Monday morning

1. OBSTETRICAL IMAGING: IMAGINE THE FUTURE

1.1 **Quantitative ultrasound in the fetus**, Lawrence D. Platt, *David Geffen School of Medicine at UCLA, Los Angeles, CA, ldplatt@gmail.com* (invited overview).

Quantitative ultrasound techniques are currently under development for assessment of the fetal lung and heart. This talk will review those techniques and discuss other fetal organ systems that have potential for quantitative assessment.

1.2 **Pitfalls of point-of-care ultrasound in obstetrics**, Joshua A. Copel, *Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, CT, joshua.copel@yale.edu* (invited overview).

In the recent past, there have been multiple attempts to develop point-of-care ultrasound technology for obstetrics. To date, none have seen great success. This talk will review some of the issues specific to this application, focusing on specific approaches that could work.

1.3 **Challenges of imaging *in vivo* biological tissues**, Timothy Hall, *Medical Physics, University of Wisconsin-Madison, Madison, WI, tjhall@wisc.edu* (invited overview).

Imaging biological tissues have special challenges because of their heterogeneity and between-subject variability. This talk will review those challenges and specific approaches to meet them.

1.4 **Quantitative assessment of cervical microstructure: application to preterm birth studies**, Helen Feltovich, *Maternal-Fetal Medicine, Intermountain Healthcare, Salt Lake City, UT and Department of Medical Physics, University of Wisconsin-Madison, Madison, WI, hfeltovich@gmail.com* (invited overview).

Preterm birth plagues the obstetrician and its incidence has not changed despite decades of research, probably because the cervix is so poorly understood. This talk will discuss emerging approaches to objective assessment of pregnant cervical microstructure.

1.5 **Multiscale studies of cervical structural function during pregnancy**, Michael D. House, *Obstetrics & Gynecology, Tufts University School of Medicine, Boston, MA, mhouse@tuftsmedicalcenter.org* (invited overview).

Understanding the cervix is imperative to understanding preterm birth. This talk will discuss a comprehensive approach to study of the cervix, using novel ultrasound techniques and tissue-engineering studies.

1.6 **Overview of current obstetrical studies in the NICHD**, Uma Reddy, *Pregnancy & Perinatology Branch, National Institutes of Health, Eunice Kennedy Shriver National Institute of Child Health & Human Development, Bethesda, MD, reddyu@mail.nih.gov* (invited overview).

Imaging studies are rarely funded through the NICHD because of a paucity of promising approaches. This talk will discuss some of the ongoing NICHD studies in obstetrics and areas for opportunity.

1.7 **Spectral coherence analysis of cervical tissue,** Lindsey Carlson,[1] Lisa M. Reusch,[1] Helen Feltovich[1, 2] and Timothy J. Hall,[1] *[1]Medical Physics, University of Wisconsin - Madison, Madison, WI and [2]Maternal Fetal Medicine, Intermountain Healthcare, Park City, UT, lcarlson2@wisc.edu*

Objectives: The application of most quantitative ultrasound (QUS) measurements to tissue characterization assumes a stationary random process. However, cervical tissue contains layers of aligned collagen. Aligned structures might produce nonstationarity, corrupting the accuracy of QUS measurements. The generalized spectrum (GS) of a radiofrequency (rf) echo signal is useful in characterizing nonstationarities such as regularly-spaced scatterers and echo-signal coherence. Our objective was to test for coherence in the echo signals from cervical tissue and identify its microstructural sources.

Methods: Rf echo data were obtained from a phantom with aligned nylon fibers (100 μm diameter) with uniform 400 μm spacing using a Siemens S2000 ultrasound system, a prototype intracavitary transducer and an 18L6 linear array transducer with beam steering angles between ± 40° in steps of 4°. The GS and collapsed average (CA) were computed at each steering angle. The relative contribution of coherence was measured by integrating the CA. Mean scatterer spacing was estimated from the peaks in the CA. Measurements were compared to a reference phantom with randomly-distributed spherical scatterers. Hysterectomy specimens from nonpregnant women (n = 10) were scanned with the transducer face parallel to the endocervical canal. Cross-sectional samples were taken from each hysterectomy specimen, fixed, sliced and optically imaged using second-harmonic generation (SHG) imaging.

Results: The integrated CA values for the fiber phantom were large and angle-dependent, compared to those from the reference phantom. Results of mean scatterer spacing in fiber phantom were 389 μm, in good agreement with nominal fiber spacing of 400 μm. Cervical tissue exhibited, on average, higher integrated CA values in comparison with reference phantom but with a higher variability. Significant peaks in CA of cervical data were observed, indicating coherent scattering and a potential periodically-spaced scatterer.

Conclusions: These results show there may be sources of coherence (likely) related to aligned collagen in the normal nonpregnant cervix that might increase QUS parameter estimate variance. Ongoing efforts will use SHG images in comparison to GS parameters to investigate these structures.

1.8 **Comparisons of optical images of human cervical tissue to ultrasonic measurements,** Lisa M. Reusch,[1] Helen Feltovich,[1, 2] Lindsey Carlson,[1] Mark L. Palmeri[3] and Timothy J. Hall,[1] *[1]Medical Physics, University of Wisconsin - Madison, Madison, WI and [2]Maternal Fetal Medicine, Intermountain Healthcare, Park City, UT and [3]Biomedical Engineering, Duke University, Durham, NC, lmmcguire@ wisc.edu.*

Objectives: Preterm birth is a major problem. A quantitative assessment of risk has been challenging due to a lack of noninvasive technology sophisticated enough to objectively interrogate the microstructure of the cervix. Progress is hampered by a lack of understanding of the cervix, which is anisotropic and inhomogeneous. Using a variety of different techniques, both acoustical and optical, we aim to increase the understanding of the cervix as well as develop noninvasive techniques for assessing risk of preterm birth.

Methods: Hysterectomy specimens (n = 10) were scanned using a Siemens Acuson S2000 ultrasound machine equipped with a prototype intracavitary transducer. All measurements were acquired with the endocervical canal parallel to the transducer face. Backscattered echo data were collected for steering angles between $\pm$40º in steps of 4º. The total backscattered power (BSP) was computed for each angle by integrating the power spectra. The BSP for each angle was normalized to the peak BSP in order to calculate the BSP loss as an assessment of anisotropy. Data from a phantom with spherical scatterers were used for system calibration. Stiffness measurements were performed through the use of Acoustic Radiation Force Impulse (ARFI) techniques in order to assess both peak displacement and induced shear-wave speeds (SWS). Lastly, to directly image the cervical microstructure, cross-sectional samples were taken from the specimen, fixed and optically imaged using second harmonic generation (SHG) imaging. Semiautomatic stitching of the images created a comprehensive image of the cross section.

Results: Registration of B-mode images with SHG images allows for direct comparison of BSP loss and ARFI measurements to the underlying pathology. Changes in the structure of the cervix (visible in the SHG images) track with changes in seen in ARFI and BSP loss measurements. The ability to track features between different modalities lays the foundation for a stronger understanding of cervical microstructure. Ongoing work aims to definitively determine collagen orientation and strength of alignment without the need for biopsies. Supported by NIH grants R21HD061896 and R21HD063031.

1.9 **Evaluation of fetal cerebral blood perfusion using three-dimensional power Doppler ultrasound angiography (3D-PDA) in normal and growth-restricted fetuses (FGR),** Alberto Rossi, Irene Romanello, Leonardo Forzano, Giorgio Fachechi and Diego Marchesoni, *Department of Obstetrics and Gynecology, University of Udine, Udine, Italy, roalbert@ tiscali.it.*

Objective: The aim of the study is to explore the possible use of 3D Power Doppler ultrasound Angiography (3D-PDA) using VOCAL™ software in the assessment of the perfusion of different fetal cerebral regions in normal fetuses and those affected by fetal growth restriction (FGR).

Methods: In a prospective study, 56 pregnancies affected by FGR (estimated fetal weight < 10th percentile) were compared with a control group of 77 appropriate-for-gestational age (AGA) fetuses, all between 24 and 36 weeks of gestation. Three groups were identified among pregnancies affected by FGR: Group 1: Late onset FGR (> 34 ws) with normal bidimensional Doppler flow analysis; Group 2 : Early onset FGR (< 34 ws) with abnormal umbilical artery (UA) pulsatilty index (PI), normal middle cerebral artery (MCA) PI and normal ductus venosus PI; Group 3 : Early onset IUGR (< 34 ws) with abnormal UA PI, abnormal MCA PI and pathological DV PI. Using 3D power-Doppler ultrasound, a volume acquisition of the fetal brain was performed. Two regions of interest (ROI) were defined within the fetal brain. 'Frontal zone' is anterior to the cavum septi pellucidi (CSP). 'Temporal zone' is defined by a rectangle obtained tracing a contour between the temporal bones as wide as the cavum septi pellucidi, corresponding to the area of the middle cerebral artery. The Flow Index (FI), the Vascularization Index (VI), the Vascularization and Flow Index (VFI) were determined for both areas.

Results: In Group 1 VI and VFI demonstrate a significant increase in 'Frontal zone' and a decrease in 'Temporal zone' comparing to Control Group (AGA). In Group 2 and Group 3, VFI of 'Temporal zone' show a statistically-significant decrease respect to AGA.

Conclusions: 3D-PDA analysis demonstrates that in late-onset FGR, there is a vascular redistribution with preferential increment in bloody supply to the Frontal zone to protect general cognitive functions. Moreover, a preferential increment in bloody supply to the Temporal zone is seen in early-onset FGR, even before abnormal bidimensional Doppler could be assessed in MCA.

2. ELASTOGRAPHY

2.1 **Accumulation of displacement estimation error over large deformations,** Matthew Bayer and Timothy Hall, *University of Wisconsin-Madison, Madison, WI, matthewbayer@wisc.edu.*

Elastography usually aims to image the stiffness of tissue. In many tissues, however, stiffness can change with deformation and this nonlinear behavior can also be used to differentiate tissue types. In order to estimate elastic nonlinearity, tissue displacement must be tracked over a much larger range of deformations than is usually required. Such large deformations have to be broken up into steps, each of which contributes an estimation error to the final result.

To study how these estimation errors accumulate and how they may be mitigated, we have performed one-dimensional simulations of radiofrequency ultrasound echo signals in a large-deformation experiment. Signals were simulated in Matlab by convolving a simple point-spread function with a dense, random collection of point scatterers. The scatterers were subjected to a sequence of compressive strains up to 20%, with the convolution repeated at each stage and uncorrelated noise added to each signal. Displacement was estimated using correlation techniques for strain steps of varying size. The variance of the accumulated displacement error was then calculated as a function of tracking-step size, correlation window size and additive noise level.

Estimation errors occur because of the additive noise but also because of the properties of the signal itself. Signal errors include the decorrelating effect of strain and the uncertainty resulting from matching only finite windows of the signal. These errors are highly correlated between subsequent strain steps, since the signal changes only slightly as the strain changes. Therefore, the accumulated variance of the signal errors increases roughly quadratically with strain. Errors due to additive noise, however, are anticorrelated with noise errors from adjacent steps, so that for low noise levels they nearly cancel out. At higher noise levels, the anticorrelation is not as complete and noise errors accumulate roughly linearly.

At the end of 20% strain accumulation, a relatively broad optimum exists between very small strain steps, where error accumulates quickly because of the many steps, and large strain steps, where the signal errors due to strain within the tracking window begin to worsen. Strain-induced signal errors usually dominate in accumulation because they are correlated between estimates, a fact that recommends the use of small windows. These results can provide guidance for accumulating displacements in tissue and also provide a framework in which to evaluate how other displacement estimation techniques, such as signal companding, affect the accumulation of displacement error. Supported by NIH grants R01CA140271 and T23CA009206.

2.2 **Robust strain estimator using combined radiofrequency and envelope crosscorrelation**, Mohammad Arafat Hussain,[1] S. Kaisar Alam,[2] Soo Yeol Lee[3] and Kamrul Hasan, [1, 3] *[1]Department of Electrical and Electronic Engineering, Bangladesh University of Engineering and Technology, Dhaka, Bangladesh, [2]Lizzi Center for Biomedical Engineering, Riverside Research, New York, NY and [3]Department of Biomedical Engineering, Kyung Hee University, Gyeonggi-do, Korea, hasan@eee.buet.ac. bd.*

In ultrasound elastography, internal tissue strain due to external deformation is estimated; the strain is smaller in stiffer than in softer tissues. At higher strains, lateral and out-of-plane tissue motions increase, resulting in noisier strain images. We investigated a novel approach for robust strain estimation by combining linear-weighted radiofrequency (rf) crosscorrelation (CC) and envelope-CC.

Displacement maps computed from the RF-CC are considered to be 'clean' at low strain and very noisy at high strain because of echo decorrelation. In comparison, displacement maps computed from the envelope-CC are less precise at low strain but robust to echo decorrelation noise at high strain. Our algorithm combines the advantages of both methods by defining a strain-dependent linear weight that adds the rf and envelope-CC functions to derive the final peak. Furthermore, before CC calculation, we use two different stretching factors (i.e., one corresponding to zero strain and the other corresponding to the applied strain) for stretching the postcompression rf and envelope data segments, which further improves estimator performance.

This method performed well for a finite-element-modeling (FEM) simulation, for experimental-phantom data and for *in vivo* breast data. For applied strains as high as 10% for the FEM simulation, 5% for experimental-phantom data and 3% for *in vivo* breast data using equal weights for RF-CC and envelope-CC. In contrast, at low strains, RF-CC by itself works best. We also located the 'knee' points in terms of approximate applied strain from the normalized CC peaks for FEM simulation, experimental phantom data and *in vivo* breast data where echo decorrelation becomes significant. Accordingly, at and after the knee, linear-weighted RF-CC and envelope-CC were summed. Before the knee, only the RF-CC was used to compute displacement and strain.

The method has been found to be robust for a wide range of strains. The image 'quality' of the phantom and the *in vivo* data are improved, which allows more-precise detection of lesion edges, fewer artifacts and less noise in homogeneous regions. Numerical indices such as SNR_e and CNR_e for the FEM simulation provide quantitative measure of the performance improvements.

2.3 **Ultrasonic characterization of muscle tissue in myofascial pain syndrome**, Diego Turo,[1] Paul Otto,[1] Tadesse Gebreab,[1] Jay P. Shah,[2] Lynn H. Gerber[1] and Siddhartha Sikdar,[1] *[1]George Mason University, Fairfax, VA and [2]National Institutes of Health, Bethesda, MD, ssikdar@gmu.edu.*

Background: We are investigating new quantitative ultrasound methods to characterize the physical properties of neck muscles in chronic soft-tissue neck pain. Chronic pain is a critical public health problem. A vast number of patients in specialty pain management centers and 95% of people with chronic pain disorders suffer from Myofascial Pain Syndrome (MPS). Despite its high prevalence, the underlying mechanisms are poorly understood. In particular, very little is known about the pathophysiology and soft tissue environment of a myofascial trigger point (MTrP). MTrPs are palpable, localized painful nodules in a taut band of skeletal muscle and are a characteristic finding in MPS. MTrPs may be associated with spontaneous referred pain in symptomatic patient and are the target for current management strategies for MPS, such as dry-needling therapy. However, they are also commonly found in asymptomatic individuals. We report preliminary results of quantitative ultrasound findings in an ongoing study of patients with chronic neck pain and palpable MTrPs.

