UITC ABSTRACTS 2014

Monday morning

1. LIGHT AND SOUND 1

1.1 **Lights, sound, action: illuminating biological structure and function at different length scales by eavesdropping at 1 to 1000 MHz**, Eric M. Strohm[1], Tae-Hoon Bok[1], Lauren A. Wirtzfeld[1], Eno Hysi[1], Gregory J. Czarnota[2] and Michael C. Kolios[1], *[1]Department of Physics, Ryerson University, Toronto, ON, Canada, M5B 2K3 and [2]Radiation Oncology and Imaging Research, Sunnybrook Health Sciences Centre, Toronto, ON, Canada M4N 3M5, mkolios@ryerson.ca* (invited overview)

Photoacoustic imaging is an emerging imaging modality that offers high sensitivity imaging with ultrasonic resolution. In photoacoustic imaging, the absorbed energy from an electromagnetic pulse (typically laser light) causes localized heating and the resulting thermal expansion creates a pressure wave that can be then detected using existing ultrasound technologies. The transient thermoelastic expansion of optically-absorbing structures creates wideband acoustic emissions (in the ultrasonic range: from MHz to GHz) that can then be detected using ultrasound detection technologies. Using this methodology, spatial maps of optical absorption can be formed based on the intensity of the photoacoustic signals. However, as in ultrasound tissue characterization, analysis of the frequency content of the photoacoustic waves generated can provide information about the (many times nonresolvable) structures that generated the photoacoustic waves. In this presentation, the physics of photoacoustic imaging will be introduced and recent biomedical applications presented. Our recent work on analysis of the wideband photoacoustic signals from single red blood cells, single blood vessels and vascular trees will be presented. In particular will show how analysis of the power spectra of the optically-illuminated specimens can be used to image and characterize vascular tissue from the mm scale (using MHz ultrasound detectors) to the μm scale (using GHz ultrasound detectors). Our recent efforts in combining conventional ultrasound tissue characterization techniques (using pulse-echo ultrasound), with photoacoustic tissue characterization techniques (applying similar signal analysis methodology on the coregistered photoacoustic signals) will be presented as well as applications in small-animal imaging of cancer-treatment response.

1.2 **Three-dimensional laser optoacoustic and laser ultrasound imaging system for biomedical research**, Sergey A. Ermilov, *TomoWave Laboratories, Inc., Houston TX, sae@tomowave.com* (invited)

Tomowave Laboratories develops a novel three-dimensional (3D) imaging system that combines optoacoustic tomography (OAT) and laser ultrasound tomography (LUT) resulting in coregistered maps of tissue optical absorption, speed of sound (SoS), and acoustic attenuation (AcA). Optoacoustic imaging and ultrasonic imaging are naturally combined in a dual modality system, since they use very similar detection principles and equipment. The utilized 3D full-aperture OAT unit is based on an instrument that already proven high-quality visualization of central and peripheral vasculature as well as blood-rich organs in small laboratory animals. The operation of optoacoustic imaging component is based on the optoacoustic (photoacoustic) effect that can be briefly described as an instantaneous generation of mechanical stress caused by optical absorption of short (100 ns or less) laser pulses. The optoacoustic imaging component employs spectrally-selective optical contrast of biological tissues and ultrasonic detection of the resultant acoustic waves to map the absorbing tissue structures with submillimeter resolution, even up to several centimeters deep. The reconstructed 3D optoacoustic images could provide information valuable for preclinical cancer research, angiography, studies of organ-specific pathologies

that change local blood content and/or oxygenation, monitoring of thermal therapy and longitudinal studies on biodistribution of optoacoustic contrast agents such as carbon nanotubes and metal plasmonic nanoparticles. Some notable technological features of the OAT system component include: (1) a 360° rotational scan of a mouse with respect to an arc-shaped array of wideband ultrasonic transducers, (2) a Q-switched laser excitation used to establish optoacoustic illumination pattern appropriate for deep tissue imaging with a tunable (730-840 nm) output wavelengths operated at 10 Hz pulse repetition rate and (3) a 532 nm wavelength output, which is mostly absorbed within a narrow superficial layer of skin and is used to outline the visualized biological object.

The purpose of LUT unit is to create three-dimensional maps of speed of sound and acoustic attenuation, which can provide additional diagnostic information about visualized object. Further, the reconstructed LUT images can be employed by an optoacoustic reconstruction algorithm to compensate for acoustic wavefield aberration and thereby improve the accuracy of the reconstructed images of the absorbed optical energy. Laser-generated ultrasound has advantages of clean nonreverberating broadband pulses, ideal for time-of-flight detection and ultrasound spectral analysis. The LUT is performed using an array of broadband laser ultrasound emitters arranged opposite to the array of transducers. This imaging geometry allows reconstruction of volumes that depict SoS and AcA distributions from the measured time of flight and transmission data.

The performance of the system is demonstrated through multiwavelength functional optoacoustic imaging coregistered with the speed of sound imaging of tissue simulating phantoms and live mice.

1.3 **Advances in the development of a fully-integrated photoacoustic micro-ultrasound system**, Andrew Needles, Jithin Jose, Jim Mehi, Andrew Heinmiller, Minalini Lakshman and Desmond Hirson, *FUJIFILM VisualSonics, Inc., Toronto, Canada, aneedles@visualsonics.com* (invited)

Introduction: Previous reports have described the development of a combined micro-ultrasound (μUS) and photoacoustic (PA) system.[(1)] The multimodal nature of this system is its main advantage; however, as with any imaging system there are application-dependent limitations with image quality and imaging depth. The goal of this current study is to evaluate new hybrid imaging techniques using the combined system to help overcome some of these limitations. New techniques include rotational compound imaging (RCI), a new light-coupling stage and spectral unmixing. This talk with focus on initial results that demonstrate how these new techniques, used separately or in combination, can improve the overall sensitivity of small animal imaging.

Methods: Imaging was performed on a Vevo® LAZR system (VisualSonics, Toronto). For RCI, a motorized stage was developed to rotate the transducer through the imaging plane. Data was collected at multiple angles and processed into a compounded image. The new light coupling stage involved a modification to an existing 21 MHz integrated fiber optic transducer (model LZ250), whereby one third of the overall fiber bundle was redirected to an external fiber. For small animal imaging, this external fiber was mounted under a customized quartz imaging platform, such that the light was delivered from underneath the animal and aligned with the integrated LZ transducer from above. Finally, spectral unmixing algorithms were implemented and used in combination with the new image acquisition techniques for detection of endogenous haemoglobin and an exogenous contrast agent (IR800CW, LI-COR Biosciences). All of the new imaging techniques were evaluated *in vivo* in healthy adult mice (kidney, liver, spleen, hind limb) and compared to the standard imaging approach, using procedures that were conducted in accordance local ethical approval.

Results: RCI improved overall image quality and improved directivity of detection in the hind-limb example. Vessels that appear in individual angled image planes clearly become continuous with RCI. The new light-coupling stage improved imaging depth by up to 50% as compared to the standard imaging technique. Finally, spectral unmixing improved sensitivity to IR800 dye by up to 5 dB. When used in conjunction with the new light coupling stage, the detection of contrast agents *in vivo* using PA imaging is significantly improved.

Conclusions: Advances in the development of a combined μUS/PA system have been demonstrated. These advances can lead to improvement in image quality and imaging depth. When used in conjunction

with spectral unmixing, even greater gains in sensitivity are achievable, which may lead to new applications in the field of photoacoustic imaging.

(1) Needles et al. *IEEE UFFC* (May 2013).

1.4 **Non-contact photoacoustic imaging utilizing interferometric techniques**, Thomas Berer[1,2] and Armin Hochreiner[2], [1]*Research Center for Non-Destructive Testing GmbH (RECENDT), Altenberger Strasse 69, 4040 Linz, Austria and* [2]*Christian Doppler Laboratory for Photoacoustic Imaging and Laser Ultrasonics, Altenberger Strasse 69, 4040 Linz, Austria, thomas.berer@recendt.at* (invited)

Photoacoustic imaging (PAI) is a noninvasive imaging modality that allows structural, functional and molecular imaging. Imaging relies on the photoacoustic effect, which describes conversion between light and acoustic waves due to absorption of electromagnetic waves and localized thermal expansion. By recording the generated ultrasonic waves, the initial distribution of absorbed energy can be assessed. For recording the ultrasonic waves in PAI, usually contacting piezoelectric transducers are used. These detectors have to be coupled to the sample by a coupling agent. While this is no major limitation for many applications, there are cases where contacting means should be avoided, e.g., in burn diagnostics or for in-line material inspection. For interoperative imaging, contacting transducers hinder the operation. Also, for many kinds of surgeries, contacting means are prohibited, e.g., in brain surgery. As an alternative to piezoelectric transducers, interferometric detection schemes can be used to acquire the ultrasonic signals.

We report on non-contact photoacoustic imaging using interferometric techniques. In these methods, the motion of a surface is measured remotely by means of interferometry. We report on two different implementations of non-contact photoacoustic imaging setups. The first implementation uses a two-wave mixing interferometer to detect the ultrasonic movements. Dynamic hologram formation in a photorefractive crystal is used to match the wave fronts of a signal and reference beam. Thus, the setup is especially suited for detection on scattering surfaces. The second setup is based on an enhanced Mach-Zehnder interferometer with optical amplification, whereby the major part of the interferometer is realized in a fiber-optic network. The fiber optics allows a simple, compact and flexible system. As a detection laser, we use a low-power laser source with an eye-safe wavelength of 1550 nm. The realization of the detection optics in a fiber-optic network allows straightforward addition of an optical coherence tomography (OCT) setup. Non-contact PAI and OCT are realized in fiber-optic networks, thus allowing multiplexing of both modalities into the same scanning head and simultaneous measurements of both modalities. Supported by the Austria science fund (FWF), project numbers P25584-N20 and S10503-N20, and the Christian Doppler Research Association.

