regions of necrosis exist in MAT tumors but not in MAT cell pellets. The scatterers are significantly different in necrotic regions than other regions where tumor cells are intact. The necrotic areas consist of fragmented cytoplasm and nuclei and there are no scatterers that are as big as tumor cells or cell nuclei; hence, different BSC curves are observed between MAT tumors and cell pellets.

Conclusion: The comparison in BSC between *ex vivo* tumors and cell pellets of the same cell lines improves our understanding of tumor scattering: the scattering from tumor is not only affected by cell type but also affected by the anatomic detail of the tumor. Such a comparison also provides a tool of identifying unique tumor scattering structures. Supported by NIH R01CA111289.