Methods: Patients with chronic (>3 months) neck pain with palpable MTrPs and healthy volunteers without spontaneous pain were recruited for this study. Subjects underwent a thorough clinical assessment and physical exam followed by imaging of the upper-trapezius muscles. Shear-wave elastography was performed using a custom handheld vibrator and simultaneous radiofrequency (rf) data acquisition using the Ultrasonix SonixRP US system and a 5-14 MHz linear array transducer at different vibration frequencies between 50~200 Hz. Rf data were processed to generate maps of the shear-wave speed within the muscle under investigation. Shear moduli were estimated by fitting a Voigt model to the dispersion of shear speed with frequency. The corresponding B-mode images were processed using an entropy filter to study the heterogeneity and texture of MTrPs and surrounding muscle tissue.

Results: Subjects with active (i.e., spontaneously-painful) MTrPs showed elliptical or band-like hypoechoic regions along with an increase in fiber alignment heterogeneity at sites where a palpable MTrP was present. Shear-wave elastography imaging showed a heterogeneous spatial distribution of shear-wave speeds at sites with active MTrPs compared to palpably normal asymptomatic muscle in normal controls. Both active MTrPs and the surrounding muscle tissue were significantly different in terms of shear-wave speeds (at frequencies higher than 100 Hz) than normal asymptomatic tissue in control subjects ($p < 0.05$). At low frequencies (~50 Hz), there were no significant differences in shear-wave speed. While there were some differences in shear moduli using Voigt model fits between active MTrPs and surrounding muscle, there was large variability in the dispersion, making the model fits less reliable. The large spatial variability in the shear-wave speed in symptomatic subjects indicates that the neighborhood of active MTrPs is heterogeneous. In contrast, shear-wave speeds of palpably normal tissues in control subjects were well clustered along a Voigt model fit, with low variability, with an average shear modulus of 3.38 kPa. Texture analysis of B-mode images using an entropy filter showed that compared to palpably normal muscle in control subjects, sites with active MTrPs have significantly lower entropy (p <0.002), and the size of the region with entropy <4 is significantly higher (p <1E-4). Several healthy volunteers had latent MTrPs, which are palpable and tender upon palpation, but are not spontaneously painful. Compared to palpably normal muscle, these latent MTrPs in control subjects have significantly lower entropy (p <0.004) and the size of the region with entropy <4 is significantly higher (p <1E-4). There were no significant differences between the neighborhood of active and latent MTrPs. Palpably normal muscle in patients with chronic pain showed large heterogeneity and were not significantly different from the milieu of active MTrPs. We are currently investigating classification techniques between these tissue types (active MTrPs and their surrounding milieu, latent MTrPs and normal asymptomatic muscle) based on the backscattered rf spectra.

Conclusions: Ultrasound imaging and elastography can be used to objectively characterize the soft tissue milieu of MTrPs associated with chronic neck pain. This technique successfully differentiates MTrPs and surrounding tissue from uninvolved tissue in subjects with or without MTrPs. Additionally, this technique suggests that MTrPs in subjects with and without pain share some common soft-tissue abnormalities while the milieu of the muscle is more heterogeneous in subjects with pain. We anticipate that these quantitative imaging methodologies will enable the development of objective clinical outcome measures for evaluating natural history and treatment efficacy and to better understand the role of MTrPs in chronic pain. Supported in part by a grant 1R01-AR057348 from National Institutes of Arthritis and Musculoskeletal and Skin Diseases at the NIH.

Monday afternoon

3. BREAST/PROSTATE

3.1 **Challenges in quantitative ultrasound of the breast,** Ivan Rosado-Mendez, Haidy Gerges Nasief, Kibo Nam, James A. Zagzebski and Timothy J. Hall, *Medical Physics, University of Wisconsin - Madison, Madison, WI, tjhall@wisc.edu* .

Objectives: Quantitative ultrasound (QUS) methods have been under development for decades and were applied to diagnosing breast tissues as one of the first applications. All who have attempted to apply these methods would agree that this is a particularly challenging problem in signal processing and data analysis. The purpose of this presentation is to provide an overview of these challenges and a summary of what we have learned from our recent efforts.

Methods: Human subjects who were scheduled for breast-core biopsy were recruited for a research ultrasound exam prior to their biopsy. Our recent data include 37 subjects who were scanned with a Siemens S2000 and the 18L6 linear array transducer. The Axius Direct ultrasound research interface was used to acquire radiofrequency echo data as the acoustic beams were steered from -20^{o} through 20^{o} in steps of 5^{o}. Each breast tumor was scanned in two perpendicular planes to obtain information about the 3D tumor. A reference phantom with acoustic properties similar to breast tissue was scanned with the same equipment settings. The Least Squares Method was used to estimate total attenuation from the transducer to the region of interest. The Reference Phantom Method was used to locally estimate acoustic attenuation and backscatter coefficients in and around the tumors. Effective scatterer sizes were computed assuming a Gaussian form factor. Six data sets were excluded due to lack of biospy confirmation of disease type. Four subjects with cysts were also excluded. Among the remaining data set, there were 9 cancers (5 invasive ductal carcinoma, 2 invasive lobular carcinoma), 12 fibroadenoma and the remaining 6 were a variety of other benign diseases.

Results: Acquiring data as a function of steering angle allows testing for evidence of anisotropy in the acoustic properties under investigation. Lacking evidence for anisotropy, these data can be spatially compounded to reduce variance in power spectral densities and QUS parameter estimates. Few tumors demonstrated evidence of anisotropy in acoustic attenuation. Obvious among the results was that some of these tumors were relatively easily analyzed with current QUS techniques and estimates among them appear robust. However, some tumors were 'challenging' to analyze and this is consistent with the observation that some US BIRADS lexicon entries include statements like 'complex' and 'combined,' indicating difficulty in simple visual assessment of some tumors.

Conclusions: A great deal of insight has been gained into what characteristics of breast tumors are well suited to current QUS techniques and what characteristics of tumors and surrounding tissues will continue to present a significant challenge to QUS. Supported, in part, by NIH grant R01CA111289 and the Consejo Nacional de Ciencia y Tecnologia of Mexico (Reg. 206414).

3.2 **Quantitative assessment of *in-vivo* breast masses using ultrasound attenuation and backscatter**, Kibo Nam, James A. Zagzebski and Timothy J. Hall, *Department of Medical Physics, University of Wisconsin-Madison, Madison, WI 5370, kibonam@wisc.edu*.

The clinical analysis of breast ultrasound is done qualitatively, facilitated with the US BI-RADS lexicon that helps standardize imaging assessments. Two descriptors in that lexicon, the 'posterior acoustic features' and the 'echo pattern,'are directly related to quantitative ultrasound parameters (ultrasound attenuation and average backscatter coefficient, respectively). The purpose of this study is to quantify ultrasound attenuation and backscatter in breast masses to provide more objective interpretation of ultrasound images and also to investigate these properties as potential differential diagnostic markers. This study quantitatively assessed variability of attenuation and backscatter within *in vivo* breast masses.

We acquired rf echo signals from breast masses prior to core biopsy. The study utilized data sets collected with a VFX13-5 linear array on the Siemens SONOLINE Antares or with an 18L6 linear array on the Siemens S2000 scanner. Both scanners were equipped with the Axius Direct research interface, providing access to raw data. Masses include 11 fibroadenomas, 7 carcinomas and 1 epithelial hyperplasia. Attenuation for paths proximal to a ROI within the mass was estimated using a Least Squares Method with constraints. Backscatter coefficients (BSCs) and attenuation coefficients of masses were measured using the Reference Phantom Method. The estimated attenuation and BSCs were compared to the 'posterior acoustic features' and the 'echo pattern' assessed by three observers. Effective scatterer diameters (ESD) were also estimated by applying a Gaussian-form factor to the backscatter data.

Attenuation of fibroadenomas ranged from 0.6-2.1 dB /cm-MHz with a mean value of 1.3 dB/cm-MHz. Attenuation in carcinomas was comparable or higher than the mean attenuation of fibroadenomas with the exception of one infiltrating lobular carcinoma with low attenuation. The product of the attenuation coefficient and AP dimension of the mass was computed to estimate the total attenuation for each mass. That value correlated well with the posterior acoustic feature in BI-RADS. Most carcinomas showed lower values of averaged BSC than fibroadenomas for the same frequency range. No strong statements could be made about the correlation of echo pattern findings in BI-RADS with the averaged BSC values since nearly all masses in this study were described as 'hypoechoic.' The mean ESD size alone did not differentiate the mass type but fibroadenomas had greater variability in ESDs within the ROI than carcinomas. The combined estimates of attenuation and backscatter in breast masses differentiated most fibroadenomas from all cancers with a linear discriminant in this limited data set.

These results are encouraging because many carcinomas exhibit posterior shadowing and hypoechoic echo patterns in B-mode. This study demonstrated the potential to quantify the attenuation and backscatter within breast masses and utilize them as a diagnostic marker. Supported by NIH grants R01CA111289.

3.3 **Noninvasive breast tumor grading using ultrasound frequency-dependent backscatter analysis**, Hadi Tadayyon,[1, 2] Naum Papanicolau,[1, 2] Sara Iradji,[1] Ervis Sofroni,[1] and Gregory Czarnota,[1, 2] [1]*Imaging Research and Radiation Oncology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada and* [2]*Department of Medical Biophysics, University of Toronto, Toronto, Canada, hadi.tadayyon@ sunnybrook.ca*.

Breast tumors larger than 8 mm are readily detected by clinical ultrasound scanners as hypoechoic regions. Unfortunately, B-mode images, formed of signal envelopes that lack frequency information, do not include microstructural features of tissues. The radiofrequency (rf) signal generated by an ultrasound transducer from backscattered ultrasound before envelope detection and image formation can provide microstructural information about the sonicated tissue when analyzed in the frequency domain by a method known as quantitative ultrasound (QUS).

The purpose of this research was to determine if QUS can be used to characterize locally-advanced breast tumors in terms of their grade. If so, the question is posed: 'What is the optimal QUS parameter that can achieve this purpose? '

We analyzed 10 MHz ultrasound rf data from 29 locally-advanced breast cancer patients who later underwent mastectomy. Surgical pathology revealed that two of these patients had grade I tumor, 15 had grade II tumor and 12 had grade III tumor. For each patient, we computed five spectral parameters — midband fit, slope, 0-MHz intercept, integrated backscatter and scatterer spacing. Each parameter was computed twice for each patient: in a region inside the tumor and in a region outside the tumor.

We have found that the 0-MHz intercept can best discriminate between the three grades of a breast tumor, with means and standard deviations of 16±1 dB, 11±10 dB and 0±7 dB, in tumors of grades I, II and III, respectively. An unpaired *t*-test proved a significant difference in grades II and III ($p = 0.0034$). Separation of grade I from other grades cannot be verified due to the small number of cases (two) and the low occurrence rate of patients presenting with grade-one tumor. The midband fit, slope, integrated backscatter and scatterer spacing demonstrated a clear separation inside and outside the tumor regions but could not distinguish well microstructural differences in cellular organization associated with tumor grades. Since midband fit, slope and integrated backscatter are affected by frequency-dependent attenuation, we believe attenuation is one of the factors that affected the separation of tumor grades using these parameters. Determining *in-vivo* local attenuation coefficients of such heterogeneous tissues as breasts is a challenge, even at the current state of the art of ultrasound tissue characterization. We will investigate the effect of attenuation on the parameters of interest in the near future.

A potential for noninvasively differentiating tumor from normal tissue and grading tumors has been demonstrated using the intercept parameter for the more commonly-occurring grades of tumor (II and III). The technology may provide a noninvasive alternative to core biopsies.

Breast tumors larger than 8 mm are readily detected by clinical ultrasound scanners as hypoechoic regions. Unfortunately, B-mode images, formed of signal envelopes that lack frequency information do not include microstructural features of tissues. The radiofrequency (rf) signal generated by an ultrasound transducer from backscattered ultrasound before envelope detection and image formation can provide microstructural information about the sonicated tissue when analyzed in the frequency domain by a method known as quantitative ultrasound (QUS).

3.4 **Acoustic microscopy imaging of human breast cancer and its optical validation**, Di Chen,[1] Fedar Seviaryn,[2] Mark Sherman,[3] Sudeshna Bandyopadhyay,[4] Lisa Bey-Knight,[1] Brett Senay,[2] Q. Ping Dou,[1] Neb Duric[1] and Roman Maev,[2] [1]*Barbara Ann Karmanos Cancer Institute, Departments of Oncology, Wayne State University, School of Medicine, Detroit, MI,* [2]*Institute for Diagnostic Imaging Research, University of Windsor, Ontario, Canada,* [3]*National Cancer Institute, Division of Cancer Epidemiology and Genetics, Rockville, MD and* [4]*Department of Pathology, Wayne State University School of Medicine, Detroit, MI, seviazy@uwindsor.ca.*

For more than three centuries, one of the major approaches for biological discoveries has been optical microscopy. However, there are many important internal features of biological materials that are barely detectable by optical imaging. The acoustic microscope can provide imaging of biological structures, such as the distribution of viscoelastic properties of a specimen. This method had been proven as another powerful tool for studying the internal microstructure of biological materials. In order to clarify characteristic correlations between optical and acoustic imaging of human cancer tissue, we investigated surgical specimens of human breast cancer by combining expertise in both optical and acoustic microscopy. Hematoxylin and Eosin (H&E) staining sections (10 μm) of frozen breast cancer tissue were investigated by optical microscopy. Frozen sections (10 μm) of the tissue from the same block of specimen were scanned by a reflective short-pulse acoustic microscope with a 80 MHz focussed transducer. Pathological diagnosis of the cancer is invasive and poorly differentiated breast ductal carcinoma (Nottingham grade 3). Non-neoplastic breast tissue shows evidence of mild fibrocystic changes. The comparison of the images from acoustic and optical microscopes showed increased acoustic attenuation in tissue regions in which main components are normal muscle cells and fiber of connective tissue containing a few cancer cells whereas lower acoustic attenuation in cancer cell-rich tissue areas. Furthermore, the cancer cell-rich areas were characterized by lower sound speed in comparison with the higher sound speed in normal muscle cell and fiber-rich areas. The results clearly demonstrate the potential of acoustic microscopy as an auxiliary method for operative detection and localization of cancer affected regions.

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

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

Fourteen patients with T2-3 prostate cancer were subjected to transrectal conventional low-frequency ultrasound scans prior to undergoing radical prostatectomy. The scans were performed with an Ultrasonix RP ultrasound system using a transrectal biplane probe with 128 elements per plane with a 7 MHz center frequency for the linear transducer and 6.7 MHz for the curved transducer. The curvilinear transducer was used to collect equidistant (0.5 cm) transverse slices with a pulsing frequency of 10 MHz and a sampling frequency of 40 MHz for radiofrequency (rf) data collection. Planes of data were collected with the linear transducer at the center of the prostate with 20° separations using the same frequency settings. Radical prostatectomy specimens were prepared by whole-mount histopathology with specimens sliced in 0.5 cm equidistant slices perpendicular to the urethra and stained with hemotoxylin and eosin for comparison. Spectroscopic analysis[(1, 2)] was carried out using custom software and normalized using a glass bead phantom to remove system artifacts. Analysis of the averaged power spectrum was performed using a -6 dB window and linear regression to extract the midband fit, 0-MHz intercept and the slope of the best fit line. Parametric maps were generated for each of the three spectral parameters. The spectral parameter maps were then compared with the histopathology images in order to measure disease detection for each of the parameters.