1.5 **Monitoring and assessment of high-intensity focused ultrasound therapy by acoustical and optical means**, Ronald A. Roy, *Department of Engineering Science, University of Oxford, Oxford, UK, ronald.roy@hmc.ox.ac.uk* (invited overview)

Exposure to high-intensity focused ultrasound (HIFU) can result in rapid and significant tissue heating by direct acoustic absorption and certain cavitation-mediated physical processes, leading to cell death and the formation of a thermal lesion. When properly controlled, this process has therapeutic value, for it is possible to selectively damage targeted tissue volumes (such as tumors) remotely and noninvasively. The gold standard for "monitoring" lesion formation is MR thermometry; however, this is an expensive process and provides only an indirect means for assessing treatment in real time. In this paper, we review other, more direct, means for monitoring HIFU therapy and assessing outcomes. We compare and contrast active and passive acoustical methods (B-mode, cavitation noise diagnostics, ARFI) with a new optoacoustic sensing method designed to detect the onset and extent of lesion formation based on changes in the optical properties of thermally-damaged tissue.

2. TISSUE PARAMETERS 1

2.1 **Ultrasound quantitative characterization of vitreous floaters and correlation with vision contrast sensitivity**, Jonathan Mamou[1], Christianne A. Wa[2,3], Kenneth M.P. Yee[2,3], Ronald H. Silverman[1], Alfredo A. Sadun[2], Jeffrey A. Ketterling[1] and J. Sebag [2,3], *[1]Frederic L. Lizzi Center for Biomedical Engineering, Riverside Research, New York, NY, [2]Doheny Eye Institute, Los Angeles, CA, [3]VMR Institute, Huntington Beach, CA and [4]Department of Ophthalmology, Columbia University Medical Center, New York, NY, jmamou@riversideresearch.org*

The contrast sensitivity function (CSF) has been shown to decrease in eyes of patients complaining of floaters, inhomogeneities occurring in the normally optically transparent-vitreous. In this study, quantitative ultrasound characterization methods were developed to assess floaters and examine correlation with CSF.

Twenty-five eyes from 20 subjects with mild to severe floaters were evaluated with the Freiburg acuity contrast test. Contrast sensitivity was quantified in Weber units (%W = 100[$L - L_b$]/ L, where L and L_b represent the luminance of the feature and background. respectively). Each eye was then scanned using a customized Quantel Aviso ultrasound system. Scans were obtained with open eyelids in three positions (nasal longitudinal, inferotemporal longitudinal and inferotemporal transverse). The ultrasound transducer had a 15-MHz center frequency, a 20-mm focal length and 7-mm aperture. Each ultrasound dataset consisted of 100 frames of log-compressed envelope data before scan conversion and video display. These data were sampled at 40 MHz with 8-bit accuracy. All the settings were kept the same on the Aviso system to allow for direct comparison of the data. Within each 2D ultrasound image, two regions of interest (ROIs) were analyzed (whole-central vitreous and premacular posterior vitreous). Each ROI was processed to yield three estimates (i.e., energy, *E*, mean amplitude, *M* and *P50*); *E* and *M* are defined as the mean of squared and raw binary values within the ROI, respectively, and *P50* is defined as the percentage of the ROI filled by echoic pixels above a noise threshold. These estimates were then averaged over the entire 100-frame dataset (frames containing obvious artifacts were excluded). Statistical analyses (Pearson correlation and associated *p* values) were performed to evaluate how *E*, *M* and *P50* correlated with CSF.

Over the 25-eye database, CSF ranged from 1.19%W (normal) to 6.32%W (worst). Results showed that correlations above 0.49 (with $p<0.05$) could be obtained for several estimates and all scan positions within the whole-central ROI were analyzed. The highest correlation (i.e., 0.59 with $p<0.01$) was obtained for the *M* estimates in the inferotemporal longitudinal position. Correlations significantly dropped and were found nonsignificant for all the analyses performed using the premacular posterior vitreous region.

These initial results suggest that estimates correlated with CSF and that ultrasound could become a valuable option to quantitatively assess the structural abnormalities underlying the functional deficit associated with vitreous floaters.

2.2 **Added value of statistical modeling of ultrasound backscatter properties in the management of breast lesions**, Isabelle Trop[1], François Destrempes[2], Mona El Khoury[1], André Robidoux[3], Louis Gaboury[4], Louise Allard[2], Boris Chayer[2] and Guy Cloutier[2], *[1]Department of Radiology, Breast Imaging Center, University of Montreal Hospital, [2]Laboratory of Biorheology and Medical Ultrasonics, University of Montreal Hospital Research Center, [3]Department of Surgical Oncology, Breast Care Center, University of Montreal Hospital, and [4]Department of Pathology, University of Montreal Hospital, Montreal, Qc, Canada, guy.cloutier@umontreal.ca*

Purpose: To determine how well characterization of solid breast lesions identified at ultrasound can be performed with a mathematical model based on the statistical backscatter properties of tissues.

Materials and Methods: This study received institutional review board approval and all subjects signed an informed consent form. Ninety-one women (mean age 50, range 22-82) with 98 indeterminate (BIRADS 3-5) solid breast lesions (mean size 13.1 mm, range 4-52 mm) were enrolled. Prior to biopsy, additional radiofrequency ultrasound images were obtained with a Terason t3000 scanner, including a 3-

second cine sequence. The lesions were segmented manually and parameters of the homodyned K-distribution (α, k, μ_n) were extracted for three regions: the intratumoral zone, a 3 mm supratumoral zone and a 5 mm infratumoral zone. The Mann-Whitney rank sum test was used to identify parameters with the best discriminating value, yielding intratumoral α, supratumoral k and infratumoral μ_n.

Results: The 98 lesions were classified as follows: 2 BIRADS 3, 48 BIRADS 4A, 16 BIRADS 4B, 7 BIRADS 4C and 25 BIRADS 5. There were 24 cancers (24.5%). The area under the ROC curve was 0.76. Overall, 23.0% of biopsies could have been spared. Limiting analysis to lesions with a lower likelihood of malignancy (BIRADS 4A-4B), this percentage increased to 25.8%. Among benign lesions, the model correctly classified 10/38 (26.3%) fibroadenomas, 3/20 (15%) fibrocystic changes and 3/8 (37.5%) stromal fibrosis.

Conclusion: The statistical model performs well in classifying solid breast lesions at ultrasound, with the potential of avoiding one in four biopsies without missing any malignancy.

2.3 **Noninvasive evaluation of locally-advanced breast cancer response to neoadjuvant chemotherapy using quantitative ultrasonic backscatter parameters,** Lakshmanan Sannachi[1, 2], Hadi Tadayyon[1,2], Ali Sadeghi-Naini[1,2], Michael Oelze[3] and Gregory Czarnota[1,2], *[1]Department of Radiation Oncology and Imaging Research – Physical Sciences, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [2]Department of Radiation Oncology and Medical Biophysics, University of Toronto, Toronto, ON, Canada and [3]Bioacoustics Research Laboratory, Department of Electrical and Computer Engineering, University of Illinois, Urbana, IL, lakshmanan.sannachi@sunnybrook.ca*

Background: In previous studies, imaging techniques based on analysis of ultrasonic backscatter have been successfully used to characterize different types of tissue. Here we demonstrate the potential of quantitative ultrasound method to assess tumor microstructure and differentiate treatment responders and nonresponders early on during chemotherapy, using estimates of ultrasound backscatter characteristics.

Methods: Tumor responses to neoadjuvant chemotherapy in 30 patients with locally-advanced breast cancer were examined using quantitative ultrasound with center frequency ~7 MHz (bandwidth range: 4.5 – 9 MHz). Patients were classified as responders or nonresponders based on their ultimate clinical and pathological response. Ultrasound backscatter parameters, integrated backscatter coefficient (IBC), average scatterer diameter (ASD) and average acoustic concentration (AAC), were estimated from regions-of-interest in tumors prior to treatment onset and at four times during neo-adjuvant chemotherapy treatment (weeks 1, 4, 8 and prior to surgery). The patients were followed clinically after their treatment with a mean follow-up period of 35 ± 10 months for recurrence-free survival.

Results: Results demonstrated that amongst all parameters, AAC was the best indicator of tumor response early after starting treatment. The AAC parameter increased substantially in responders as early as one week and attained a maximum of 7 dB/cm^3 at week 8. Similarly, the IBC parameters increased in responders and changes were significant at week 4. Nonresponders did not show any significant changes in all the backscatter parameters over treatment times. The best prediction of treatment response was achieved with the combination of AAC and ASD at week 4 (82% sensitivity, 100% specificity and 86% accuracy) of 12-18 weeks of treatment. The survival of responding patients determined based on ultrasound parameters was higher than nonresponding patients (p = 0.043).

Conclusions: This study demonstrates that the backscatter parameters derived from ultrasound backscatter power spectrum have the potential for quantifying histological changes in tumors during treatment noninvasively and distinguishing treatment responders and nonresponders as early as 1 week from the start of treatment. This is important for the customization cancer therapies for nonresponding patients early after treatment initiation and can potentially increase their survival rate. This finding suggests that it is possible to use this method to aid clinicians in making decisions to modify cancer therapy early on and personalize treatment.

2.4 **Simultaneous evaluation of changes in tumor stiffness and bioacoustic characteristics in breast cancer patients receiving chemotherapy using quantitative ultrasound spectroscopy and elastography**, Ali Sadeghi-Naini[1,2], Michael C. Kolios[3] and Gregory J. Czarnota[1,2], *Department of*

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Background: Development of tumor response to cancer treatments frequently results in microstructural and gross functional alterations in tumors, accompanied by measurable changes in tumor bioacoustic and biomechanical properties. Changes in such characteristics of tumors can be evaluated using imaging techniques including quantitative ultrasound spectroscopy and elastography. The quantification of these microscopic changes in tumor physiology has a high potential for accurately predicting ultimate tumor response early on during a course of treatment. In addition, investigating the relationship of changes in different characteristics of tumor in response to treatment is important, as it can lead to a better understanding of the mechanisms behind development of response in malignant tissues.

Methods: A clinical study was undertaken monitoring simultaneously changes in bioacoustic characteristics and stiffness of tumor in responses to cancer treatment, using quantitative ultrasound spectroscopy and elastography techniques. Patients (n = 13) with locally-advanced breast cancer received anthracyline and taxane-based chemotherapy treatments over four to six months. Data collection consisted of acquiring ultrasound B-mode and strain images and radiofrequency data from the tumor region, prior to treatment onset and at four times during neoadjuvant chemotherapy (weeks 0, 1, 4, 8 and pre-operatively). Data collection was carried out using an Ultrasonix-RP and an L15-5 6cm transducer. The majority of patients went on to have a modified radical mastectomy and correlative whole mount histopathology.

Results: Results obtained indicated considerable increases in ultrasound spectral backscatter power, followed by decreases in tumor stiffness, in patients who clinically responded to treatment. This was accompanied by significant increases in quantitative ultrasound spectral parameters such as mid-band fit and 0-MHz intercept, as well as in tumor strain ratio. Patients categorized as poor responders clinically demonstrated significantly lower increases, no change, or even decreases in quantitative ultrasound spectral parameters and tumor strain ratio. Based on the results obtained from linear discriminant analyses, mid-band fit and 0-MHz intercept, in a combination, could predict treatment response of patients with 80% sensitivity and 87.5% specificity at week 1 and with 100% sensitivity and 62.5% specificity at week 4 after the start of treatment. Tumor strain ratio could differentiate between treatment responding and non-responding patients with 60% sensitivity and 50% specificity at week 1 and with 80% sensitivity and 75% specificity at week 4 of treatment. These quantitative ultrasound spectral and elastographic parameters in a hybrid profile could separate the two patient populations with 80% sensitivity and 75% specificity at week 1 and with 100% sensitivity and 75% specificity at week 4 after the start of treatment. In addition, whereas no considerable correlation was found between changes in tumor echogenicity and alteration in tumor stiffness at week 1, significant inverse correlations were observed after 4 weeks of treatment between such variations in characteristics of tumor (r = -0.71, p = 0.007).

Conclusions: This study demonstrates the potential of simultaneous quantitative ultrasound spectroscopy and elastography to quantify changes in tumors in response to cancer treatment administration in a clinical setting. The results indicate that these two imaging modalities can be complementary in this context and can detect patient responses early on during a course of chemotherapy. This can permit ineffective treatments to be changed to more efficacious ones and potentially lead to improved treatment outcomes.

2.5 **Quantitative ultrasound assessment of tumor responses to chemotherapy using a time-integrated multiparameter approach**, Hadi Tadayyon[1,2], Ali Sadeghi-Naini[1,2], Lakshmanan Sannachi[1,2] and Gregory Czarnota[1-3] *[1]Department of Medical Biophysics, University of Toronto, Toronto, Canada, [2]Physical Sciences, Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, Toronto, ON, Canada and [3]Department of Radiation Oncology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, gregory.czarnota@gmail.com*

Background: Conventional assessment of tumor response to anti-cancer therapy is based on measurements of tumor size using the RECIST criteria. However, these measurements are typically a late indicator of tumor response (detectable after several weeks to months). There is currently no standard clinical method to assess tumor response early in the course of therapy. In this study, a quantitative ultrasound (QUS) method was used to characterize treatment responding (N = 40) and nonresponding (N = 20) tumors in breast cancer patients receiving neoadjuvant chemotherapy by examining their frequency-dependent attenuation and backscatter properties. Seven QUS parameters were investigated for this purpose: attenuation coefficient estimate (ACE), spacing among scatterers (SAS), linear-regression spectral parameters (spectral midband fit (MBF), spectral slope (SS), and 0-MHz intercept (SI)), and backscatter coefficient (BSC) parameters (average scatterer diameter (ASD), and average acoustic concentration (AAC)) derived from the Gaussian form factor.

Methods: Radiofrequency ultrasound data were collected from 60 breast cancer patients prior to treatment and at 1 week, 4 weeks and 8 weeks after the onset of their several-month treatment, using a clinical ultrasound scanner operating a ~7 MHz linear array probe. ACE, SAS, spectral and BSC parameters were computed from 2 × 2 mm rf segments within the tumor region of interest (ROI) and averaged over all segments to obtain a mean value for the ROI. The results were separated into two groups -- responders and nonresponders -- based on the ultimate clinical/pathologic response based on residual tumor size and cellularity. Quadratic discriminant analyses were performed using single parameter and multiparameter approaches to evaluate the ability to correctly classify a patient's response.

Results: Using a single-parameter approach, the best prediction of response was achieved using the ACE parameter (76% accuracy at week 1). In general, more favorable classifications were achieved using spectral parameter combinations (82% accuracy at week 8), compared to BSC parameter combinations (73% accuracy). Using the multiparameter approach, the best prediction was achieved using the set [MBF, SS, SAS, ACE] and by combining week 1 QUS data with week 4 QUS data to predict the response at week 4, providing accuracy as high as 91%.

Conclusions: This study demonstrated the importance of the history of ultrasonic signatures from an individual patient in order to obtain an accurate response measurement at a particular time. Patient responses were better predicted using linear-regression spectral parameters since breast tumors have complex scattering structures and the Gaussian scattering model used here was rather simplistic. Yet, attenuation and scatterer spacing played an important role in differentiating responding tumors from nonresponding ones. The proposed QUS method may potentially provide early response information and guide cancer therapies on an individual patient basis.

Monday afternoon

3. LIVER FIBROSIS

3.1 **Hepatic fibrosis: clinical significance and current evidence**, Hitoshi Maruyama, Tadashi Yamaguchi, and Osamu Yokosuka, *Department of Gastroenterology and Nephrology, Chiba University Graduate School of Medicine, Japan, maru-cib@umin.ac.jp*

The grade of hepatic fibrosis is a definitive indicator of the severity of liver disease. The most advanced stage of chronic liver disease is cirrhosis, which confirms a poor prognosis for patients because of the risk of developing hepatocellular carcinoma, portal hypertension and hepatic failure. Clinical management of these patients should be implemented based on the stage of fibrosis.

Liver biopsy remains the gold standard for the evaluation of the grade of hepatic fibrosis. However, its application for patients with chronic liver disease is sometimes controversial because it is invasive in the patients with impaired coagulation due to liver dysfunction and it has a possibility of sampling error in the

liver due to heterogeneously-distributed fibrosis. The long-term clinical course of chronic liver disease may require an available noninvasive method that can be applicable in clinical practice.

Noninvasive predictors of the hepatic fibrosis grade are emerging, such as biochemical markers and imaging tools. Particularly, application of ultrasound may be presumed reasonable as it is the modality most frequently used in the management of chronic liver disease. However, the diagnostic accuracy of conventional ultrasound for cirrhosis (62-84%) is not high in alcoholic and/or viral cirrhotic patients.

This presentation overviews the current evidence about the clinical significance of hepatic fibrosis and discusses the recent technique for the grading fibrosis using radiological imaging modalities.

3.2 **Tissue characterization of liver fibrosis using multiple frequencies**, Tadashi Yamaguchi[1], Kenji Yoshida[1], Jonathan Mamou[2] and Hitoshi Maruyama[3], *[1]Center for Frontier Medical Engineering, Chiba University, Japan, [2]Lizzi Center for Biomedical Engineering, Riverside Research, 156 William St., 9th floor, New York, NY 10038 and [3]Department of Gastroenterology and Nephrology, Graduate School of Medicine, Chiba University, Japan, yamaguchi@faculty.chiba-u.jp* (invited)

The development of a quantitative diagnostic method for liver fibrosis using ultrasound would be highly medically significant. Detection and classification of tissue disease using the characteristics of the ultrasound echo signal, such as power spectrum, texture parameters, local attenuation and statistical characteristics requires an understanding of the relationship between complicated scatterer structures and the echo signal.

In our research, a quantitative ultrasound (QUS) method for detecting and classifying liver fibrosis on the basis of the estimation of scatterer density from the statistical analysis of echo envelopes is proposed. Fibrotic tissue is inhomogeneous; therefore, its envelope probability density function (PDF) cannot be accurately modeled by a single PDF. Additionally, some regions have variable scatterer densities. In order to detect and characterize the fibrotic liver quantitatively, the relationship between the scatterer distribution and the PDF of echo envelopes of inhomogeneous scattering media were fitted by multi-PDFs model. The validity of the theory of multi-PDFs model has been verified by computer simulations, and the analysis parameters in the simulated fibrotic tissue were successfully used to characterize liver fibrosis in clinical data sets.