Preliminary results indicate that relative changes in the spectral parameters correlate to disease in the corresponding whole mount sections. A relative decrease in the midband fit parameter of 5-10 dBr corresponded to areas where disease was present in the whole mount sections. Spectral slope was however relatively invariant. A decrease in the 0-MHz intercept as an indication of the concentration of acoustic scatterers corresponded well with the whole-mount histology sections. The mean percent difference between 0-MHz and MBF with H&E, was 14% (SD 38%) and 21% (SD 24%), respectively.

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

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3.6 **Characterization of pancreas and lymph nodes by endoscopic ultrasound spectrum analysis using electronic-array echoendoscopes,** Ronald E. Kumon,[1, 2] Aparna Repaka,[3, 4] Matthew Atkinson,[4] Ashley L. Faulx,[4] Richard C. K. Wong,[4] Gerard A. Isenberg,[4] Yi-Sing Hsiao,[2] Madhu S. R. Gudur,[2] Cheri X. Deng[2] and Amitabh Chak[4] *[1]Department of Physics, Kettering University, Flint, MI, [2]Department of Biomedical Engineering, The University of Michigan, Ann Arbor, MI, [3]University of Medicine and Dentistry of New Jersey, New Brunswick, NJ [4]Division of Gastroenterology, University Hospitals Case Medical Center and Case Western Reserve University, Cleveland, OH, research@kumonweb.com.*

The purpose of this study was to assess the ability of spectral analysis of endoscopic ultrasound (EUS) rf signals acquired *in vivo* with electronic array echo-endoscopes to distinguish between (1) benign and malignant lymph nodes and (2) pancreatic cancer and chronic pancreatitis. All data was acquired in prospective studies using an Olympus Exera EU-ME1 system with GF-UE160-AL5 radial and GF-UC140P-AL5 curvilinear scopes. Malignancy was determined by histology from either fine-needle aspiration or resected tissue specimens while other states were determined using established diagnostic criteria. Mean midband fit, slope, intercept and root-mean-square (RMS) deviation from a linear regression of the calibrated power spectra were computed over regions of interest defined by the endoscopists. Linear-discriminant analysis was then performed to classify the resulting regression parameters.

For the lymph-node study, data was obtained from 19 patients, including 8 patients with benign-appearing lymph nodes and 11 patients with malignant lymph nodes, with multiple nodes imaged in some patients. For benign (n = 16) vs. malignant (n = 12) lymph nodes, midband fit and intercept provided classification with 89% accuracy and area under ROC curve (AUC) of 0.95. For the pancreas study, data was obtained from 41 patients, including 15 patients with pancreatic cancer, 15 with chronic pancreatitis and 11 with normal pancreas. For chronic pancreatitis (n = 15) vs. PC (n = 15), mean midband fit, intercept and RMS deviation provided 83% accuracy and AUC of 0.83. The results from both studies are comparable to or better than results from our previous studies obtained using single-element, mechanically-scanning echo-endoscopes. Given that electronic-array echo-endoscopes have widely replaced mechanical echo-endoscopes over the last decade, it is encouraging to see that similar or better results can be obtained using the more prevalent imaging technology. Supported by the National Institutes of Health (K24 DK002800 to A.C.), University Hospitals Case Medical Center, University of Michigan, and Kettering University. We would also like to thank Olympus Corporation for making the rf data available and providing technical assistance.

3.7 **Ultrasound-speed microscope findings of prostate needle-biopsy specimens,** Yoshifumi Saijo,[1, 2] Hideki Tanoue[1] and Yoshihiro Hagiwara,[2] [1]*Graduate School of Biomedical Engineering, Tohoku University, Sendai, Japan and* [2]*Graduate School of Medical Sciences, Tohoku University, Sendai, Japan, saijo@idac.tohoku.ac.jp*.

Typically, conventional transrectal ultrasound (TRUS) imaging of the cancer tissue is hypoechoic in echo texture. However, TRUS does not reliably distinguish between cancerous and noncancerous tissue in the prostate. In the present study, the sound speeds of prostate needle biopsy specimens are measured by an ultrasound-speed microscope (USM) to construct a database for interpreting clinical TRUS images. Biopsy specimens were formalin-fixed and sectioned approximately 5 μm in thickness. They were mounted on glass slides without cover slips. The ultrasonic transducer with a center frequency of 120 MHz was mechanically scanned over the specimen to measure sound-speed distributions. Sound speed was 1544.8 ± 29.1 m/s in well-differentiated adenocarcinomas, 1565.1 ± 24.8 m/s in moderately-differentiated adenocarcinomas, 1567.0 ± 36.4 m/s in poorly-differentiated adenocarcinomas, 1581.6 ± 48.1 m/s in the interstitial tissue, 1550.1 ± 30.8 m/s in the normal prostatic gland, 1511.3 ± 9.3 m/s in the cystic tissue and 1604.9 ± 60.8 m/s in the inflammatory tissue, respectively. Echo intensity of TRUS images were qualitatively classified into three categories: hyperechoic, isoechoic and hypoechoic areas. The sound speed was 1596.9 ± 28.2 m/s in hyperechoic, 1571.2 ± 35.8 m/s in isoechoic and 1562.6 ± 35.1 m/s in hypoechoic area, respectively. However, echo intensity showed no significant relationship to malignancy of prostatic tissue. Echo intensity of TRUS is significantly affected with tissue components and USM findings would provide important information for interpretation of TRUS images.

4. TISSUE PARAMETERS

4.1 **Effect of broad scatterer-size distributions on estimates of effective scatterer diameter,** Eric P. Nordberg and Timothy J. Hall, *Medical Physics, University of Wisconsin - Madison, WI, nordberg@wisc. edu.*

Objective: To describe the behavior of acoustic scatterers within biological systems composed of broad distributions of scatterer sizes and varied acoustic impedance changes. Acoustic-form factors are accurate models for deviations from Rayleigh scattering in media with discrete scatterers. Gaussian-form factors have been used to model the autocorrelation function of continuously-varying acoustic impedance changes within a tissue and have been shown to accurately model the acoustic backscatter behavior of some tissues (e.g., kidney) where scatterer-size distributions are narrow and a discrete scattering model is appropriate. In contrast, exponential-shaped form factors seem to fit systems with potentially more varied scatterer sizes (e.g., liver). This work investigates the possibility that a broad range of scatterer sizes, individually well described by a Gaussian-form factor scattering model, contributing linearly to a compound backscatter spectrum, can lose the character of a Gaussian-form factor and mimic an exponential-form factor with a single scatterer size.

Methods: The scattering function for individual scatterers was modeled with a Gaussian-form factor. The scattering from a distribution of scatterers was modeled as the incoherent sum of the contribution from each scatterer weighted by its scatterer size and the number of each of those scatterers. Distributions of scatterer sizes were created to have a Gaussian profile of scatterer sizes and each distribution had a mean scatterer diameter of 50 μm. Two sets of scatterer distributions were generated using two different assumptions about the relative size distribution. The first was created by scaling the volume fraction of each scatterer size (e.g., equal volume fraction of 40 μm and 60 μm scatterers). The second distribution was created by scaling the number density of each scatterer size (e.g., equal numbers of 40 μm and 60 μm scatterers). The standard deviation of scatterer diameters ranged from 5% to 90% of the mean. The composite scattering functions were fit to a single-diameter Gaussian and exponential model within the 3-15 MHz frequency range (over which clinical transducers would be sensitive). The χ^2 test was used to identify relative goodness of fit.

Results: For relatively narrow distributions (standard deviations up to 30% of the mean value), the composite scattering functions retained the character of their constituent models, i.e., the result of a single-diameter fit would yield a characteristic size (d) within 15% of the mean size and still have acceptable χ^2 values. For wider distributions, fitting both volumetric scaling and number density scaling to a single diameter model yield a linear size increase but a logarithmic increase in χ^2 values. However, when an exponential-form factor single-diameter fit is used, χ^2 values are small and are roughly independent of distribution width with volumetric scaling. When the distribution width is larger than 30% of the mean, an exponential model produces a better fit than the single-diameter Gaussian model. For the case of number density scaling, exponential fit χ^2 values increased roughly equal to the Gaussian form factor with increasingly widened size distributions.

Conclusions: The composite scattering functions from a wide distribution of scatterer sizes with Gaussian-form factors have been shown to display the characteristics of a single size exponential- form factor rather than a single size Gaussian form-factor. Because of this, when extracting scatterer-size information from radiofrequency data, a single size fit may be insufficient to accurately describe the measured system. While a single parameter fit may be sufficient for an empirical diagnostic test, additional parameters (or prior information) might be required to obtain a true understanding of a similarly complex scattering system. Supported by National Institutes of Health grants R21HD061896, R01CA111289 and T32CA009206.

4.2 **Ultrasonic tissue characterization of cancellous bone using a backscatter difference technique**, Brent K. Hoffmeister, Anne R. Wilson and Matthew J. Gilbert, *Department of Physics, Rhodes College, Memphis, TN 38112, hoffmeister@rhodes. edu.*

Ultrasonic backscatter techniques may offer a useful approach for detecting changes in cancellous bone caused by osteoporosis. The goal of this study is to investigate the utility of a spectral-difference technique for this purpose. Backscatter measurements were performed on 22 cube-shaped specimens of human cancellous bone using four broadband transducers with center frequencies 2.25, 5, 7.5 and 10 MHz. A difference spectrum $D(f)$ was obtained by subtracting the power spectrum (in dB) of a gated portion of the backscatter signal from the power spectrum of an earlier portion of the same signal. $D(f)$ was measured at multiple sites on each specimen to obtain a single spatially-averaged $D(f)$ for each specimen. The spatially- averaged $D(f)$ generally was a quasilinear, monotonically-increasing function of frequency. The frequency averaged mean of the spatially-averaged $D(f)$ demonstrated good linear correlations with specimen density (R = 0.70-0.95) depending on transducer. These results suggest that backscatter-difference techniques may be sensitive to the degenerative effects of osteoporosis. Supported by a grant from the National Institutes of Health (NIH R01AR057433).

4.3 **Comparison of single-mode analysis and Bayesian-separated fast and slow wave mode analysis: correlations with structural parameters of calcaneal bone**, Amber M. Nelson, Joseph J. Hoffman, Mark R. Holland and James G. Miller, *Washington University in St. Louis, St. Louis, MO, amber@hbar.wustl.edu.*

Background: We have previously shown that Bayesian probability theory permits separation of ultrasonic fast and slow waves in cancellous bone even in cases when the two modes overlap substantially.

Objective: The goals of the current study were to determine whether the fast and slow waves obtained from Bayesian separation of an apparently single-mode signal individually correlate with intrinsic structural parameters of the bone and to test whether the Bayesian parameters yield additional diagnostic information.

Methods: Through-transmission data were collected from eight human calcaneal bone samples with a pair of 500 kHz broadband transducers oriented in the medial/lateral direction. The acquired signals were first analyzed assuming a single wave to yield the apparent phase velocity (SOS) and slope of attenuation (nBUA). The Bayesian-separated fast and slow waves were then determined and the phase velocity, slope of attenuation and relative wave amplitude were obtained for both the fast and slow waves. Anatomical parameters of the samples were measured by X-ray microCT.

Results: The fast and slow wave parameters obtained from Bayesian analysis each showed a good correlation with sample porosity. The speed of sound (SOS) and slope of attenuation (nBUA) obtained from the one-mode analysis also correlated well with porosity.

Discussion: It is known that SOS and nBUA correlate with bone quality. The six parameters generated by the Bayesian method (fast and slow wave speed, fast and slow wave slope of attenuation and fast and slow wave amplitude) provide new avenues beyond one-mode analysis for investigating bone quality. Including these additional parameters may improve clinical assessment of bone quality with ultrasound. Supported, in part, by NIH/NIAMS grants R01AR057433 and P30AR057235.

4.4 **Mapping local myofiber orientation using echocardiographic methods,** Michelle L. Milne, Gautam K. Singh, James G. Miller and Mark R. Holland, *Washington University in St. Louis, St. Louis, MO, mmilne@physics.wustl.edu.*

Background: Previous studies from our laboratory and others have demonstrated the impact of myocardial architecture on acquired echocardiographic images. However, until now, the reverse approach of using acquired echocardiographic images to infer myocardial architecture had not been reported.

Objective: The goal of this study was to demonstrate the feasibility of imaging the myocardial fiber structure of whole, intact hearts from analyses of echocardiographic images.

Methods: A series of 37 apical images of seven whole, fixed sheep hearts were acquired using a clinical echocardiographic system (GE Vivid 7) with the image plane systematically rotated in 5° increments over 360°. Radial line profiles, representing the measured level of backscatter within the ventricular walls of the heart and corresponding to a series of specific heights from the apex, were generated from each set of apical images. These line profiles were assembled to create a composite image of the heart in the short axis view at each height. The fiber angle for each location within the heart tissue was determined from the backscatter data, using a previously-measured relationship between the backscatter level and the angle of insonification relative to local tissue fiber orientation. The findings were compared with the fiber orientation found using Diffusion Tensor Magnetic Resonance Imaging.

Results: The fiber orientations determined by echocardiography exhibited similar fiber maps as those obtained from Diffusion Tensor Magnetic Resonance Imaging measurements for each of seven hearts, with the mid-myocardial fibers oriented within the short axis plane (i.e. an angle of 0°) and gradually rotating out of the plane towards the epicardial surface and towards the endocardium. For the seven hearts, we measured maximum angles between 60° and 75° at the epicardial surface and maximum angle between 60° and 70° at the endocardial surface, in agreement with values from the literature.

Conclusion: In view of these results, the echocardiography-based approach shows promise as a method for obtaining information regarding myofiber orientation in intact hearts. Further development of this method may provide a clinically-useful approach for mapping the fiber orientation in individual patients over the heart cycle. Supported by NIH R01 HL040302.

4.5 **Time-delay spectrometry for measurement of hydrophone phase response,** K.A .Wear, P.M. Gammell, S. Maruvada, Y. Liu and G.R. Harris, *Food and Drug Administration, 10903 New Hampshire Blvd, Silver Spring, MD, 20993, keith.wear@fda.hhs.gov.*

Since the phase of a hydrophone frequency response is considered more difficult to measure than the magnitude, hydrophones are often characterized simply by the magnitudes of their frequency responses. However, in order to fully deconvolve the effect of a hydrophone on acoustic measurements, it is important to know the phase in addition to the magnitude. In this presentation we (1) present a new method for measurement of phase response based on time delay spectrometry (TDS) and (2) examine the hypothesis that hydrophones behave as minimum-phase systems, which would imply that their phase responses can be computed from measurements of their magnitude responses via a Hilbert transform. A swept-frequency system based on TDS was used to measure both magnitude and phase responses of several types of hydrophones used in medical ultrasound exposimetry. These included PVDF spot-poled membrane, needle and capsule designs. TDS-based measurements of phase shifts were compared with phase shifts calculated from magnitude responses via Hilbert transform. Validation experiments on electric circuit filters with known frequency-dependent phase responses indicate that the error of the new TDS-based phase measurement method is less than 10° over the 5 -15 MHz frequency range studied. Additional validation experiments involving axial displacements of a hydrophone indicate that the phase measurement is accurate enough to measure axial shifts to within 3 μm. Over 5-15 MHz, TDS-based measurements and Hilbert-transform-based estimates of phase shifts were in good agreement for the several hydrophone types considered. A new TDS-based phase-measurement method is sufficiently accurate to characterize hydrophone phase response. TDS-based measurements of hydrophone phase responses support the hypothesis that several common hydrophone types (those tested here) behave as minimum phase systems and, therefore, their phase responses may be derived from measurements of the magnitude responses.

Tuesday morning

5. ARFI/ELASTICITY 1

5.1 **Review of clinical experience with radiation-force-based imaging methods**, Kathryn R. Nightingale, *Department of Biomedical Engineering, Duke University, Durham, NC, kathy.nightingale@duke.edu* (invited overview).

Acoustic radiation force (ARF)-based elasticity imaging methods have been under investigation in research laboratories for over 15 years. In the past three years, both Siemens Medical Systems and Supersonic Imagine (SSI) have released commercial ARF-based products. The Siemens product was initially released for abdominal imaging, with two features: one that provides qualitative stiffness images and another that provides quantitative estimates of shear wave speed. Multiple studies have been presented in the clinical literature investigating the utility of the quantitative tool for staging liver fibrosis. The studies indicate that SWS can be used to diagnose advanced hepatic fibrosis and cirrhosis, obviating the need for liver biopsy in many cases. Reports using the qualitative tool include identification and differentiation of tumors in the liver, breast and thyroid, among others. The SSI system was initially released for breast-imaging applications and provides quantitative images of shear-wave speed. Recently, results from a multicenter clinical study were released, indicating that when combined with the ultrasonic BI-RADS score, the maximum elasticity score from the SSI system increased both the specificity and positive predictive value of the combined score over that of the ultrasonic score alone. Both manufacturers are now expanding their clinical application base and the range of transducers which are capable of ARF-based elasticity imaging. A review of findings in the clinical literature using these systems will be presented.

5.2 **ICE ARFI: Applications in surgical guidance and infarct mapping,** Gregg E. Trahey, Douglas Dumont, Peter Hollendar, Robi Goswami and Patrick Wolf, *Department of Biomedical Engineering, Duke University, Durham, NC, gregg.trahey@duke.edu* (invited).

Application of radiation-force-based imaging and measurement methods are limited by acoustic exposure during transthoracic cardiac applications. However, the utilization of intracardiac echocardiography (ICE) methods allows for successful qualitative ARFI imaging and quantitative shear-wave velocimetry (SWV) measurements in the beating heart. We describe current results from ongoing canine and porcine trials using these methods. We present results using 2D ARFI imaging, in conjunction with electroanatomic mapping, to guide cardiac-ablation surgeries. We also report results of studies utilizing 2D and M-Mode ARFI and SWV to characterize local cardiac contractility and stiffness in order to map infarcts and characterize heart failure. We discuss signal and image processing methods to achieve these goals and discuss future translations of these methods to clinical applications. Supported by NIH Grants R01-EB-012484, R21-EB-007741 and 5R37HL096023.

5.3 **ARFI-Monitored Hemostatic Challenge for noninvasive, *in-vivo* hemostasis assessment,** Leslie M. Baggesen,[1] Mallory R. Scola,[1] Timothy C. Nichols[2,3] and Caterina M. Gallippi,[1] [1]*Joint UNC/NCSU Department of Biomedical Engineering,* [2]*Department of Pathology and Laboratory Medicine and* [3]*Department of Medicine, the University of North Carolina at Chapel Hill, 150 MacNider Hall, Chapel Hill, NC 27599-7575, cmgallip@bme.unc.edu* (invited).

Acoustic Radiation Force Impulse (ARFI)-Monitored Hemostatic Challenge is a novel bleeding assay that assesses bleeding rate and time to hemostasis, established indicators of hemostatic status *in vivo*. Unlike conventional *in-vivo* assessments of clinical hemostasis, which monitor relatively major surrogate end-points such as drop in hemoglobin/hematocrit, pain at the bleeding site, visible or palpable hematoma, hypotension or need for surgical intervention or blood transfusion, ARFI-Monitored Hemostatic Challenge directly observes *in-vivo* bleeding and is relevant in early stages. Unlike conventional preclinical hemostasis assays that monitor bleeding at the nail cuticle, ARFI-Monitored Hemostatic Challenge measures *in-vivo* bleeding in clinically-relevant subcutaneous locations. ARFI-Monitored Hemostatic Challenge distinguishes hemorrhage by exploiting impulsive acoustic-radiation-force excitations. The ARFI-induced dynamic displacement responses of blood an inelastic material can be differentiated from those of soft tissue, a viscoelastic material and luminal blood, which flows with physiologic pulsation, by displacement variance. Once hemorrhagic pixels are identified, the cross-sectional area of hemorrhage is calculated in each of several serially-acquired ARFI data sets and bleeding rate and time to hemostasis are measured from the change in hemorrhagic area over time. In this overview, the methods of ARFI-Monitored Hemostatic Challenge are described in detail. Clinical application is demonstrated in diagnostic percutaneous cardiac catheterization patients, where a validated *in-vivo* test of hemostasis in urgently needed to develop antidotes to reverse bleeding complications associated with antithrombotic therapies. Preclinical application is also demonstrated in dog models of hemophilia A and von Willebrand's disease, where there is a critical need for a reliable *in-vivo* diagnostic hemostasis assay to test the efficacy of novel clotting-factor replacement therapies. Finally, the reproducibility of ARFI-Monitored Hemostatic Challenge is evaluated. Supported by unrestricted funding from Marine Polymer Technologies, Inc. and Novo Nordisk.

5.4 **Speckle-noise suppression in shear-wave velocity estimation,** Etana Elegbe and Stephen McAleavey, *Department of Biomedical Engineering, University of Rochester, Rochester, NY, stephen.mcaleavey@rochester.edu* (invited).

Ultrasound radiation force based methods for *in-vivo* estimation of tissue shear wave velocity and shear modulus imaging are being actively studied by many groups. These methods include ARFI,[(1)] SDUV,[(2)] Supersonic Imaging[(3)] and SMURF.[(4)] Within this group, we define two classes: multiple-track-location (MTL) methods, which track tissue motion ultrasonically at multiple locations (A-lines) and single-track-location (STL) methods, which track tissue motion along a single A-line and rely on the generation of a shear wave of known wavelength or shape to estimate shear-wave velocity. Examples of MTL methods include SDUV, Supersonic Imaging and ARFI Time-to-Peak (TTP). SMURF and similar methods[(5)] are implementations of the STL method.

We have shown that ultrasound speckle can be a significant source of variance in the estimation of shear-wave velocity. Previous work by our group suggests that STL methods that use multiple or shaped push beams to generate shear waves of known wavelength are nearly immune to speckle noise. This noise suppression results from tracking the same set of scatterers subjected to similar transient shear waves with different starting points. When all other aspects of the two shear waves are the same but for the difference in arrival time, then any speckle-induced tracking error will be the same for both and will disappear when the difference in shear-wave arrival time or phase is calculated to yield a velocity or modulus estimate. Minimizing speckle noise reduces is expected to reduce the need for spatial averaging and allow shear-wave velocity to be estimated with better precision over a smaller sample volume.

We present simulation, phantom and excised tissue data comparing STL and MTL shear-wave velocity estimation under matched conditions. The results demonstrate the expected speckle-noise suppression with STL for stationary targets and shear wavelengths on the order of the ultrasound beam. A decreased benefit is seen for longer wavelength shear waves and in the presence of significant tissue motion.

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5.5 **Characterization of ocular tissues with acoustic radiation force,** Ronald H. Silverman[1,2], Raksha Urs,[1] Harriet O. Lloyd[1] and Y-C Chen,[3] [1]*Department of Ophthalmology, Columbia University Medical Center, New York, NY,* [2]*Lizzi Center for Biomedical Engineering, Riverside Research, New York, NY and* [3]*Department of Physics and Astronomy, Hunter College, New York, NY, rs3072@columbia.edu* (invited).

Absorption of acoustic radiation generates a force that can induce tissue compression that can be used to assess tissue stiffness by detecting displacements in the phase-resolved pulse-echo ultrasound waveforms. We describe use of acoustic radiation force (ARF) to characterize the cornea and retina.

We used a single-element transducer with a 25-MHz center frequency, a 6-mm aperture and an18-mm focal length. Using a Tabor arbitrary waveform generator and ENI radiofrequency (rf) power amplifier, we exposed corneas to ARF tone bursts for 10 ms at a 25% duty cycle such that pulse-echo data could be acquired once every ms during time segments when ARF was

inactive. Rf data were acquired at 400 MSample/s, 12-bits/sample.

Initial studies were performed on intact *ex-vivo* pig eyes. We examined the effect of intraocular pressure (IOP) on displacements. Results demonstrated that as IOP was increased, overall displacement of the posterior cornea surface decreased but changes in corneal thickness were largely unaffected. *In-vivo* studies were performed on anesthetized New Zealand white rabbits. We examined the effect of biochemically-induced stromal collagen crosslinking on stress/strain. We also investigated the utility of measurement of corneal displacements in harmonic images using a dual-element transducer with coaxial and confocal 18 MHz (outer) and 36 MHz elements. We found the harmonic images to provide better lateral resolution than fundamental images at 18 or, especially, 36 MHz. Harmonic images of the cornea also had higher internal backscatter, enabling improved tracking of internal displacements.

We have also investigated the use of photoacoustic (PA) imaging as an adjunct to ARF-studies of the retina. The probe had a 5-mm diameter central aperture through which 532 nm laser pulses were introduced and brought to a common focus (10 µm laser-spot diameter) with the ultrasound focal point. Laser pulses were 5 ns in duration, 0.25 µJ in intensity and emitted simultaneously with excitation of the transducer by a 20-MHz monocycle at a pulse repetition frequency of 500 Hz. The PA system was useful in retinal ARF imaging because PA signals are only generated by the retinal pigment epithelium (RPE) rather than all layers of the posterior coats of the eye, as is the case with pulse-echo ultrasound. This allows identification of the RPE by fusion of photoacoustic with pulse-echo data and attribution of displacement to particular tissue components. PA imaging *in vivo*, however, is complicated by the presence of intervening optically-refractive elements (cornea and lens). This co-registration problem applies also to monitoring of retinal/choroidal displacements by OCT. Supported in part by NIH grants R01 EY021529 and R01 EY019055, the Riverside Research Biomedical Engineering Research Fund, an Endowment for Education and Research grant from the American Institute of Ultrasound in Medicine and an unrestricted grant to the Department of Ophthalmology of the Columbia University Medical Center from Research to Prevent Blindness.

5.6 **Acoustic-radiation-force creep and shear-wave propagation method for elasticity imaging,** Carolina Amador, Matthew W Urban, Shigao Chen and James F Greenleaf, *Ultrasound Research Laboratory, Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, MN 55905, amadorcarrascal.carolina@mayo.edu.*

Elasticity-imaging methods have been used to study tissue mechanical properties and have demonstrated that tissue elasticity changes with disease state. Quantitative mechanical properties can be measured in a model-independent manner if both shear-wave speed and attenuation are known. However, measuring shear-wave speed and attenuation is challenging in the field of elasticity imaging. Typically, only shear-wave speed is measured and rheological models, such as Kelvin-Voigt, Maxwell and Standard Linear Solid, are used to solve for shear viscoelastic-complex modulus. Acoustic-radiation force has been used to study quasistatic viscoelastic properties of tissue during creep and relaxation conditions; however, as with shear-wave propagation methods, a rheological model needs to be fit to the creep or relaxation experimental data to solve for viscoelastic parameters. A method to quantify viscoelastic properties in a model-independent way by estimating complex shear elastic modulus over a wide frequency range using time-dependant creep response induced by acoustic-radiation force is presented. The acoustic-radiation-force-induced creep (RFIC) method uses a conversion formula that is the analytic solution of the constitutive equation relating time-dependent stress and time-dependent strain. The RFIC method, in combination with shear-wave propagation, is used to measure the complex shear modulus so that knowledge of the applied radiation force magnitude is not necessary. Numerical simulation of creep strain and compliance using the Kelvin-Voigt model shown that the conversion formula is sensitive to sampling frequency, the first reliable measure in time and the long term viscosity approximation. Experimental data are obtained in homogeneous tissue-mimicking phantoms and excised swine kidneys.

5.7 **Dispersion and shear-wave velocity in a mouse liver model using crawling waves,** Zaegyoo Hah, Alexander Partin, Christopher T. Barry, Robert A. Mooney, Deborah J. Rubens and Kevin J. Parker, *University of Rochester, Rochester, NY, zaegyoo.hah@rochester.edu.*

Background: There is a growing concern about nonalcoholic fatty liver disease (NAFLD) that can potentially lead to nonalcoholic steatohepatitis (NASH). The natural history of NAFLD progressing to NASH is incompletely understood. Development of an inexpensive, easy-to-use, painless and noninvasive method to be able to measure the degree of steatosis in a liver is essentially needed.

Objective: The goal of this study is to measure the dispersion of mice liver samples *ex vivo* in a titrated experiment sequence and compare the results with pathologically-measured fat concentrations.

Methods: A total of 70 mouse liver specimens were scanned *ex vivo* at intervals during the progressive accumulation of fat in the livers. All mice experiments were performed in accordance with IACUC protocol of University of Rochester. C57Bl6 mice were divided into two major groups: 35 fed a regular diet (Lean) and 35 fed a high fat diet (Obese). The experiments were performed over a 5-month period. At month 0, only seven mice (all lean) were sacrificed and scanned. At month 1 to month 4, seven lean mice and seven high-fat mice were sacrificed and scanned. Additionally, 7 NASH mice were scanned at month 4. Liver specimens were suspended in a gelatin phantom using cube-shaped molds after hepatectomy.

The gelatin phantom was a mixture of 10% porcine gelatin, 0.9% NaCl and 0.15% agar. The mixture, heated to 55˚C and subsequently cooled to 30˚C, was poured into the mold and then placed in an ice water bath for about 2 hours. The solid gelatin

phantoms were removed from the molds and allowed to rest at room temperature to reach at least 14˚C.

A GE Logiq 9 ultrasound machine modified to show vibrational sonoelastographic images was used to scan the samples with two vibration sources (Model 2706, B&K). The vibration sources were driven at several frequencies (200 Hz – 400 Hz) with a small frequency offset (<1 Hz) between the sources to generate crawling waves. Acquired rf data were processed using previously-developed algorithms to produce a shear-wave velocity set from which dispersion is calculated per 100 Hz. The calculated dispersion is then compared to pathologically-measured fat concentrations.