Additionally, it must be devised to understand the complex interaction between ultrasound and tissue and scattering models based on tissue properties for application to definitive diagnosis and high accuracy of the QUS method. Towards this aim, speed-of-sound (SOS) and attenuation from three types of rat livers (normal, fatty and fibrosis) were measured with a scanning acoustic microscope using transducers with center frequencies from 1-MHz to 250-MHz. Results indicated that SOS and attenuation measured with each transducer showed the following trend. Variability in SOS and attenuation values of normal liver was much smaller than other livers at any frequencies. In the fatty liver, SOS was 20 m/s slower and the attenuation was 1.0 dB/cm/MHz larger than in the normal liver. In fibrosis, SOS and attenuation had values between those of normal and fatty liver. Additionally, the relation between the pathologic state of liver and SOS and attenuation was investigated. Correlation between the ultrasound wavelength and the distribution and size of fat or fiber deposits in the liver was investigated using the corresponding stained-histology photomicrograph.

3.3 **Liver stiffness and controlled attenuation-parameter measurements using shear-wave-based quantitative elastography**, Magali Sasso, Véronique Miette and Laurent Sandrin, *Echosens, Research Department, Paris, France, laurent.sandrin@echosens.com* (invited)

Introduced in 2003, Vibration-Controlled Transient Elastography (Fibroscan®, Echosens, France) disruptive technology is now widely used in routine clinical practice and research. Indeed, a large body of evidence demonstrated that liver stiffness measurement significantly correlates with liver fibrosis. Other factors, such as chronic inflammation, mechanic cholestasis and liver congestion have been shown to increase liver stiffness.

Recently, a new parameter has been introduced: Controlled Attenuation Parameter (CAP).[(1)] CAP is a measure of ultrasound attenuation developed to assess steatosis. With CAP, Fibroscan® can help assessing both liver fibrosis and steatosis.

In this paper, the different quantitative shear-wave based techniques will be presented. Advantages and limitations of each technique will be described in terms of technology, clinical results, examination procedure, etc. The performance of CAP will be detailed and we will show how it can be enhanced using a dedicated liver-guidance tool.

(1) Sasso et al, Ultrasound Med Biol *36*, 1825-1835 (2010).

3.4 **Viscoelastic characterization of renal transplants**, Matthew W. Urban, Carolina Amador, Ivan Z. Nenadic and James F. Greenleaf, *Department of Physiology and Biomedical Engineering, Mayo Clinic College of Medicine, Rochester, MN 55905, urban.matthew@mayo.edu* (invited)

Renal transplantation is one therapy for end-stage renal disease. In current clinical practice, protocol biopsies are used to monitor the health of the renal transplant over time. Renal biopsies are an invasive process associated with some complications. Elasticity-imaging methods offer a noninvasive means to examine soft tissues and their material properties. Shear-wave-based measurements can be used to evaluate viscoelastic properties.

Shear-wave measurements were performed in 14 patients with renal transplants and the native kidneys in 6 control subjects. The study was approved by the Mayo Clinic Institutional Review Board. A Verasonics system (Verasonics, Inc., Redmond, WA) was equipped with a linear and curved-array transducer to make shear-wave measurements generated by radiation force. The shear-wave motion was measured using compound plane-wave imaging.

The group velocity of the shear waves was estimated using a method based on the Radon transform. A two-dimensional fast Fourier transform method was used to evaluate the wave speed dispersion. Shear-wave attenuation was also characterized. A Voigt model was fit to the phase velocity data to evaluate the shear elasticity and shear viscosity. The group velocity was correlated with serum creatinine levels from all subjects and observed a positive correlation. Additionally, we compared the group velocity values with the interstitial fibrosis Banff biopsy scores from the patients with renal transplants.

Shear-wave-based measurements could provide measurements of elastic and viscoelastic properties to be used for monitoring of interstitial fibrosis of renal transplants. Supported in part by NIH grant DK092255 from the National Institute of Diabetes and Digestive and Kidney Diseases.

3.5 **Derivation and analysis of viscoelastic properties in human liver using a linear-dispersion model**, Ned C. Rouze, Michael H. Wang, Mark L. Palmeri and Kathryn R. Nightingale, *Department of Biomedical Engineering, Duke University, Durham, NC, ned.rouze@duke.edu*

Background: Commercially-available shear-wave imaging systems measure group shear-wave speed (SWS) and often report stiffness parameters applying purely elastic-material models. Soft tissues, however, are viscoelastic, and higher-order material models are necessary to characterize the dispersion associated with broadband shear waves. A Voigt model has commonly been used to characterize this dispersion by expressing the measured phase velocity in terms of the elasticity μ and viscosity η of the tissue.[(1-3)] However, when phase-velocity measurements are only available in a narrow frequency range, the Voigt model is susceptible to fitting artifacts due to the complicated frequency dependence of the model.

Methods: We have developed a robust, Radon-like sum and model-based algorithm to perform shear-wave dispersion analysis in traditionally ``difficult-to-image" subjects. Instead of a Voigt model, a linear-dispersion model is used to characterize the phase velocity as a function of frequency in terms of an intercept c_0 and slope dc/df. We compare the performance of the linear dispersion model with the group SWS to stage hepatic fibrosis in a cohort of 135 nonalcoholic fatty-liver-disease patients.

Results: The linear dispersion analysis was successfully performed in 107 of 135 patients. Separation of advanced liver fibrosis ($\geq$ F3) from mild-to-moderate fibrosis ($\leq$ F2) was performed using the velocity evaluated as a function of frequency derived from the linear fit to the measured dispersion and calculating

the area under the ROC curve (AUROC). The greatest AUROC occurred at 204 Hz with AUROC = 0.88, sensitivity = 0.79, specificity = 0.81 and threshold speed of 2.66 m/s. Using the slope dc/df as the test metric gave AUROC = 0.70, sensitivity = 0.69, specificity = 0.71 and threshold = 5.47 m/s/kHz. Using the group SWS as the test metric for the full population of 135 patients gave a value of AUROC = 0.94, sensitivity = 0.92 and specificity = 0.91.

Conclusions: The linear-dispersion model allows the analysis of viscoelastic properties in human liver without artifacts possible with the Voigt model. However, the higher order model gives lower AUROC, sensitivity, and specificity values when compared to the use of the group SWS as the test metric for separation of fibrosis stages ≤ F2 from stages ≥ F3. Supported by NIH grants R01EB2132 and R01CA142824. We thank the Ultrasound Division at Siemens Medical Solutions, USA, Inc. for their technical and in-kind support.

(1) Chen, et al. *J Acoust Soc Am, 115*, 2781-2785 (2004). (2) Catheline et al. *J Acoust Soc Am 116*, 3734–3741 (2004). [3] Chen et al. *Radiology 266*, 964–970 (2013).

4. IMAGING 1

4.1 **Use of ultrasound imaging to detect activity of functional muscle compartments for upper extremity prosthetic control**, Nima Akhlaghi, Hozaifah Zafar, Katherine Mcdonald, Karthik G. Murthy, Huzefa S. Rangwala, Wilsaan M. Joiner and Siddhartha Sikdar, *George Mason University, Fairfax, VA, ssikdar@gmu.edu*

With recent developments in the electromechanical design of upper-extremity prosthetics, the need for more sophisticated and advanced control strategies for such prosthetics has increased. The current commercially-available noninvasive control strategy relies on the amplitude of myoelectric signals from flexor and extensor muscles in the forearm using two surface electromyography (sEMG) electrodes. This method provides only two control signals, thus relying on mode switching to utilize the available grasps on advanced commercially-available dexterous prosthetic hands. More sophisticated approaches utilizing pattern recognition algorithms with multiple electrodes have the potential for more intuitive control but do not provide a robust graded signal. There is, therefore, a continuing need for a better prosthetic-control strategy.

In order to provide robust signals from the functional muscle compartments, we propose a new strategy for sensing the muscle activity based on ultrasound imaging. This strategy can lead to the design of more flexible and sophisticated upper-extremity prostheses and control systems, with more degrees of freedom. In previous work, we have shown that this method can reliably differentiate between individual digit movements with 97% accuracy. In this study, we demonstrate that the ultrasound-based strategy can reliably differentiate between functional movements including grasping, wrist pronation and grasping with wrist pronation and accomplish graded control in real time.

Dynamic ultrasound images of the forearm muscles were obtained from six healthy volunteers using a Sonix RP system with a 5-14 MHz linear array transducer and analyzed to map muscle activity based on the changes in the ultrasound echogenicity of the contracting muscles during different movement performance. Using the sequences of ultrasound images, we generated patterns of muscle activity for 15 different complex movements. For each subject, these patterns were correlated with previously-acquired training data to classify different movements. On average, the movement pattern was found to be 87% accurate for a total of 15 different movements for all subjects. Further improvements are possible by optimizing the design of the ultrasound cuff to prevent movement artifacts.

To demonstrate the graded control possible using the ultrasound-based approach, we developed a real-time ultrasound-based muscle computer interface (MCI) to control a computer cursor. To investigate the robustness of the control and the ability to differentiate between movements, we developed a one-dimensional task in which the normalized activation of a pre-determined muscle compartment (corresponding to index-finger flexion), was designated to increase the radius of a circle on a screen while

a separate compartment (corresponding to ring-finger flexion) was designated to decrease the cursor radius. The task involved manipulating the circle radius to match three different target radii on a computer screen. Over time, we found that the subject was able to learn the task within 50 seconds and achieve the desired manipulation interactively.

The results verified that the key advantage of the ultrasound-based methods is the ability to produce robust signals from contiguous functional compartments deep inside muscle, a capability exceeding that of sEMG. Ultrasound imaging could potentially be attractive as a sensing strategy for upper extremity prosthetic control and as a muscle-computer interface for rehabilitation robotics and exoskeletons.

4.2 **Quantitative ultrasonic tracking of muscle kinematics using tracklet-based stitching**, Paul Otto[1], Frances Gavelli[2], Bhushan Borotikar[2], Hyun Soo Im[2] and Siddhartha Sikdar[1], *[1]Department of Electrical and Computer Engineering, George Mason University, Fairfax, VA, 22030 and [2]Functional and Applied Biomechanics Section, Rehabilitation Medicine Department, National Institutes of Health, Bethesda, MD, 20892, ssikdar@gmu.edu*

Background and Objective: In recent years, ultrasound imaging (US) has become an important tool for dynamic functional assessment of muscles and tendons. Musculoskeletal kinematics are clinically important as outcome measures for movement disorders and rehabilitation as well as for understanding mechanisms of injury and subsequent adaptation. Yet, current US methods for tracking musculotendon kinematics are limited by the need for visualizing the entire muscle fascicle, which can only be accomplished for a small set of muscles. Thus, the objective of this study is to develop and validate a robust algorithm for tracking muscle dynamics that can track a wide variety of muscles by overcoming the limitations of past techniques, while maintaining that capability of being available to an office-based setting by using B-mode imagery from commercially-available equipment.

Methods: The tracking algorithm uses a tracklet-based framework where B-mode features points are identified and tracked over time. To form a tracklet, a set of feature points that share a spatial neighborhood and are also adjacent temporally are linked in a time-series chain. These tracklet chains are limited in length due to speckle decorrelation; however, partially-overlapping tracklets are stitched together to create a final trajectory for the regions in the muscle. This automatic method enables a quantitative characterization of motion across different regions of the muscle.

To validate this algorithm for tracking the rectus-femoris muscle velocities, we compared the US-based results against cine phase contrast (CPC) magnetic-resonance imaging (MRI). Each subject was first placed in a supine position in the MRI scanner with their knee slightly bent and supported by a cushion. While the subject performed cyclic knee flexion and extension, in time to a metronome, CPC anatomic and velocity data were collected. Then the subject remained on the scanning plinth as it was moved out of the MRI scanner to an exam room. The rectus femoris was then imaged using an Ultrasonix SonixTouch US system and a 5-14 MHz linear array transducer while the subject repeated the same cyclic motion. The B-mode image sequences were analyzed offline using MATLAB to generate velocity estimates.

Results and Discussion: The average rectus femoris velocities measured using US over 12 cycles were 19.94 ±4.78 mm/s during extension and 20.13±7.34 mm/s during flexion. Using MRI, for a single cycle we measured velocities of 22.5±0.6 mm/s during extension and 21.6± 0.6 mm/s during flexion over four spatial locations in the rectus femoris. The variance of the US data includes cycle-to-cycle variation in the subject's movement that is absent in the single-cycle estimate from MRI. This absence is due to the MRI's postprocessing assumption that the cycles are indistinguishable, by compensating small motion variations with interpolation and integration. Remaining motion variations are manifested as signal noise. These preliminary results indicate that the new tracking framework is capable of providing accurate velocity measures. Data from additional subjects are currently being analyzed. In the near future, the framework will be expanded to provide Bayesian filtering given an *a priori* dynamics model, which will improve the displacement estimates, thus providing a reliable technique to track complex muscle groups. Supported in part by Grant Number 0953652 from the National Science Foundation and by the Intramural Research Program of the National Institutes of Health Clinical Center, Bethesda, MD.

4.3 **Real-time kidney stone detection using an optimized Doppler imaging sequence**, Bryan W. Cunitz[1], John C. Kucewicz[1], Barbrina Dunmire[1], Marla Paun[1], Ryan Hsi[2], Franklin Lee[2], Jonathan D. Harper[2], Mathew D. Sorensen[2], Oleg A. Sapozhnikov[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, bwc@apl.washington.edu*

The imaging standard in the management of nephrolithiasis, or kidney stones, is computed tomography (CT), not ultrasound. This is primarily due to ultrasounds broad range of sensitivity (20% - 80%) and specificity (70% - 100%) in the detection of stones. Previous work has shown that kidney stones imaged under color-flow Doppler ultrasound, appear to "twinkle". That is to say, there is a rapidly-changing Doppler velocity measurement above the background noise threshold on the stone's location. This added signature though is currently considered an unpredictable artifact and has not been shown to significantly improve the detection of kidney stones with ultrasound. Recent investigation suggested that the source of this artifact is micron-sized bubbles in the cracks of the stone. Under this hypothesis, and using Doppler ultrasound as a starting method, an algorithm is being developed to detect stones in real-time with better sensitivity and specificity than with B-mode.

A Verasonics Ultrasound engine with an HDI P4-2 and C5-2 imaging probe was used for a clinical study with 9 patients/27 stones (mean size 4.4 ± 3.3 mm). The standard Doppler sequence and detection algorithm had a sensitivity of 80%, specificity of 89.6%, positive predictive value of 76.2% and negative predictive value of 91.5%. The algorithm eliminated two false positives identified with B-mode alone. False positives are important because they can lead to unnecessary surgery.

Further development has been to optimize the Doppler parameters based on a Doppler power metric. The results from *in-vitro* experiments agreed with the hypothesized bubble model. *In-vitro* results also showed improved detection over B-mode in detecting stones <2 mm. The optimized parameters were then included into a real-time imaging sequence allowing for the detection of kidney stones without confusion with blood flow or motion artifact. These results show that an algorithm tuned to detecting small bubbles on hard structures, rather than soft tissue applications, can improve the detection of kidney stones. Development and *in-vivo* testing of the new detection method is continuing and will be discussed, as well as other potential diagnostics that can evolve from this technology. Supported by NIH DK43881 and DK092197 and NSBRI through NASA NCC 9-58.

4.4 **Ultrasonic sizing of kidney stones**, Barbrina Dunmire[1], Franklin Lee[2], Bryan Cunitz[1], Jonathan Harper[2], Mathew Sorensen[2], Marla Paun[1] and Michael Bailey[1], *[1]Applied Physics Lab, University of Washington and [2]Department of Urology, University of Washington, Seattle, WA, mrbean@uw.edu*

The clinical management of kidney stone, a disease that will affect 1 in 11 Americans, is largely dictated by the stone location and stone size. Computed tomography (CT) is the most common imaging modality for patients with suspected nephrolithiasis; the use of ultrasound is limited because of its decreased sensitivity and specificity in detecting stones, and overestimation of stone size relative to CT.

We explored the use of the acoustic shadow, alternative B-mode imaging schemes and an automated computer algorithm in improving stone size estimation with ultrasound. Forty five calcium oxalate monohydrate (COM) kidney stones ranging from 1-10 mm were imaged in a water bath using a software-based research ultrasound system and C5-2 transducer. The width of the stone and the width of the acoustic shadow behind the stone were measured using a computerized algorithm that automatically set the focal depth, power and gain. Measurements were made for flash-angle imaging (FA), wide-beam harmonic imaging (HI) and conventional ray-line imaging (RL). The measurements were repeated at three depths: 6 cm, 10 cm and 14 cm.

Stone size was consistently overestimated when based on stone width and overestimation increased with depth. Average overestimation when measured manually with the on-screen calipers was 2.05 ± 1.06 (RL). Average overestimation with the automated program was 0.58 ± 1.42 (RL), 0.88 ± 1.56 (FA) and 1.31 ± 1.68 (HI). For the case of ray-line imaging, the automated approach improved the overall accuracy from the traditional manual measurement but with increased variance. Repeating the analysis

for the acoustic shadow, neglecting measurements for stones below 4 mm because there is no shadow, the results were 0.13 ± 0.79 (RL manual), 0.47 ± 1.31 (RL), 0.48 ± 4.23 (FA) and 1.52 ± 3.59 (HI).

The results show that for traditional manual measurements, stone shadow may prove a better predictor of stone size than the stone width itself. Stone-size measurements can also be improved using an automated computer program that computationally optimizes the system settings and eliminates user dependence. More work is needed to reduce the variance in this approach. Alternative imaging schemes such as flash angles and harmonic imaging do not seem to improve stone-size accuracy with ultrasound. Supported by NIH DK43881 and DK092197, and NSBRI through NASA NCC 9-58.

4.5 **Functional brain imaging using transcranial tissue pulsatility imaging**, Joseph Hecker[1], Von Botteicher[2], Raul Ramirez[3], Tyler Shaw[3], Raja Parasuraman[3] and Siddhartha Sikdar[2], *[1]Departments of [1]Electrical and Computer Engineering, [2]Bioengineering and [3]Psychology, George Mason University, Fairfax, VA, jhecker@gmu.edu*

Ultrasonic pulsatility imaging measures brain tissue motion induced by cerebral blood flow during the cardiac cycle. Recent literature has documented localized variations in brain tissue pulsatility amplitudes during functional tasks. The objective of this study was to characterize the backscattered ultrasound echoes during a cognitive task and extract parameters that are sensitive to functional changes.