Results: Lean mouse livers with a regular diet had less than 5% fat while the mouse livers with a high fat diet produced fat concentrations ranging from 5% to up to 90%. The livers were categorized into three groups: less than 10% fat, 10-50% and 50% and higher. Measured shear-wave velocities for mouse livers using the crawling-wave analysis were grouped together to calculate two representative parameters: shear wave dispersion per 100 Hz (m/s/100 Hz) and shear wave velocity (m/s) at 250 Hz. For the lean mouse liver group, (shear-wave dispersion, shear-wave velocity) results were (0.06, 2.47); for the 10-50% group (0.23, 2.6); and for the 50% and up (0.49, 2.54).

Conclusion: The results of this study demonstrate statistically-significant differences of shear-wave velocity dispersion over a range of fat concentrations of the liver. This result shows the consequence of adding a viscous component to the liver and increasing/decreasing collagen content.

5.8 **Acoustic-radiation-force techniques for imaging cardiac infarct *in vivo:* methods and initial results,** Peter J. Hollender,[1] David P. Bradway,[1] Robi Goswami,[2] Patrick D. Wolf[1] and Gregg E. Trahey,[1] *[1]Duke University, Department of Biomedical Engineering, Durham, NC and [2]Duke University Medical Center, Department of Cardiology, Durham, NC, peter. hollender@ duke.edu.*

Acoustic Radiation Force (ARF) techniques, including Acoustic Radiation Force Impulse (ARFI) Imaging, M-Mode ARFI and Shear Wave Elasticity Imaging (SWEI) were used *in vivo* to image and identify infracted regions in porcine myocardium. Eight animals were enrolled and imaged and seven were embolized with foam injection to create infarct. Three of the animals achieved a stable infarct state and were imaged over 12 weeks along with the control. Transthoracic and Intracardiac Echocardiography (ICE) ARF imaging methods were used in each animal to image healthy and diseased regions of myocardium. 3D registration using the CartoXP was used to register of ICE ARF imaging against histology and MRI. Infarcted regions were successfully imaged as stiffer and less contractile compared to healthy myocardium but displacement-magnitude and shear-wave imaging were limited by tissue depth and motion. Supported by NIH Medical Imaging Training Grant EB001040, NIH 5R37HL096023 and NIHR01EB01248.

5.9 **Transthoracic cardiac acoustic-radiation-force impulse imaging: *in-vivo* feasibility, methods and initial results,** David P. Bradway,[1] Peter J. Hollender,[1] Robi Goswami,[2] Patrick D. Wolf[1] and Gregg E. Trahey,[1] *[1]Duke University, Department of Biomedical Engineering, Durham, NC and [2]Duke University Medical Center, Department of Cardiology, Durham, NC, david.bradway@duke.edu.*

A Verasonics ultrasound system with a Philips/ATL P4-2 echocardiography transducer was used to collect transthoracic B-Mode images and M-Mode Acoustic Radiation Force Impulse (ARFI) images through the cardiac cycle in animal and human subjects. The research system's robust power supply and full parallel-receive capabilities enabled sustained excitations and fast off-axis tracking. Scanning and processing methods were initially tested and refined in a study of eight porcine subjects at Synecor, LLC. ARFI data were acquired for the left ventricular lateral wall, anterior wall or septum from 4-chamber, parasternal or apical views. Early results indicated transthoracic ARFI measurements were possible at depths up to 7 cm. In some cases and views however, image clutter, vigorous motion and rib shadowing limited access to myocardial regions of interest. Safety measurements and finite-element analysis simulations were then completed to ensure sequences were within FDA acoustic-exposure limits for intensity and tissue heating. Finally, transthoracic cardiac ARFI imaging was used in an IRB-approved clinical pilot study of healthy volunteers and Duke University Medical Center patients with known cardiac infarcts. Supported by NIH 5R37HL096023 and NIHR01EB01248.

6. IMAGING 1

6.1 **Clutter reduction in *in-vivo* cardiac images with short-lag, spatial-coherence (SLSC) imaging**, Muyinatu A. Lediju Bell,[1] Robi Goswami[2] and Gregg E. Trahey,[1, 3] *Departments of [1]Biomedical Engineering, [2]Cardiology and [1,3]Radiology, Duke University, Durham, NC, muyinatu.lediju@duke.edu*.

Clutter, a problematic noise artifact in echocardiography, appears as a diffuse haze that obscures endocardial borders and inhibits accurate diagnoses. Several approaches are available to reduce clutter in cardiac images, yet difficult-to-image patients still exist. We have recently developed a novel imaging method, termed short-lag spatial coherence (SLSC) imaging, that has demonstrated potential to reduce clutter in simulated and experimental data.[(1, 2)] With this technique, images are created from the same individual channel signals used to form B-mode images, but instead of applying a conventional delay-and-sum

beamformer, the data are cross-correlated to measure and display differences in spatial coherence. This technique was applied to *in-vivo* cardiac images.

Individual channel signals were acquired to form matched B-mode and SLSC images of the left ventricle (short-axis and apical 4-chamber views) in fourteen human volunteers, after IRB approval and informed consent. The volunteers consisted of five Duke University employees and nine patients scheduled for routine echocardiograms at the Duke University Medical Center. A Verasonics^{TM} ultrasound scanner (Redmond, WA) and a 64-element ATL P4-2 transducer were utilized to acquire thirty-five frames of data at a rate of seven frames per second, with an axial sampling frequency of 30 MHz. The transmit frequency was 2.0 MHz. The contrast and contrast-to-noise ratio (CNR) of the ventricle and the signal-to-noise ratio (SNR) of the endocardium were measured in the same locations in matched B-mode and SLSC images. In SLSC images created with a short-lag value equivalent to 16% of the transmit aperture, contrast and CNR was improved by 9±7 dB and 0.4±0.2, respectively, in the SLSC images. The average SNR of the endocardium was 1.7±0.4 in the SLSC images and 1.8±0.4 in the B-mode images. We also report on image performance metrics as a function of the short-lag value. The presented approach demonstrates a new method to reduce clutter in cardiac images, clarify endocardial borders and thereby improve visualization of cardiac abnormalities and border-dependent cardiac measurements, such as volume, mass and ejection fraction. Supported by the UNCF-Merck Graduate Research Dissertation Fellowship and NIH Grant R37HL096023.

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6.2 ***In-vivo* application of SLSC and HSCI imaging in human liver,** Marko Jakovljevic, Gregg E. Trahey and Jeremy J. Dahl, *Department of Biomedical Engineering, Duke University, Durham NC 27708, marko.jakovljevic@duke.edu.*

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 in *in-vivo* ultrasound images of the liver. Even though they appear similar to B-mode images, SLSC and HSCI images are based purely on the spatial-coherence function of backscattered echoes at fundamental and harmonic frequencies, respectively and do not depend on the echo magnitude. In this paper, we present the results of the patient study conducted to determine if SLSC and HSCI produce higher-quality liver images than the delay-and-sum beamforming methods currently used in clinic. Specifically, individual channel data was collected *in vivo* on the liver vasculature, common bile duct and other hypoechoic/anechoic hepatic structures of interest in 17 patients at the Department of Radiology, Duke University Hospital. From the channel data, we created matched SLSC and fundamental B-mode images and matched HSCI and harmonic B-mode images. Target contrast and CNR values were calculated for all images. In addition, based on the contrast and CNR values, B-mode images were classified as high, medium or poor quality.

SLSC and HSCI images display sharper delineation of blood vessel walls, lower clutter inside the vessel lumen and higher uniformity of the surrounding tissue when compared to their matched B-mode images. These observations are supported by statistically-significant improvements in target contrast and CNR, going from fundamental B-mode to SLSC and from harmonic B-mode to HSCI (in all cases $p < 0.001$). The results also indicate that magnitudes of relative improvements in both contrast and CNR increase as the quality of B-mode images decrease. The highest relative improvements are observed for poor quality fundamental B-mode images (288 % for contrast and 533% for CNR). We also discuss the potential limitations and trade-offs of SLSC and HSCI as well as the limitations of the study itself. Supported by NIH grants R21-EB008481 from the National Institute of Biomedical Imaging and Bioengineering and R01-CA114093 from the National Cancer Institute. The authors wish to thank the Ultrasound Division at Siemens Medical Solutions USA, Inc. for their in-kind and technical support.

6.3 **Two-dimensional, short-lag, spatial-coherence imaging: analysis of imaging characteristics using simulation,** Dongwoon Hyun, Gregg E. Trahey and Jeremy J. Dahl, *Department of Biomedical Engineering, Duke University, Durham, NC, dongwoon.hyun@duke.edu.*

Short-lag spatial coherence (SLSC) imaging is a new method of ultrasonic imaging that creates images using the coherence of backscattered echoes across the receive aperture. We have previously implemented SLSC with 1D transducer arrays and demonstrated with simulation, phantom and clinical studies that SLSC reduces clutter and offers improved contrast-to-noise ratio (CNR) of lesions compared to B-mode imaging. In this study, we expand SLSC to include the elevation dimension and use Field II simulations to compare the imaging performance of B-mode, SLSC and hybrid combinations of the two under varying noise conditions. In these simulations, one anechoic and two hypoechoic lesions of -12 dB and -6 dB intrinsic contrast were imaged using a 64x64 matrix array transducer. B-mode images were formed by scan converting the 3D received data volume and taking a 2D slice through the center of the lesion. 2D SLSC images were created in the same way. Element groups of 2x2, 4x4, 8x8, 16x16 and 32x32 were summed to create 32x32, 16x16, 8x8, 4x4 and 2x2 element effective apertures, respectively. The contrast, CNR, and signal-to-noise ratio (SNR) of each lesion phantom was calculated and compared in matched B-mode and SLSC images for each of the array configurations.

The B-mode had CNRs of 1.76±0.04, 1.42±0.06 and 0.92±0.08 for the anechoic, -12dB, and -6dB lesions, respectively, whereas the 64x64 SLSC had CNRs of 3.86±0.2, 2.99±0.2 and 1.43±0.2. In the case of Field II simulations where the SNR is infinite, even infinitesimal echoes can have a large normalized cross-correlation coefficient. Adding acoustical clutter enhances the CNR of SLSC images because the noise suppresses the coherence of lower-amplitude signals returning from within a hypoechoic region. With added noise, the CNRs for the 64x64 SLSC improved to 4.25±0.2, 3.38±0.1 and 1.78±0.2. The same

trends were observed in the hybrid SLSC receive apertures. With noise, the 32x32 SLSC aperture had CNRs of 4.26±0.2, 3.36±0.1 and 1.77±0.2, while the 16x16 aperture had CNRs of 4.24±0.2, 3.31±0.2 and 1.72±0.2. These two apertures exhibited little or no loss in CNR compared to the 64x64 aperture while acquiring a robustness to noise proportional to sqrt(*N*), where *N* is the number of elements summed. We conclude that 2D SLSC imaging exhibits the same improvements in lesion detectability as 1D SLSC imaging and that summing signals prior to computing the 2D SLSC can be beneficial in high-noise environments. Supported by the NIH grant R21-EB008481 from the National Institute of Biomedical Imaging and Bioengineering.

6.4 **Aperture-domain coherence imaging: comparison of techniques for imaging with the coherence of ultrasonic wavefronts,** Jeremy J. Dahl and Gregg E. Trahey, *Department of Biomedical Engineering, Duke University, Durham, NC, jjd@duke.edu.*

The spatial coherence of a backscattered ultrasound wave is the similarity of the wavefront at one point with respect to another point. While the spatial coherence of wave reflected from tissue is a well-known, analytical function, the spatial coherence of a wave corrupted by reverberation clutter, phase aberration or off-axis scattering presents deviations from this ideal function. We have recently introduced a class of aperture-domain imaging methods for creating ultrasonic images based on the coherence of ultrasound. These 'coherence imaging' displays are images of wavefront coherence at each pixel, rather than target reflectivity as observed in conventional B-mode imaging. The coherence imaging methods include short-lag spatial coherence (SLSC), generalized-coherence factor (GCF), phase-coherence factor (PCF) and waveform-similarity factor (WSF) imaging. We compare these coherence imaging methods under various imaging conditions, including reverberation clutter, phase aberration and target contrast, using a full-wave simulation tool. We also compute the 'short-lag' equivalent GCF and PCF images and compare them to the characteristics observed in SLSC and HSCI images.

The coherence-imaging methods demonstrated, on average, a mean increase in contrast-to-noise ratio (CNR) over conventional B-mode imaging of 0.50, 0.06 and 0.22 for SLSC, GCF and WSF imaging, for a 12 dB imaging target when imaging through an abdominal-tissue layer. For an anechoic target, the CNR increase improved to 0.80, 0.20 and 0.36, respectively. With phase aberration removed, all coherence imaging methods demonstrated constant CNR with increasing clutter-to-signal ratio (CSR) while the CNR in B-mode imaging declined with increasing CSR. The short-lag equivalent PCF imaging method demonstrated similar characteristics to SLSC imaging in that when the size of the aperture is reduced to 1/3 of its initial value, the resolution was not significantly degraded. The short-lag equivalent GCF method demonstrated characteristics similar to the effects of reducing the B-mode aperture in that a significant loss in resolution was observed.

The four aperture-domain coherence imaging methods demonstrate an overall ability to reduce clutter compared to B-mode imaging because these imaging methods are sensitive to the changes in the spatial coherence function. In general, this class of imaging techniques shows better contrast, CNR and speckle signal-to-noise ratio compared to B-mode imaging. We demonstrate these aperture-domain coherence imaging methods on *in-vivo* images of the carotid artery. Supported by the NIH grant R21-EB008481 from the National Institute of Biomedical Imaging and Bioengineering. In-kind and technical support provided by the Ultrasound Division at Siemens Medical Solutions USA, Inc.

Tuesday afternoon

7. ARFI/ELASTICITY 2

7.1 **ARFI atherosclerotic plaque characterization performance: a statistical reader study,** Russell H. Behler,[1] Tomasz J. Czernuszewicz,[1] Chih-Da Wu,[2] Timothy C. Nichols,[3, 4] Hongtu Zhu,[2] Jonathon W. Homeister,[3] Elizabeth P. Merricks,[2] Melissa C. Caughey[4] and Caterina M. Gallippi,[1] *[1]Joint Department of Biomedical Engineering, University of North Carolina and North Carolina State University, Chapel Hill, NC, [2]Deparment of Biostatistics, University of North Carolina, Chapel Hill, NC, [3]Department of Pathology and Laboratory Medicine, University of North Carolina, Chapel Hill, NC and [4]Department of Medicine, University of North Carolina, Chapel Hill, NC, tomekc@unc.edu.*

Background: Acoustic Radiation Force Impulse (ARFI) ultrasound imaging has been shown to be relevant to detecting atherosclerotic lesions and describing plaque composition and structure. To maximize ARFI's pertinence to materially characterizing atherosclerotic plaques, the most appropriate beam sequences must be used. The following presents a statistical analysis of ARFI beam sequence performance for plaque characterization.

Methods: A blinded, multireader study was conducted evaluating seven beam sequences in 22 arterial segments from six pigs, *ex vivo*. Three types of ARFI excitations were combined with three types of tracking to generate the sequences. The three types of excitations included: (1) single push with a F/1.5 focal configuration (SP1.5), (2) single push with a F/3 focal configuration (SP3) and (3) double push with a F/1.5 focal configuration, with the two excitation impulses spaced 0.8 ms apart (DP). The three types of tracking included: (1) single receive (SRx) in the region of excitation (ROE), (2) 4:1 parallel receive (ParRx)

in the ROE and (3) 4:1 parallel receive lateral to the ROE (LatRx), the last being a method comparable to shear-wave elasticity imaging (SWEI). Receiver-operating-characteristic (ROC) curve analysis was used to quantify performance using spatially-matched immunohistochemistry as the gold standard.