Raw post-beamformed radiofrequency (rf) ultrasound echoes were acquired through the left and right temporal acoustic windows of volunteers while they performed a vigilance experiment. The experiment consisted of four ten-minute tasks in which the participant viewed rapidly appearing mock radar screens and was instructed to signal when lines on the screen would intersect. The four tasks were split between high and low cognitive workload conditions by manipulating the distances and angles between the lines. Baseline measurements were made when no targets were presented. An Ultrasonix Sonix RP system with a 2-4 MHz phased-array transducer was used for data collection. The ultrasound transducer was fixed to the head with a custom-built head frame and the brain stem was located as an anatomical landmark. Ultrasound signals were analyzed to yield tissue-velocity waveform, integrated backscatter and rf spectral measurements.

Empirical analysis of the data from 11 subjects demonstrates that the peak systolic tissue velocity is an indicator of a change in cognitive load. Specifically, in seven subjects, a higher peak systolic tissue velocity correlated to a high cognitive load task as determined through a paired Student's *t*-test ($p<0.05$). In the remaining four subjects a notable lower peak systolic tissue velocity correlated with higher cognitive load. The sign of the variation in tissue velocity held for both hemispheres of the brain. Of the 11 subjects, eight demonstrated lateralization of the cognitive task, exhibiting higher peak systolic tissue velocities under vigilant cognitive load for the right hemisphere of the brain versus the left hemisphere. Vigilance is known to be right hemisphere dominant. Interestingly, the rf spectra showed cyclic variations during the cardiac cycle. These results are consistent with changes in brain tissue properties during cardiac pulsations. Further analysis is ongoing as to the impact of cognitive load on these parameters. Preliminary results indicate the potential of ultrasound as a portable functional neuroimaging modality.

4.6 **Ultrasound-mediated actuation and monitoring of implantable devices for localized drug delivery**, Parag V. Chitnis[1], Olga Ordeig[2] and Samuel K. Sia[2], *[1]F.L. Lizzi Center for Biomedical Engineering, Riverside Research, 156 William St., 9th Floor, New York, NY and [2]Department of Biomedical Engineering, Columbia University, New York, NY, pchitnis@riversideresearch.org*

Direct local delivery of therapeutics can significantly improve long-term outcome and quality of life for cancer patients. We present an image-guided drug-delivery approach that employs ultrasound for remotely actuating drug-loaded implants consisting of porous NiPAAm hydrogels as well as for guiding and monitoring drug release. The hydrogels were 1 mm thick and 6 mm in diameter. The NiPAAm formulation was designed to contract to 30% of original size when heated to 45°C. A 1.5-MHz focused-ultrasound (FUS) transducer operating at low intensities (<500 W/cm^2) elevated the gel temperature to 45°C in 32.6 ± 19 s (N = 10). The capsule was loaded with 20-kDa TRITC-Dextran and placed in a custom-designed PDMS chamber containing deionized water. Temperature elevation was monitored

noninvasively by tracking the change in sound speed in ultrasound pulse-echo data acquired using a 7.5-MHz diagnostic transducer. Ultrasound-based temperature was employed as feedback to modulate (on/off) FUS in real-time to maintain gels at 45ºC for 10 min, which resulted in a release of 10.6 ± 0.3 μg of dextran quantified by absorbance at 540/580 nm. Capsules were then implanted in eight mice; four mice were subjected to FUS. Diagnostic ultrasound was employed to align FUS transducer with the implants and monitor temperature elevation *in vivo*. FUS actuated release *in vivo* as evidenced by fluorescence imaging of mice.

4.7 **Virtual rigid body: a new tracking paradigm in ultrasound-guided interventions**, Alexis Cheng[1], Nishikant Deshmukh[1] and Emad M. Boctor[1-3], *Departments of [1]Computer Science, [2]Electrical and Computer Engineering and [3]Radiology, Johns Hopkins University, Baltimore, MD, 21218, acheng22@jhu.edu*

Interventional ultrasound (US) is a common medical imaging modality used for image-guided therapy (IGT) systems. In general, IGT systems will have an integrated external tracking device that allows tools and devices used during IGT to be registered together. Optical tracking is an example of such a tracking system. These systems track markers or fiducials attached to the US transducer but there are some limitations to current markers and fiducials, especially in the laparoscopic environment. This type of surgical environment has a very limited workspace. It is therefore ideal for the markers to be as small as possible. However, it is also known that larger markers can provide better tracking accuracy. Another issue is that the tracked markers are most likely not within the region of interest. The optical tracker must then be placed in a suboptimal position such that both the region of interest and the marker is within its field of view.

In this work, we developed a prototype of a novel optical-tracking technology for interventional US guided interventions. Instead of a marker, a light projection device is placed on the US transducer. This device then projects a pattern onto the surface. By tracking the projected pattern on the surface with a conventional optical tracker or a custom stereocamera system, the pose of the US transducer can be recovered. This approach addresses the aforementioned limitations. The size of the fiducial is no longer limited by the constrained workspace but by the field of view of the cameras. In addition, since the pattern can be projected onto the region of interest, the optical tracker can be placed in an optimal position to view the region of interest. A related advantage is that the optical tracker no longer has to have line-of-sight to the US transducer. Preliminary experiments have shown that this approach can achieve positional accuracy comparable to conventional optical trackers. Further experiments are currently being conducted to evaluate the rotational accuracy and the effects that the projected pattern can have on the overall accuracy.

4.8 **Clear Guide ONE: local optical tracking of instruments and probe for interventional ultrasound imaging**, Philipp J. Stolka, Pezhman Foroughi, Matthew Rendina, Clifford Weiss, Gregory D. Hager and Emad M. Boctor, *Clear Guide Medical, Baltimore, MD, stolka@clearguidemedical.com*

Background: Ultrasound guidance for needle-based interventions is a widespread approach to assist in precise targeting of anatomical structures for diagnostic (e.g., for biopsies) or therapeutic (e.g., tumor ablation or anesthesia) purposes. However, limited imaging quality (due to attenuation or suboptimal structure/instrument echogenicity), required hand/eye coordination for probe and instrument placement and anatomical constraints make instrument localization and targeting difficult. Therefore, systems based on mechanical, optical or electromagnetic tracking aim to provide guidance for the operator. However, these systems are cumbersome, expensive, difficult to learn and use and time-consuming to set up and therefore have not achieved widespread physician acceptance or use.

Objectives: Intervention-agnostic, unobtrusive guidance that works immediately after startup, at any time during the intervention, without additional setup steps, for any needle without required markers, and without the need for special environments (including aspects such as reference bases, EM compatibility etc.) can significantly improve adoption of ultrasound guidance. The use of ultrasound guidance for

needle procedures is the gold standard of care and is associated with high-quality medicine and superior clinical outcomes.

Methods: Using probe-mounted miniature stereo cameras, the described novel local instrument tracking approach (Clear Guide ONE™, Clear Guide Medical, Baltimore, MD) provides probe-relative localization of needle-like instruments. Real-time observation, detection and 3D reconstruction of instruments allow the overlay of predicted needle trajectories on ultrasound video streams. In order to ensure a uniform, clear target, a 2.4 mm steel ball (BB) was suspended by a crosswire and embedded in a Sigma-Aldrich gelatin from porcine skin at a depth of 6 cm. The BB target is highly visible in ultrasound, thus removing any ambiguity of the target location. For comparison, biopsy lesions in liver and kidney discovered by CT are usually 5–10 cm deep and have a minimum diameter of 5 mm. Imaging was performed using linear (L14-5/38) and convex (L5-2/60) handheld ultrasound probes on an Ultrasonix SonixTablet (Ultrasonix Inc., Richmond, BC, Canada). The augmented US plus guidance video streams were shown to two physicians (Fellows in Interventional Radiology at Johns Hopkins University). The subjects were not familiar with the device beforehand, and performed 41 guided-needle insertions in total. They were instructed to align the needles with the target bb before insertion and then minimize directional adjustments during placement. This is unlike with conventional "blind insertion", where the needle is reoriented under ultrasound visualization to reach the target and consequently causes tissue trauma and needle bending. After each trial, two orthogonal digital photographs were taken of the BB and the placed needle as they appeared in the transparent phantom. These images were then manually analyzed to triangulate the distance of the needle to the target.

Results: Needle placement was successfully completed in all cases, with minimal training required (approximately 15min "free trialing" to become familiar with both the ultrasound machine and the Clear Guide ONE). Overall target accuracy was 3.27/2.85 mm average/median (range 0.3–10.5 mm; 2.28 mm standard deviation). As expected, accuracy for the lower-frequency convex probe was lower (3.8/4.21 mm avg./med.; range 0.3–7.3 mm; 2.17 mm std. dev.; $N = 15$) than for the high-frequency linear probe (2.96/2.11 mm avg./med.; range 0.7–10.5 mm; 2.33 mm std. dev.; $N = 26$).

Conclusion: The described fully-handheld local tracking system allows precise and repeatable interventional needle placement with minimal training and hardware footprint. We would expect greater adoption of ultrasound guidance by all physicians inserting needles or interventional tools into the body and therefore better clinical outcomes.

Tuesday morning

5. 3D/4D IMAGING

5.1 **Turning 3D into the future of ultrasound**, Brett Byram, *Dept. of Biomedical Engineering, Vanderbilt University, Nashville, TN, brett.c.byram@vanderbilt.edu* (invited overview)

Volumetric ultrasound has existed in various forms for several decades. Current forms of 3D ultrasound primarily rely on matrix arrays or mechanical wobblers. The clinical utility of these solutions is application dependent. In most cases, these transducers as they are implemented clinically are not fully consistent with technical research goals. This has led to the pursuit of other strategies for acquiring 3D data. Current clinical methods for 3D acquisition as well as some of the recently proposed alternatives will be reviewed.