Results: The beam sequence(s) with the highest median area under the curve (AUC) for detecting the following compositional features were, with sensitivity and specificity listed respectively: (1) Lipid Pool/Necrosis – SP3-SRx (0.80, 0.86), (2) Fibrous Cap – SP3-SRx (0.86, 0.82), (3) Calcium – SP1.5-LatRx (0.84, 0.89) and SP3-SRx (0.96, 0.85), (4) Disrupted Internal

Conclusions: The most consistent beam sequence for detecting atherosclerotic plaque features was SP3-SRx, which consistently yielded high median AUCs. Furthermore, ARFI was seen to be sensitive to detecting degraded IEL, a feature that has been shown to predict plaque vulnerability and is currently not detected by other conventional noninvasive imaging modalities. While this study was performed *ex vivo*, the sensitivity and specificity values achieved compare to published values for MRI and CT, suggesting that ARFI imaging is relevant for describing atherosclerotic plaque composition and could be used to help identify vulnerable plaques.

7.2 **Impact of tracking beam focal configuration on combined ARFI/SWEI image quality,** Yufeng Deng, Ned C. Rouze, Mark L. Palmeri, Stephen J. Rosenzweig and Kathryn R. Nightingale, *Duke University, Durham, NC, yufeng.deng@duke.edu.*

Background: With the advent of research systems capable of providing individual channel data, plane-wave imaging is becoming ubiquitous in research laboratories. The use of plane-wave imaging for tracking tissue motion in ARFI and SWEI imaging is attractive due to the high frame rates that can be achieved, which facilitates monitoring tissue response throughout an entire image plane from a single ARFI excitation. However, the lack of transmit focusing in plane-wave imaging is associated with decreased SNR as compared to focused transmits, which can lead to increased jitter in ARFI image data. Herein, we investigate the impact of using different types of tracking beam transmit beamforming on the contrast-to-noise ratio (CNR) in ARFI images.

Methods: ARFI imaging was performed on a liver-mimicking phantom with a 20 mm diameter lesion situated 60 mm deep in the phantom. The stiffness of the lesion and of the background was 16.7 kPa and 4.1 kPa respectively, with an attenuation of 0.7 dB/cm/MHz. Using the Verasonics Imaging system with the ATL C5-2 curvilinear-array transducer, the radiation force was delivered by three 384 cycle consecutive F/2 multifocal excitation pulses (focused at 90 mm, 75 mm and 50 mm) and a range of tracking beam transmit beamforming approaches were investigated, including unfocused/plane-wave, F/2 focused at 70 mm and F/4 focused at 70 mm. Multiple realizations were performed for each focal configuration in different phantom locations. The ARFI image displacements were estimated using the Loupas phase-shift algorithm, normalized to axial depth, and the resulting images were filtered by a 2 mm×2 mm median filter. The lesion CNR was calculated at 1.4 ms, 1.8 ms and 2.2 ms after the push events for each tracking method.

Results: The CNR from the unfocused tracking sequence at the three time steps was calculated to be 2.04 ± 0.19, 3.11 ± 0.02, 4.20 ± 0.27 (mean ± standard deviation). The CNR from F/2 tracking was 2.76 ± 0.50, 4.34 ± 0.70, 5.99 ± 0.72. The CNR from F/4 tracking was 2.63 ±0.38, 4.14 ± 0.11, 5.01 ± 1.33. Both F/2 and F/4 tracking beams result in higher CNR in ARFI images as compared to unfocused tracking beams.

Conclusion: Results of this study indicate that focused tracking beams improve lesion CNR in ARFI images and that plane-wave tracking is associated with decreased signal-to-noise ratio. The focused tracking improved the lesion CNR by over 35% at each time step investigated. On the other hand, the focused tracking beams compromise the field of view in combined ARFI/SWEI images. Optimal beamforming for combined sequences will be determined based upon these tradeoffs.

7.3 **Tracking acoustic-radiation-force-induced displacements with harmonic imaging**, Joshua R. Doherty,[1] Jeremy J. Dahl[1] and Gregg E. Trahey,[1, 2] *[1]Departments of [1]Biomedical Engineering and [2]Radiology, Duke University, Durham, NC, joshua.doherty@duke.edu.*

Acoustic radiation force imaging methods, including Acoustic Radiation Force Impulse Imaging (ARFI) and Shear Wave Elasticity Imaging (SWEI), have shown promise for their ability to characterize the mechanical properties of soft tissue. Traditionally, these ultrasound-based elasticity imaging techniques have used conventional B-mode imaging pulses to track the displacements induced by an applied acoustic radiation force. As such, the displacement estimates are corrupted by the same noise mechanisms, such as clutter, that are known to degrade B-mode image quality. Harmonic-imaging methods have been applied in B-mode imaging to reduce clutter but have not been adopted by acoustic radiation force imaging techniques. In this work, we developed a new Harmonic Acoustic Radiation Force Impulse (HARFI) imaging technique that uses harmonic imaging to track acoustic radiation force induced displacements. The performance of this method was evaluated in phantoms and *in vivo* experiments. We compare the resulting displacement jitter errors associated with harmonic vs. nonharmonic tracking and demonstrate images formed by both techniques. We also discuss the advantages/disadvantages of filter-based and pulse-inversion harmonic techniques for acoustic radiation force applications.

7.4 **Analysis of multipush, multifocal zone ARFI imaging**, Stephen Rosenzweig, Mark Palmeri and Kathy Nightingale, *Duke University, Department of Biomedical Engineering, Durham, NC, stephen.rosenzweig @gmail.com.*

Acoustic radiation force impulse (ARFI) imaging has been used to visualize structures in the breast, prostate, liver and other organs with high contrast.[1-3] Previous work has shown that image contrast suffers outside of the region of excitation (ROE) of the push beam and that acquiring multiple ARFI images with different push beam foci can improve image contrast.[4] Although this configuration improves image quality, the acquisition duration and acoustic exposure are proportional to the number of focal zones acquired. Technological improvements in current ultrasound scanners and power supplies now allow for multiple pushes in rapid succession prior to tracking displacements within the now extended ROE, similar to the supersonic shear imaging approach pioneered by Fink et al for shear-wave imaging.[5] Therefore, it is possible to acquire multifocal zone ARFI images without any increase in acquisition duration or acoustic exposure.

In this work, previously validated finite-element model (FEM) simulations were utilized to analyze the displacement profiles in a uniform medium and compared to phantom data acquired using the Siemens Acuson SC2000 and the longitudinal side-fire array on an Acuson ER7B transducer that is being developed for use in prostate ARFI studies. Measurements in a homogeneous phantom closely match the simulation results, which show considerably larger (25%) maximum displacement when the pushing focal locations are ordered deepest to shallowest as compared to shallowest to deepest. Three focal zones were employed, evenly spaced throughout the image field of view. Additional phantom experiments were performed to compare the contrast of lesions in the concurrently-acquired multifocal zone ARFI push configuration and the traditional sequentially-acquired single focal zone ARFI configurations for a variety of foci. We will present results of both simulation and phantom experiments. Supported by NIH grants EB001040 and CA142824. We thank the Ultrasound Division at Siemens Medical Solutions, USA, Inc. for their technical and in-kind support.

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7.5 **Multipush (MP) ARF assessment of viscoelastic properties in tissue-mimicking phantoms,** Mallory R. Scola and Caterina M. Gallippi, *Joint Department of Engineering, Biomedical The University of North Carolina at Chapel Hill, Chapel Hill, NC, mrscola@unc.edu.*

Background: We have developed a new method, MultiPush Acoustic Radiation Force (MP-ARF) ultrasound, for quantitatively assessing the relationship between elasticity and viscosity. By comparing the displacements achieved by successive ARF excitations, we can calculate the relaxation time for constant stress (τ_σ), given by the ratio of viscosity (*Pa·s*) to the relaxed elastic modulus (*Pa*). We hypothesize that MP-ARF ultrasound can be used to quantitatively assess viscoelastic parameters of tissue.

Methods: Five homogeneous, agar/gelatin tissue-mimicking phantoms were prepared with different concentrations of gelation to vary elasticity and different concentrations of xanthan gum to alter viscosity. Imaging was performed using a Siemens ACUSON Antares™ imaging system, specially equipped for research purposes, and a VF7-3 linear array transducer. MP-ARF was implemented using two 300–cycle ARF excitations administered to the same region of excitation and separated by 0.8 ms in time. For each phantom, τ_σ was calculated and elasticity and viscosity were characterized using Shear Wave Dispersion Ultrasonic Vibrometry (SDUV)[1] and corroborated with Shear Wave Spectroscopy.[2] Phantom elasticity was also characterized using a compressional mechanical-testing device. MP-ARF was also demonstrated in a structured-gelatin phantom with comparable elasticities and different viscosities and in healthy canine-skeletal muscle.

Results: The following values of τ_σ were calculated in the homogenous phantoms with the reference value calculated from SDUV results given in parentheses: (1) 0.062 ± 0.019 ms (0.068 ± 0.013 ms), (2) 0.074 ± 0.018 ms (0.074 ± 0.006 ms), (3) 0.076 ± 0.032 ms (0.076 ± 0.003 ms), (4) 0.081 ± 0.028 ms (0.088 ± 0.005 ms) and (5) 0.091 ± 0.015 ms (0.121 ± 0.016 ms). Parametric images of τ_σ in the structured phantom discriminated the viscous lesion with a contrast-to-noise ratio (CNR) of 1.2 whereas conventional parametric peak displacement and recovery images showed poor contrast of the lesion from the background, with a CNR of 0.09 and 0.39, respectively. In the canine muscle, parametric τ_σ images discriminated regions of fat and collagen deposition as confirmed by histochemistry.

Conclusions: Results showed good agreement of τ_σ values calculated from MP-ARF with those calculated with SDUV and demonstrate the feasibility of MP-ARF for delineating the viscoelastic properties of tissue.

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7.6 **Validation of single-heartbeat, electromechanical-wave imaging in canines *in vivo***, Jean Provost, Stanley Okrasinski III, Alexandre Costet, Julien Grondin, Alok Gambhir, Hasan Garan and Elisa E. Konofagou, *Columbia University, New York, NY, jp2643@columbia.edu.*

Arrhythmias are a major cause of death and disability worldwide. However, no noninvasive imaging modality that can map the electrical activation is available to the physician. Electromechanical Wave Imaging (EWI) can noninvasively and transmurally map the electromechanical wave, i.e., the transient deformations occurring in response to the electrical activation. EWI

maps have previously been shown to correlate with electrical activation times in canines *in vivo* and recent clinical studies in humans have also demonstrated the potential of EWI as a surrogate for invasive cardiac mapping. In this study, we developed novel imaging sequences based on unfocussed transmit beams to perform single-heartbeat EWI (SH-EWI) at 2000 fps in canines *in vivo*.

SH-EWI was implemented on a 64-channel Verasonics system (Verasonics, Redmond, WA) used to sample prebeamformed rf signals from a 2.5-MHz phased-array probe. The SH-EWI sequence consisted of a 2-s-long, 2000-fps flash transmit beams for motion estimation followed by a 1.5-s-long, 30-fps, standard B-mode transmit beam sequences to map the anatomy. Axial displacements and strains were estimated at 1000 Hz with a 4.6 mm crosscorrelation window and a 10.7 mm least-squares kernel, respectively, in 3D biplane views. The first part of this study was conducted on conscious, closed-chest canines, before and after radiofrequency ablation of the atrio-ventricular (AV) node and insertion of a pacemaker lead in the right ventricle. The second part of this study was conducted in open-chest canines *in vivo*, in which SH-EWI maps were compared against electrical mapping performed using a basket catheter (Boston Scientific, Natick, MA) and a custom-built 64-channel acquisition system during sinus rhythm and pacing.

Before ablation of the AV, SH-EWI maps were in agreement with previously-published results of the normal electromechanical activation sequence in canines: in the atria, the EW originated in the right atrium and propagated towards the left atrium. The ventricle then underwent electromechanical activation from multiple sites corresponding to the expected Purkinje fiber terminals. After ablation, SH-EWI could map the activation sequence of both the dissociated atrial and ventricular activations, i.e., activation driven by the sinus node in the atria and by the pacemaker in the ventricles. In open-chest canines, a strong correlation between the electrical and electromechanical activation was observed, with linear correlation coefficients above 0.8.

In this study, we have demonstrated the feasibility and reliability of SH-EWI. The possibility of using SH-EWI in a clinical setting expands the field of application of EWI beyond periodic rhythm. For example, it allows the study of irregular rhythms such as atrial fibrillation, atrial flutter or ectopic beats. An example of such nonperiodic rhythm was provided in the form of atrio-ventricular dissociation. The reliability of the method was assessed with direct comparison with electrical mapping. Most invasive electrical mapping techniques currently used in the clinic rely on the periodicity of the arrhythmia studied to generate maps of the activation times. Such an approach is limited in many cases where the arrhythmia is not periodic, such as in atrial fibrillation. Flash and wide-beam EWI do not require the propagation pattern studied to remain periodic and is thus suitable for the study of nonperiodic arrhythmias, i.e., it could be employed for the study of atrial fibrillation, atrial flutter or ectopic beats.

7.7 **Improved detection of kidney-stone twinkling using autoregressive signal-processing method**, John Kucewicz, Barbrina Dunmire and Michael Bailey, *Applied Physics Laboratory, University of Washington, Seattle, WA 98105-6785, kucewicz@u.washington.edu.*

Introduction and Objectives: The Twinkling Artifact (TA) is the rapidly changing, random pattern of colors on and deep to kidney stones during ultrasound color Doppler imaging. The potential clinical benefit of TA is well documented but the use of TA is not without limitations. The origin of TA is not well understood; it appears to be influenced by multiple system settings and without a specific knob to control it, twinkling can be intermittent. Furthermore, twinkling can be misinterpreted as true blood flow, reducing its sensitivity to the detection of stones. The objective of this work is to develop signal-processing methods that are highly sensitive to kidney stones and insensitive to blood flow.

Methods: Conventional Doppler autocorrelation (AC) methods are optimized to detect blood flow based primarily on backscattered power and Doppler frequency shift. Tissue is typically high power and low frequency and blood flow is typically low power and high frequency. Twinkling is characteristically high power with broad frequency content, i.e. high amplitude noise. An autoregressive (AR) method has been developed that is able to differentiate between narrowband, coherent signals from tissue and blood flow and broadband, incoherent signals characteristic of TA.

Ultrasound data were collected from a tissue phantom containing a human *ex-vivo* kidney stone and a 5 mm flow channel. Water with cellulose was pumped through the flow channel to simulate blood flow. Ultrasound data prior to any Doppler-specific signal and image processing were collected with an Ultrasonix RP (Ultrasonix Medical Corporation, Canada) while varying acoustic output and receiver gain. Twinkling was measured using an AC Doppler method and our AR method.