Even though 3D ultrasound is clinically available and has been readily adopted by physician researchers, with a few exceptions, 3D ultrasound has not modified current clinical practice. There are several hypotheses for why this may be the case, including shortcomings of current technology and difficulty interpreting the massive amount of data available in real-time volumetric data sets. These shortcomings represent significant opportunities for the ultrasound research community and a number of

researchers are already pursuing a range of solutions. Technical shortcomings are being addressed by advanced transducer technology like cMUTs and beamforming strategies like 3D short-lag spatial coherence (SLSC) imaging. Information overload is being addressed through various parametric techniques that use 3D ultrasound technology but create reduced dimension images or images that are more directly interpretable for the diagnosis in question. This includes 3D ultrasound for procedure guidance and 3D cardiac-strain methods. Successful solutions to 3D ultrasound's current shortcomings should expand 3D's current footprint making subsequent developments easier to introduce clinically.

5.2 **Volumetric ultrasound imaging with Capacitive Micromachined Ultrasonic Transducers (CMUTs)**, Amin Nikoozadeh and Pierre T. Khuri-Yakub, *Stanford University, Stanford, CA 94305, aminn@stanford.edu* (invited)

Capacitive Micromachined Ultrasonic Transducers (CMUTs) have been under development as alternative to piezoelectric transducers for generating and detecting ultrasound. The advent of silicon micromachining enables the realization of the full potential of these transducers and provides performance that makes CMUTs competitive and superior to piezoelectric transducers in many applications.

CMUTs have been operated in the frequency range of 10 kHz to 75 MHz, with an electromechanical coupling coefficient close to unity, and included in systems with a dynamic range of the order of 150 dB/V/Hz. Custom electronics have been developed and integrated with arrays of transducers either via flip-chip bonding or direct bonding to ASIC wafers. For medical imaging, CMUTs are realizable with fractional bandwidth of over 100%, and are made in the form of single element, one-dimensional (1D) or two-dimensional (2D) arrays of tens of thousands of elements.

This presentation will first review the operation of CMUTs, the technologies used to make them and integrate them to electronics, and highlight some 2D/3D medical imaging applications. Applications other than diagnostic medical imaging will also be briefly presented to provide a broader picture where CMUTs are being utilized today.

5.3 **Volumetric Short-Lag Spatial Coherence imaging**, Jeremy J. Dahl, Donwoon Hyun, Marko Jakovljevic, and Gregg E. Trahey, *Department of Biomedical Engineering, Duke University, Durham, NC, jjd@duke.edu* (invited)

We have recently introduced a beamforming technique called short-lag spatial coherence (SLSC) imaging that displays images of wavefront coherence rather than the target reflectivity, as in conventional B-mode imaging. This method has been demonstrated in 1D transducers with significant improvements in imaging performance compared to conventional B-mode imaging when incoherent noise, such as reverberation clutter, is present. Here, we extend the SLSC algorithm to 2D matrix arrays and volumetric SLSC imaging, although the extension from 1D to 2D is not as straightforward as it may appear due to the dependence of SLSC on the relative distance between elements rather than their physical position.

We apply volumetric SLSC imaging to a simulated 64×64 element transducer and a commercially-available matrix array. Our simulations indicate that volumetric SLSC images show greater lesion detectability through higher contrast-to-noise ratio (CNR) and texture signal-to-noise ratio (SNR), despite the loss in contrast, compared to volumetric B-mode images. Limiting the elevation short-lag information also yielded higher CNR than comparative SLSC imaging on 1D arrays. Due to the high computational cost of volumetric SLSC imaging, efficient strategies are employed to reduce computational resources. These strategies increase the processing speed of the SLSC volumes with no reduction in image quality and include subaperture beamforming and sparse coherence function calculations. In simulations, subaperture beamforming was found to have little effect on SLSC imaging performance for subapertures of up to 8×8 elements, and sparse coherence function calculations required only 20% of the aperture information to yield equivalent contrast, CNR and texture information. We demonstrate the application of volumetric SLSC imaging to phantom and *in vivo* experiments using a clinical 3-D ultrasound scanner and commercially-available matrix array using the subaperture beamforming approach. 2D and 3D images rendered from the SLSC volumes display reduced clutter and improved visibility of liver

vasculature compared to their B-mode counterparts. Supported by the NIH grants R01-EB013361 and R01-EB015506 from the National Institute of Biomedical Imaging and Bioengineering. In-kind and technical support was provided by the Ultrasound Division at Siemens Medical Solutions USA, Inc.

5.4 **Automation of renal ultrasound examination and 3D visualization of the acquired images,** Reza Seifabadi, Bamshad Aziz, Nabile Safdar and Kevin Cleary and Sheikh Zayed, *Institute for Pediatric Surgical Innovation, Children's National Medical Center, 111 Michigan Ave NW, Washington, DC 20010, rseifaba@childrensnational.org*

Among all ultrasound diagnostic exams, renal ultrasound is the most common and requires scanning of the bladder, right kidney and left kidney. In Children's alone, 3000 renal ultrasound procedures were reported last year. Renal ultrasound examination is performed free hand by a skilled sonographer who uses a 2D ultrasound probe to capture 2D images of the kidneys and bladder. However, one potential problem with free hand ultrasound is that the quality of the images is highly dependent on the sonographer's skills. Furthermore, ultrasound acquisition is a challenging task because of the 2D nature of the imaging and the small window through which good images can be obtained. In addition, ultrasonography is a physically demanding job, as 80% of sonographers can have shoulder/neck problems and 20% may quit their job early due to these issues.

We propose a gantry apparatus for acquiring the ultrasound images. Similar to CT or MRI, the patient lies flat. 2D images are continuously acquired as the probe is tracked and moved over the skin. Custom software then assembles these tracked 2D images together to create a 3D volume. 3D volumes may have advantages for renal ultrasound exams and could potentially improve the accuracy of diagnosis. The image acquisition may also be faster since the sonographer no longer has to acquire images from multiple angles.

For proof of concept, we designed and manufactured a five degree of freedom gantry-like prototype where the probe is moved manually. Optical tracking was used to track ultrasound image acquisition. Open source software was used for 3D volume reconstruction. Four adult volunteers were imaged. The acquired images were showed to three radiologists who stated that the images are adequate for renal diagnosis. In the next step, we are motorizing the system and then will conduct additional evaluation studies.

5.5 **High-frequency 3D ultrasound for characterizing overall tumor response to vascular targeting strategies**, Ahmed El Kaffas, Anoja Giles and Gregory J. Czarnota, *Imaging Research and Radiation Oncology, Sunnybrook Health Sciences Centre and Departments of Radiation Oncology and Medical Biophysics, University of Toronto, Toronto, ON, Canada, aelkaffas@gmail.com*

Introduction: Quantitative ultrasound methods are ideal for assessing tumor response to cancer treatments. More specifically, ultrasound spectroscopy methods offer insight on tumor cell death while power Doppler ultrasound is ideal for assessing the volumetric vascular response. Used together, these provide valuable information on the dynamics of overall tumor response. With recent interest in strategically combining vascular targeting agents with radiation therapy to treat cancer, such imaging methods enable clinicians and researchers to characterize the response of different components of the tumor microenvironment in order to optimize treatment delivery.

Materials and Methods: Tumor xenografts were treated with single 5 Gy radiation doses in conjunction with ultrasound-stimulated microbubbles (USMB), followed by an anti-vascular agent to prevent vascular rebounds. Treatment response was assessed with high frequency three-dimensional ultrasound acquired before, during and after treatment using a VEVO770. The vascularity index (VI) was used to quantify power Doppler data while quantitative ultrasound spectroscopy (QUS) was used to monitor tumor cell death and tissue structural changes. Staining using ISEL and CD31 of tumor sections was used to measure and correlate cell death and tumor vasculature distributions following treatments to ultrasound parameters.

Results: Our results suggest significant tumor response in animals treated with USMB combined with radiation, followed by an anti-vascular maintenance therapy, leading to a synergistic tumor growth delay

of up to 24 days. This is linked to rapid cell death and a sustained tumor vascular shutdown, detected with ultrasound. At 24 hours after the treatment delivery, we noted a VI decrease of up to 55 ± 8.6% and 60 ± 5.3% for animals treated with radiation followed by the anti-vascular agent only, or combined with USMB, respectively. At 7 days, although the VI had decreased to 30 ± 17% in tumors treated with radiation and the anti-vascular agent, tumors receiving the triple combination therapy had a sustained vascular shutdown with a VI of 51 ± 4.8%. Quantified cell death paralleled VI results, suggesting that these may be directly linked to overall levels of vascular shutdown. In addition, we observed that the anti-vascular agent, when administered alone, induced morphological tumor tissue changes that are potentially reflected in QUS parameters.

Conclusion: Overall, our results demonstrate the potential of combining both of these ultrasound-based methods when studying complex treatment regimens such as vascular-targeting strategies. These also suggest a link between relative vascular shutdown and relative increases in tumor cell death. Finally, we present evidence suggesting QUS parameters sensitivity to tumor vascular remodeling.