Results: AR power was typically 0 to 2 dB less from the stone and 5 to 10 dB less from the flow channel relative to power measured by AC. The relative difference between the AR and AC powers was able to differentiate stone twinkling and flow with a sensitivity of 0.94 and a specificity of 0.89.

Conclusions: Twinkling is a potentially useful method of imaging kidney stones with ultrasound but its value will remain limited without an imaging mode optimized for the unique ultrasound signals that typify stones. Autoregression is a simple, computationally-efficient alternative signal-processing method to conventional autocorrelation processing that addresses the limitation of ambiguity between kidney stone twinkling and true blood flow. Supported by NIH DK43881, DK092197 and NSBRI through NASA NCC 9-58.

7.8 **Ultrasonic propulsion of kidney stones**, Bryan W. Cunitz,[1] John C. Kucewicz,[1] Yak-Nam Wang,[1] Julianna C. Simon,[1] Wei Lu,[1] Barbrina Dunmire,[1] Peter J. Kaczkowski,[1] Marla Paun,[1] Frank Starr,[1] Jonathan D. Harper,[2] Mathew D. Sorensen,[2] Oleg A. Sapozhnikov,[2] Lawrence A. Crum[1] and Michael R. Bailey,[1] *[1]Center for Industrial and Medical Ultrasound, Applied Physics Laboratory, University of Washington, 1013 NE 40th St. Seattle WA 98105 and [2]Dept. of Urology, University of Washington School of Medicine, 1959 NE Pacific St., Seattle, WA 98195, bailey@apl.washington.edu.*

Background: Stones afflict 10% of the U.S. population. The approach to stone treatment is often conservative since most are small enough to pass naturally. Smaller stones and those located near the opening to the ureter are more likely to pass. Up to 98% of stones < 5 mm and 53% of stones 5-10 mm pass from the proximal ureter. However, when stone fragments are located in the lower pole of the kidney, fewer than 35% pass naturally. If small stones can be moved near the opening to the ureter (the renal pelvis or uretero-pelvic junction (UPJ)), they are likely to pass and the patient can avoid surgery. In addition, surgery leaves residual fragments in 65% (shockwave lithotripsy -SWL) and 50% (ureteroscopy) of lower-pole cases, which act as nuclei for new stone growth and lead to intervention in 50% of those cases within five years. Urologists have tried various noninvasive manipulations to reposition small stones, such as inversion and percussion, with limited success.

Objective: Our envisioned product is an office-based, noninvasive ultrasound machine with new capability to both image and expel stones from the kidney. Our first market is to aid passage of residual fragments (>500,000 annual U.S. urology office visits) and our ultimate market is to treat new stones before they require surgery.

Method: The prototype system uses a Verasonics imager with 'push' capability and a Philips/ATL HDI C5-2 or P4-1 probe. We define a burst average intensity that is below the pulse average intensity limit for diagnostic machines as done in this reference (1). Human stones or metalized glass beads (because they show up better on x-ray) were ureteroscopically implanted into the kidneys of eight pigs by urologists. Two stones/beads were implanted in the upper pole as reference and two in the lower pole to reposition. Both kidneys were used. An experienced sonographer simulated clinical treatment of moving the stones to the ureter or UPJ. Stone movement was documented by ultrasound and fluoroscopy.

Results: At least 17 of the 24 beads/stones treated were moved the entire distance from the lower pole to the UPJ or ureter. In a separate study (n = 6) without stone implantation surgery, no injury was observed to kidneys exposed to the same exposures.

Conclusions: There is a need to reposition kidney stones. We have developed a commercializable prototype and have a fairly straightforward regulatory pathway. These results are part of an effort to obtain approval for a feasibility study in humans. Supported by NIH DK48331, NIH DK092197 and NSBRI through NASA NCC 9-58.

(1) Herman BA, et al. *Ultrasound Med Biol 28,* 1217–1224 (2002).

8. IMAGING/TRANSDUCERS 2

8.1 **Assessment of the imaging performances of a high-frequency, annular-array-based ultrasound scanner using anechoic-pipe phantoms,** Erwan Filoux,[1] Jonathan Mamou,[1] Carmel M. Moran,[2] Stephen D. Pye[3] and Jeffrey A. Ketterling,[1] *[1]Riverside Research, Lizzi Center for Biomedical Engineering, New York, [2]Center for Cardiovascular Sciences, University of Edinburgh, Edinburgh, UK and [3]National Health Service Lothian, Royal Infirmary of Edinburgh, Edinburgh, UK, efiloux@riversideresearch.org.*

A resolution-integral method was used to assess the image quality of three 40 MHz ultrasound scanners. The resolution integral was defined as the ratio between the depth-of-field (DOF) and spatial resolution of a transducer and provided a single figure-of-merit representative of the imaging performances of a scanner in terms of contrast, resolution and penetration depth. Three different scanners with similar axial and lateral resolutions were used: one featured a spherically-focused single-element transducer, one a linear-array transducer of 256 elements and one a spherically-focused annular-array transducer of 5 elements. The custom annular array could be excited by either an impulse or chirp-encoded signal optimized for increased penetration depth and signal-to-noise ratio. Images of anechoic pipes embedded in a tissue-mimicking phantom were acquired with each scanner and manually segmented to determine their resolution integral. The pipes had diameters ranging from 92 to 1470 µm and none of the systems could detect the smallest 92 µm pipe. The single-element transducer was able to resolve pipes down to 140 µm over its limited DOF (~1.5 mm) and obtained a resolution integral value of 24. In comparison, the linear-array transducer could only resolve pipes above 200 µm in diameter but its DOF was about 10 times larger, resulting in images of much higher quality and a resolution integral value of 47. The highest resolution integral value of 48 was obtained with the annular array and chirp excitation as it combined the advantages of fine resolution (140 µm pipes could be resolved) and extended DOF (~10 mm). These results were in good agreement with previous results reported in the literature(1) and showed that our custom annular-array system could achieve superior image quality with a small number of elements.

(1) Moran, et al. *Ultrasound Med Biol 37* (2011).

8.2 **Rapid transient-pressure computations in the nearfield region of a rectangular transducer with frequency-domain, time-space decomposition,** Yi Zhu,[1] Erwin J. Alles,[1, 2] Koen W.A. van Dongen and Robert J. McGough[1], *[1]Department of Electrical and Computer Engineering, Michigan State University, East Lansing, MI and [2]Laboratory of Acoustical Imaging and Sound Control, Delft University of Technology, Delft, The Netherlands, mcgough@egr.msu.edu.*

The fast near-field method, combined with the previously-derived, time-space decomposition approach, is a rapid and accurate numerical technique for calculating transient nearfield pressures generated by ultrasound transducers. However, this combination is only applicable to certain analytical representations of the temporal component of the particle velocity evaluated on the transducer surface. To enable time-space decomposition for arbitrary temporal excitation signal representations, a new frequency-domain, time-space decomposition (FDTSD) approach is derived. Results with the frequency-domain, time-space decomposition approach are evaluated for a rectangular transducer and then compared with results obtained with the impulse response and Field II. The results show that FDTSD calculations, when combined with the fast nearfield method, consistently outperform the impulse response and Field II in terms of computation time, numerical error and computer memory usage. Numerical results show that, for nearfield pressure calculations that achieve the same numerical error, FDTSD calculations combined with the fast nearfield method often reduces the computation time by one or two orders of magnitude relative to Field II. This reduction in the computation time is achieved with significantly less computer memory, which enables the FDTSD approach and the fast nearfield method to simulate much larger transient problems with the computer memory that is available on a standard desktop computer. Plans to incorporate the new FDTSD approach in the FOCUS medical ultrasound simulation package for phased-array calculations will also be discussed. Supported in part by NIH grant 5R01EB012079-02.

8.3 **Numerical evaluation of transient nearfield errors produced by the KZK equation,** Xiaofeng Zhao and Robert J. McGough, *Department of Electrical and Computer Engineering, Michigan State University, East Lansing, MI, mcgough@egr.msu.edu.*

The nonlinear KZK equation is often applied to simulations of nonlinear propagation in medical ultrasound. The KZK equation is effective for farfield calculations but the numerical errors generated by the KZK equation are significant in the nearfield region. In an effort to exploit the strengths and compensate for the weaknesses of the KZK equation in the farfield and nearfield regions of a circular piston, the sources of the errors in the linear KZK equation are characterized and strategies to compensate for these errors are identified. For example, the nearfield pressures inputs for the KZK equation are often represented by a plane-wave approximation and results show that replacing the plane-wave approximation with a more accurate nearfield pressure distribution in linear KZK simulations produces nearly identical results in the farfield without any significant improvement in the nearfield. This result suggests that additional modifications to the KZK equation are needed in the nearfield region. Results also show that the linearized version of the KZK equation computes the direct-wave component of the transient pressure correctly in the nearfield region of a circular piston but the arrival time, duration and shape of the edge wave component are incorrect. This result suggests that the correct direct-wave contribution in the nearfield region can be extracted from KZK calculations as long as there is no temporal overlap between the direct-wave and edge- wave components. Efforts to further improve the nearfield errors in nonlinear ultrasound simulations will be described and plans to include an improved nonlinear model in the FOCUS simulation package for medical ultrasound will be discussed. Supported in part by NIH grant 5R01EB012079-02.

8.4 **Combined high-frequency ultrasound and photoacoustic imaging of mouse embryos**, P. V. Chitnis,[1] O. Aristizabal[2], A. Sampathkumar,[1] E. Filoux,[1] D. Gross,[1] J. Mamou,[1] D. H. Turnbull[2] and J. 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.*

The mouse embryo is the preferred animal model for studying development of mammalian physiology and congenital diseases. Embryonic vasculature is a morphologically-complex structure; its development is intimately related to cell differentiation and proliferation. Therefore, study of embryonic development necessitates fine-resolution, *in-vivo* imaging methods for providing vascular and related anatomical information. The present study demonstrates the utility of a scanning biomicroscopy method that combines photoacoustic (PA) and high-frequency ultrasound (HFU) imaging for *in vivo* examination of embryonic vasculature.

The integrated PA-HFU system consisted of a 5-element, 40-MHz, annular-array transducer with a 12-mm geometric focus and an overall aperture of 6 mm combined with a pulsed 532-nm laser. An intact conceptus (E11.5 to E13.5 days of gestation) from an anesthetized mouse was surgically exposed into a PBS-filled petri-dish. Laser pulses synchronized with impulse ultrasound excitation of the central array element resulted in PA and HFU signals at each scan location. These acoustical signals were simultaneously recorded on all five receiving channels, separated from each other, and postprocessed. The transducer was raster scanned over the entire embryo in 50-µm increments to acquire 3-D image. Delay-and-sum beamforming was performed on the 5-channel data at each scan location to extend the depth-of-field and enhance the signal-to-noise ratio.

The HFU data provided exquisitely detailed anatomic information and the PA data provided visualization of the vascular plexus and individual blood vessels, which were inherently co-registered with the anatomical HFU images. Major blood vessels in the embryonic head, including the superior saggital sinus, transverse sinus, middle cerebral artery, vertebral artery and

the basilar artery, were accurately depicted. Near-real-time, spatially co-registered, dual-modality biomicroscopy of live mouse embryos was achieved.

8.5 **All-optical photoacoustic-spectroscopy (PAS) system for remote, nondestructive characterization of biological tissues**, A. Sampathkumar and Parag V. Chitnis, *Frederic L. Lizzi Center for Biomedical Engineering, Riverside Research, New York, NY, ashwin@riversideresearch.org.*

Conventional photoacoustic spectroscopy (PAS) employs wavelength-tunable light pulses (~nanoseconds) to produce a spectral photoacoustic (PA) effect in tissue and detects the resulting acoustic wave using an ultrasound transducer. However, this conventional approach is limited by the sensitivity and bandwidth of the ultrasound transducer, which constrain the spatial and temporal resolutions available for dynamic interrogation. A superior alternative is an all-optical interferometric technique that can provide a noninvasive, remote means of detecting the broadband PA response emanating from the target tissue. We have developed such an all-optical spectroscopy system that utilizes a wavelength-tunable, pulsed light source to excite and a single-wavelength continuous-wave (cw) light source to detect the PA effect in tissue. The induced PA effect results in a pressure wave that produces a surface displacement that is sensed by an optical beam incident on the tissue surface. The phase-encoded sensing beam is demodulated using a homodyne optical interferometer. The detected time-domain signal is time reversed using *k*-space reconstruction methods to characterize tissue optical-absorption and scattering properties. Tissue-mimicking phantoms with embedded nanoparticles with known absorption and scattering properties are used as test samples. Preliminary results characterizing the sizes and spatial distributions of these nanoparticles from optically-detected PA signals will be presented. This all-optical photoacoustic-spectroscopy system potentially can become an important tool for a wide range of biomedical applications, including skin-burn assessment, pressure-ulcer monitoring, retina evaluations, tissue characterization and section-less histological assessment of biopsied tissue specimens.

Wednesday morning

9. THERAPY MONITORING 1

9.1 **Conventional frequency quantitative ultrasound evaluation of tumor cell death response in locally-advanced breast cancer patients to chemotherapy treatment administration**, Gregory J. Czarnota,[1, 2] Naum Papanicolau,[1, 2] Ali Sadeghi-Nani1, [2] Omar Falou1,[2] Rebecca Dent,[3] Sunil Verma,[3] Maureen Trudeau,[3] Jean Francois Boileau,[4] Jacqueline Spayne,[2] Sara Iraji,[1] Ervis Sofroni,[1] Justin Lee,[1, 2] Sharon Lemon-Wong,[5] Martin Yaffe[1, 2] and Michael Kolios,[6] *[1]Imaging Research and Radiation Oncology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [2]Departments of Radiation Oncology and Medical Biophysics, University of Toronto, Toronto, ON, Canada, [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* (invited overview).

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

A clinical study was undertaken investigating the efficacy of ultrasound to quantify cell death in tumor responses with cancer treatment. Patients (n = 25) with locally-advanced breast cancer received anthracyline and taxane-based chemotherapy treatments over four to six months. The majority of patients went on to have a modified radical mastectomy and correlative whole mount histopathology.

Data collection consisted of acquiring tumor images and radiofrequency data prior to treatment onset and at four times during neoadjuvant chemotherapy (weeks 0, 1, 4, 8 and preoperatively). Data collection was carried out using an Ultrasonix-RP and an L15-5 6 cm transducer pulsed at 10 MHz. Data indicated increases of approximately 9 dBr (±1.67) maximally in ultrasound backscatter in patients who clinically responded to treatment. Patients assessed as responding poorly demonstrated significantly lower increases (2.3 ±1.7 dBr). Increases in 0-MHz intercept followed similar trends while increases in spectral slope were observed locally from tumor regions, demonstrating increases in tissue echogenicity.

Using spectral parameters, there was a clear separation of patients who had an ultimate complete clinical response at 4-6 months of chemotherapy from clinical partial-responders and nonresponders. This was apparent at week 4 for the midband-fit and 0-MHz intercept and at week 1 for the midband-fit parameter.

This study demonstrates the potential of ultrasound to quantify changes in tumors in response to cancer treatment administration in a clinical setting. The results indicate that such responses can be detected early during a course of chemotherapy

and should permit ineffective treatments to be changed to more efficacious ones, potentially leading to improved treatment outcomes.

9.2 **Use of quantitative ultrasound for monitoring and assessing thermal therapies** Jeremy Kemmerer, Goutam Ghoshal, Chandra Karunakaran, Xin Li and Michael Oelze, *Bioacoustics Research Laboratory, Department of Electrical and Computer Engineering, The University of Illinois at Urbana-Champaign, oelze@illinois.edu* (invited).

Currently, MRI-guided focused ultrasound is the accepted clinical means of conducting surgical procedures with high-intensity focused ultrasound (HIFU). However, MRI is expensive, requires specialized ultrasonic equipment for compatibility and is not highly accessible. Therefore, the development of inexpensive methods for monitoring HIFU treatment that can provide real-time feedback is highly medically significant. Several ultrasonic methods have been proposed for monitoring and assessing HIFU therapy but none of these techniques have supplanted MRI due to different weaknesses, i.e., most of these ultrasound-based techniques are not robust against motion artifacts or cannot map directly to temperature. Therefore, new approaches using ultrasound are required to overcome these roadblocks.

Quantitative ultrasound (QUS) techniques using the backscattered power spectrum and envelope statistics are hypothesized to be sensitive to changes in tissue properties due to HIFU exposure. Furthermore, these QUS techniques are robust against tissue motion because they depend on the absolute properties of the underlying tissue. Therefore, QUS techniques were used to monitor and assess thermal therapy *in vitro* and *in vivo*. Changes in scatterer properties were assessed during heating of tissues and after heating of tissues through spectral-based parameters, envelope statistics and the change in the backscattered energy. Freshly-excised liver samples, excised tumor samples and tumors in live rats were treated with heat (a water bath or HIFU). The capabilities of different QUS approaches were analyzed for their ability to track temperature changes induced in tissues from heating and to acutely assess damage to tissues from heating. Different QUS parameters were able to monitor thermal therapy and assess damage with different degrees of success depending on the frequency of the ultrasound and the method used for heating the sample. The results of this analysis and conclusions from these studies will be presented. Supported by NIH Grant R01-EB008992.

9.3 **Texture analysis on quantitative ultrasound images for early prediction of breast cancer therapy response**, Ali Sadeghi-Naini,[1, 2] Omar Falou,[1, 2] Naum Papanicolau,[1, 2] Sara Iradji,[1] Ervis Sofroni,[1] and Gregory J. Czarnota,[1, 2] *[1]Departments of Imaging Research/Radiation Oncology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada and [2]Departments of Medical Biophysics /Radiation Oncology, University of Toronto, Toronto, ON, Canada, ali.sadeghi-naini@sunnybrook.ca.*

Textural properties of breast ultrasound (US) images and quantitative ultrasound (QUS) parametric maps have been proposed for the first time to predict cancer therapy response early following the treatment commenced. Early prediction of cancer treatment response can offer a better prognosis for patients since treatment alterations can be made or salvage regimens instituted, i.e., it can facilitate personalized medicine in cancer-treatment procedures.

A clinical study was performed to investigate the efficacy of textural characteristics of quantitative ultrasound images to distinguish between clinically-responding and nonresponding patients, as early as a week after treatment initiation. Patients (n = 20) with locally-advanced breast cancer received neoadjuvant chemotherapy, as 'up-front' treatment, followed by a mastectomy with axillary-nodal clearance.

Data collection consisted of acquiring tumor ultrasound images and radiofrequency data prior to neo-adjuvant treatment onset and at four times during treatment (weeks 1, 4, 8 and preoperatively). In addition, pathology examinations were performed on resected specimens after mastectomy through three-dimensional whole-mount histopathology where data on size, grade, histologic subtype and tumor response were recorded.

Three texture features, namely contrast, correlation and homogeneity, were extracted from ultrasound b-mode images as well as parametric maps of midband fit and 0-MHz intercept. The relative changes of these nine texture features were calculated one week after the treatment commenced, compared to the pre-treatment scan. Statistical analysis performed (unpaired t-test, two-sided, $\alpha = 0.05$; p-values = 0.4016, 0.0018**, 0.0396*, 0.0229*, 0.0445*, 0.3177, 0.2544, 0.0051** and 0.0350*, for the nine texture features applied, respectively) suggested that six of the applied texture features exhibit statistically-significant differences between clinically-responding and nonresponding patients.

The promising results obtained implied a very good potential for texture features of quantitative ultrasound parametric maps, acquired only one week after the chemotherapy initiation, for detecting clinical response in the tumor, which may be completed many months later.

9.4 **Elastography evaluation of therapy response in breast cancer patients**, Omar Falou,[1, 2] Ali Sadeghi-Naini[1, 2] Sameera Prematilake,[1] Sara Iradji,[1] Ervis Sofroni,[1] Naum Papanicolau[1, 2] and Gregory J. Czarnota,[1 2] *[1]Imaging Research and Radiation Oncology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada and [2]Departments of Radiation Oncology and Medical Biophysics, University of Toronto, Toronto, ON, Canada, omar.falou@sunnybrook.ca.*

The aim of this study was to investigate for the first time the potential of elastography for monitoring treatment response of women with locally-advanced breast cancer (LABC) receiving neo-adjuvant chemotherapy.

Fifteen women receiving neo-adjuvant treatment for breast cancer had the affected breast scanned five times: before, 1

week, 4 weeks and 8 weeks following initiation of the treatment and prior to surgery. A Sonix RP (Ultrasonix Medical Corporation, Richmond, BC, Canada) ultrasound device was used to collect elastography data of the breast using a 10 MHz multielement transducer at 12 frames per second. The resulting elastography maps were displayed using 256-color mapping for each pixel according to the degree of strain. For each scan, the relative stiffness of the tumor (mean) was calculated by averaging the pixel intensities inside the tumor. Strain ratios and strain differences between tumor and surrounding tissue were also calculated. After completion of treatment, residual tumors were examined on whole-mount pathology slides and data on tumor size, grade, histologic subtype, content of cellularity and overall tumor response were obtained.

Patients who responded to treatment showed a decrease in strain ratios and strain differences compared to nonresponders. For responders, strain ratios and strain differences, typically decreased by 77±3% and 5±15%, within four weeks of treatment initiation, respectively. These changes were found to be statistically significant using a *t*-test (2 sided, $\alpha = 0.05$).

These promising results indicate that elastography has the potential to quantify changes in tumors during treatment and, hence, may provide a noninvasive method to monitor treatment response in breast-cancer patients.

9.5 **Ultrasound-guided characterization of ablated tissue using rf time series,** Farhad Imani,[1] Mohammad Daoud,[2] Andras Lasso,[3] Everett C. Burdette[4], Gabor Fichtinger,[1,3] Purang Abolmaesumi[5] and Parvin Mousavi,[1, 3] *[1]Electrical and Computer Engineering Department, Queen's university, ON, Canada, [2]Department of Computer Engineering, German Jordanian University, Jordan, [3]School of Computing, Queens University, ON, Canada, [4]Acoustic MedSystems Incorporation, IL and [5]Department of Electrical and Computer Engineering, University of British Columbia, BC, Canada, farhad@cs.queensu.ca* .

Thermal-ablation therapy is a minimally-invasive procedure for localized-cancer treatment. One of the current challenges in the application of this procedure in clinic is accurate monitoring of the ablation zone to avoid necrosis of healthy tissue and enable complete targeting of tumors. Recently, our group has proposed a tissue characterization method that uses rf time-series signals acquired from stationary tissue and transducer following continuous irradiation of the tissue over a few seconds. This method has been effectively used to distinguish between various tissue types, including healthy and cancerous prostate tissue. Here, we report the application of rf time series for characterizing ablated tissue. Rf time-series echo signals are acquired prior to and following high-intensity ultrasound ablation from *ex vivo* tissue samples. We calculate time and frequency domain features of the time series and correlate them with ablated and non-ablated tissue properties in a supervised framework. The results show promising classification accuracies for characterizing ablated tissue. We also investigate the physical process underlying the interaction of the time series with the tissue. It is shown that acoustic propagation in tissue increases temperature where its rate of change is tissue-dependent. The change in temperature, in turn, alters tissue sound speed and causes virtual displacement of backscattered signals. In summary, the results of this study suggest rf echo time series as a promising approach for characterizing ablation and capturing the changes in the tissue microstructure as a result of heat-induced necrosis.

10. THERAPY MONITORING 2

10.1 **Real-time monitoring of HIFU lesion formation using the interaction of light and sound,** Ronald A. Roy,[1] Puxiang Lai[2] and Todd W. Murray,[3] *[1]Dept. of Mechanical Engineering, Boston University, Boston, MA, [2]Dept. of Biomedical Engineering, Washington University in St. Louis, St. Louis, MO and [3]Dept. of Mechanical Engineering, University of Colorado at Boulder, Boulder, CO, ronroy@bu.edu* (invited overview).

This talk will focus on the acousto-optic (AO) sensing of optical variability in a diffusive medium – a relatively new technique based on the interaction of multiply-scattered coherent laser light with an ultrasonic field. The two waves 'mix' and the light emanating from the interaction region is phase modulated at the ultrasound frequency. This technique yields information on both the optical and acoustical properties of the interaction volume, which, since the optical field is diffuse, is determined by the dimension of the ultrasonic beam. We describe a system in which AO sensing can be used to monitor – in real time – lesion formation by high-intensity therapeutic ultrasound (HIFU). Here, the HIFU beam serves to both create the lesion and pump the AO response, thereby facilitating alignment of the sensing and treatment volumes and maximizing sensitivity. Results obtained with excised chicken breast show correlation between the change in AO signal level and the HIFU lesion volume. Supported by the Center for Subsurface Sensing and Imaging Systems via NSF ERC award no. EEC-9986821.

10.2 **Photoacoustic methods for noninvasively monitoring temperature changes during thermal therapy**, Daniel Gross, Jonathan Mamou and Parag V. Chitnis, *Riverside Research, New York, NY, dgross@riversideresearch.org.*

Background: High-intensity focused ultrasound (HIFU) has enormous clinical potential for noninvasive treatments of malignant and benign tumors and cardiac disease. However, clinical acceptance of HIFU is severely inhibited by a lack of reliable, noninvasive, cost-effective and patient-friendly means of monitoring localized temperature changes in tissue.

Objective: The purpose of this study was to establish the feasibility of an imaging system that combines photoacoustic imaging (PAI) with B-mode ultrasound imaging (USI) for visualizing local anatomy and simultaneously monitoring temperature changes in real-time during HIFU exposures.

Methods: The focus of a 60-mm diameter, 90-mm focal length 1.5-MHz HIFU transducer was a orthogonally aligned with the output of a 780-nm laser that delivered 40 mJ in a 5-ns pulse. The laser pulse excited a thermal expansion of the tissue, leading to a PA pressure wave that was recorded by a 5-MHz, 128-element, linear, diagnostic transducer (Philips L7-5) driven by the Verasonics ultrasound engine, which was also aligned orthogonally to the HIFU and laser beams. The HIFU transducer was driven in two modes: continuous wave (CW) mode and pulsed mode; and two focal intensities: 1 kW/cm^2 (cavitation absent) or 4 kW/cm^2 (cavitation present). In all cases, a thermocouple was present in the phantom (although not always at the HIFU focus) to validate the results. Phantoms that mimic the optical and acoustic properties of several human tissues were prepared and placed at the co-aligned focus of all three devices. For each laser pulse, the diagnostic transducer would record one frame of PA data and then perform a standard imaging pulse-echo data acquisition.

Results: The PA data was rearranged into matrixes corresponding to position and laser pulse number and the single-value-decomposition (SVD) of these matrixes were found. The eigenvector that corresponded to the PA amplitude recorded during CW HIFU treatment and also during off cycles of pulsed HIFU treatment exhibited a direct correlation with the temperature in and around the HIFU focus as measured by the thermocouple and as modeled using the bio-heat equation. Despite the presence of broadband, cavitation-associated noise in the CW HIFU case, our algorithm and method was able to extract the local temperature accurately with a root-mean-squared error of less than 5°C.

Conclusion: The photoacoustic-signal amplitude provides a viable, noninvasive method for monitoring temperature changes associated with thermal-ablative therapy. Supported by the Riverside Research Internal Research and Development Fund.

10.3 **Quantitative ultrasound imaging for monitoring HIFU application**, Goutam Ghoshal, Jeremy P. Kemmerer, Chandra Karunakaran and Michael L. Oelze, *Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, gghoshal@illinois.edu*.

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

Experiments were conducted on fresh liver samples from rats and lesions were formed using a HIFU system (1-MHz, f/1.2). *In-vivo* experiments were also conducted on rat mammary adenocarcinoma (MAT) tumors grown in rats. A needle thermocouple was inserted into the sample to monitor temperature elevation. Backscattered time-domain waveforms were recorded using a clinical-imaging system (Ultrasonix, L14-5 linear array) during the HIFU application and backscatter coefficients were estimated using a reference-phantom technique. Two parameters were estimated from the backscatter coefficient (effective scatterer diameter (ESD) and effective acoustic concentration (EAC)) and two parameters were estimated from the envelope statistics (k parameter and μ parameter) of the backscattered echoes.

At maximum temperature elevation the ESD, EAC, k parameter and μ parameter changed in the treated region of the liver samples by 20%, 20%, 15% and 15%, respectively, compared to the untreated region. Similarly, for the *in-vivo* experiments, the ESD, EAC, k parameter and μ parameter changed in the treated region of the tumor by 25%, 40%, 30% and 30%, respectively, compared to the untreated region at maximum temperature elevation. Furthermore, changes in QUS parameters followed the shape of the temperature profile recorded by the thermocouple. These results suggest that QUS techniques could be used for noninvasive thermometry of HIFU. Supported by NIH Grant R01-EB008992.

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

High-Intensity Focused Ultrasound (HIFU) is a promising modality for noninvasive therapy but challenges remain for monitoring and assessment of HIFU treatment. Quantitative Ultrasound (QUS) is a diagnostic modality with the potential to detect changes in tissue microstructure resulting from therapeutic treatment. In this study, 18 rodent tumors (MAT) were exposed to focused ultrasound produced by a 1-MHz single-element transducer (f/1.2) for 1 minute at several intensities. Tumor assessment scans were performed pre- and postexposure using clinical (Ultrasonix L14/5, 3-9 MHz) and small animal high-frequency (VisualSonics MS-200, 10-18 MHz) ultrasound systems. For comparison with QUS assessment, tissue damage was also quantified by tumor histology slides and TTC vital staining.

The resulting data were processed to estimate the backscatter coefficient (BSC), effective scatterer diameter (ESD) and effective acoustic concentration (EAC) using a spherical Gaussian-scattering model and a reference-phantom technique. The BSC versus frequency was observed to increase with the highest treatment intensity across most of the analyzed frequency band. The increase in the BSC resulted in an increase in EAC of 3 dB from untreated to treated tumors. ESD changed by less

than 5% from untreated to treated tumors. The results of this study are promising and suggest that QUS can noninvasively assess HIFU therapy. The work was supported by NIH Grant R01-EB008992.

11. REVIEW, PRIORITIES AND FUNDING OF NIH PROGRAMS

11.1 **NIH/CSR,** Lee Rosen, *Center for Scientific Review, NIH* (invited).

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

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

PANEL DISCUSSION