5.6 **Reducing reflection artifacts using 4D directional filters and evaluating the effects elevational extent using real-time 3D shear-wave monitoring,** Samantha L. Lipman, Ned C. Rouze, Michael H. Wang, Mark L. Palmeri and Kathryn R Nightingale, *Department of Biomedical Engineering, Duke University, Durham, NC, samantha.lipman@duke.edu*

Background: Shear-wave speed (SWS) images reconstructed from time-of-flight methods are susceptible to artifacts at boundaries due to constructive interference of wave reflections. 2D (plane-wave monitoring) shear-wave elastography imaging (SWEI) is limited to 2D filtering in the frequency domain to remove waves travelling in the opposing direction from the assumed direction of propagation[(1)]; however, this does not account for reflections from the out of plane dimensions, which can have significant impact on shear wave reconstructions.[(2)] 3D real-time volumetric imaging can be performed using a 2D matrix array, and a spatiotemporal filter adapted from that used by Manduca et al[(3)] can be applied to isolate the shear wave moving in the assumed direction of propagation. However, the use of matrix arrays is not ubiquitous, and the burden of processing and storing large 4D data sets is not ideal. This work evaluates the feasibility of using a four-dimensional directional filter with 3D volumetric data to improve shear-wave reconstructions in heterogeneous media, in particular the removal of soft center artifacts from spherical lesions[(2-4)]. Furthermore, this work investigates the extent of data in the elevation dimension necessary to remove the confounding out-of-plane shear waves.

Methods: LS-DYNA was used to simulate a Gaussian Acoustic Radiation Force Impulse (ARFI) excitation focused at 21 mm in a 3 kPa uniform phantom with a 5 mm, 18.75 kPa spherical lesion located at a depth of 21 mm, 5 mm off-axis. In this 4D data, a cosine-squared spatial filter and a quadrant-based temporal filter were applied in the frequency domain. The local shear-wave speeds were reconstructed using the filtered displacement through time profiles over a lateral kernel of 2 mm, using the time-to-peak slope (TTPS) algorithm to determine wave-arrival time. The 4D dataset was reduced in the elevation dimension to simulate a smaller field of view and then zero-padded to undergo the same processing as the full data set. These methods were compared to the traditional 2D directional filtering methods by using only the elevation position of 0 mm for comparison.

Results: Shear-wave speeds were successfully reconstructed from a right-propagating shear wave at all lateral locations after 4D filtering. In the TTPS and 2D-filtered TTPS, there are large SWS artifacts near the right lesion boundary that are caused by a refocusing of shear-wave reflections off of the lesion boundary, both in the lateral and elevation dimensions. Application of the 4D filter significantly reduces these reflection-based reconstruction artifacts. Similar reduction in artifact was seen using a reduced elevational field of view.

Conclusions: Constructive interference of both in- and out-of-plane reflected waves can cause soft appearing artifacts in stiff inclusions in SWS images. By applying a four-dimensional directional filter to ARFI induced displacement fields and monitoring propagation in 3D, these artifacts are reduced and more accurate SWS reconstructions can be performed in SWEI. Supported by NIH grants EB002132 and

T32-EB001040. We thank the Ultrasound Division at Siemens Medical Solutions, USA, Inc. for their technical and in-kind support.

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5.7 **Use of C-scan images for 3-D QUS in the breast**, Haidy Gerges Nasief, Timothy Hall, Ernest Madsen and James Zagzebski, *Medical Physics, University of Wisconsin - Madison, Madison, WI, nasief@wisc.edu*

Objectives: Quantitative ultrasound (QUS) parameters such as the attenuation coefficient (Att), the backscatter coefficient (BSC) and the effective scatter diameter (ESD) can give important insight into the characteristics of focal breast masses. In previous presentations, we described promising initial results using a Bayesian classifier incorporating these parameters to distinguish benign from malignant masses for 2D scans. The purpose of this presentation is to explore extension of QUS to data acquired using 3D imagers.

Methods: RF data from two phantoms were acquired using a Siemens S2000 scanner equipped with both an automated breast volume (ABVS) - 14L5BV transducer and an 18L6 linear array transducer. The ABVS device scans a volume by mechanically sweeping its 15 cm linear array, coupled to the sample via a porous membrane. One phantom, composed of agar gel, is an 8 cm cube with a 1 cm diameter sphere at its center having ESD and Att contrast. A second phantom, manufactured for the American College of Radiology (ACR), has masses of various sizes and shapes embedded in a simulated breast parenchyma, with a proximal layer of tissue-mimicking fat forming an irregular boundary. The first phantom was scanned with the ABVS machine, acquiring 250 frames of rf data. Data from 53 slices covering the sphere and surrounding TM material were analyzed. For the second phantom 24 slices surrounding a hypoechoic high attenuating mass were collected using the 18L6 transducer translated elevationally in 1/2 mm steps. For each slice, attenuation coefficients were measured using the reference phantom method and backscatter coefficients were measured by compensating for attenuation using a least-squares method described previously. ESDs were estimated from the BSC by applying a Gaussian form factor. Both "acquired plane" views and C-scans of ESDs and Att were displayed.

Results: C-scans could be generated for each of the different QUS parameters. Att C-scans of the sphere exhibited a 20% overestimation in the overall attenuation values. However, this view was successful in capturing the complex shape of the simulated tumor in the ACR phantom. Higher apparent attenuation values were noticed at the edges of the inclusion, which might be due to refraction or to backscatter artifacts that sometimes plague the RPM method in estimating attenuation. ESD C-scans of the sphere were smoother compared to the ATT C-scans due to the use of the least-squares method when correcting for attenuation. Both ATT and ESD maps of the hypoechoic, attenuating masses were successful in capturing the shape of the inclusions and the difference and similarities in the scattering properties between the mass and surrounding region. A bias of about 20% also existed in estimates of ESD.

Conclusions: 3D QUS of parameters such as attenuation coefficients and effective scatter diameters is very promising. Shapes of masses in the C-scan view may offer insight regarding the nature of a mass. Varying the thickness of the reconstructed slices, both in conventional, acquisition plane views as well as in C-scan views can reduce statistical variations beyond the reductions achieved using 2D processing. Supported, in part, by NIH grants R21HD061896 and R01CA111289.

5.8 **Carotid artery plaque composition analysis using 3D ultrasound imaging**, Khalid AlMuhanna[1], Murad Hossain[1], Limin Zhao[3], Brajesh Lal[3,4] and Siddhartha Sikdar[1,2], *Departments of [1]Electrical and Computer Engineering and [2]Bioengineering, George Mason University, Fairfax, VA, [3]University of Maryland Medical Center, Baltimore, MD and [4]Department of Veterans Affairs Maryland Health System, Baltimore, MD, ssikdar@gmu.edu*

Background: Debris from carotid-artery plaque contributes to about 20% to 30% of ischemic strokes. The currently-used method of assessing the severity of carotid stenosis is Doppler ultrasound. Evidence is

mounting that severity of stenosis alone is not a good indicator of vulnerable plaque with a higher likelihood of rupture. Characteristic signatures of vulnerable plaque include large deposits of necrotic lipid core and hemorrhages in the plaque. Ultrasonic tissue characterization of carotid plaque has typically been performed in longitudinal B-mode images. However, the volumetric tissue characteristics of plaque have not been investigated extensively using ultrasound. The objectives of this study are to measure plaque volume and identify its composition using 4D ultrasound imaging.

Methods: Ultrasound image volumes were acquired from patients with asymptomatic carotid stenosis using an Ultrasonix MDP system equipped with a 4D L14-5/38 transducer as part of the ongoing Asymptomatic Carotid Stenosis and Cognitive Function (ACCOF) study. The plaque volumes were manually segmented by a trained observer using a standardized protocol developed by our research group. The Stradwin software(1) was used for visualizing and segmenting the volumes. The volume images were then normalized by assigning fixed gray levels to the lumen and the brightest point of the adventitia and using a linear scale for all intermediate gray levels. In previous work, our group has established ranges of normalized echogenicity for different plaque tissue types, such as calcified, fibrous, muscular, lipid and hemorrhagic based on histologic comparisons.(2) In this study, these methods were extended to 3D, and volumetric maps of estimated tissue composition were generated.

Results: Five subjects with asymptomatic carotid stenosis (age: 66 ± 7 years) were included in this study. The total plaque volumes measured are 656.2 ± 348 mm^3. The volume measurements for the composition types were 9.2 ± 17.6 mm^3 for calcium; 39.8 ± 32.9 mm^3 for fibrous tissue; 163.5 ± 61.8 mm^3 for muscular tissue; 191.2 ± 170.2 mm^3 for lipids; and 2 ± 3.1 mm^3 for hemorrhagic plaque. As percentages of the total plaque volume calcifications accounted for 1.7 ± 3 %; fibrous tissue 7 ± 6.2 %; muscular tissue 26.2 ± 3.5 %; lipid core 26.1 ± 11.4 %; and hemorrhage 0.2 ± 0.2 % . The volume values are consistent with ranges reported in the literature using MRI.(3)

Discussion: While 3D ultrasound imaging has the potential for quantification of plaque tissue composition volumes as opposed to areas from 2D B-mode images, there are a number of challenges. The ranges of echogenicities validated against histology are applicable to longitudinal images but it is unclear whether they can be extended to volumes acquired using cross-sectional slices. These results would need to be validated against alternative imaging methods such as MRI or histology. We also plan to compare our results with tissue classification using rf ultrasound images of the same plaques. Further analysis on image volumes acquired from the subjects on follow up visits is ongoing.

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6. TISSUE PARAMETERS 2

6.1 **Attenuation variability in the human cervix**, Q. W. Guerrero[1], Lindsey C. Carlson[1], Helen Feltovich[1,2] and Timothy J. Hall[1], *[1]Medical Physics Department, University of Wisconsin - Madison, Madison, WI 53706 and [2]Maternal Fetal Medicine Department, Intermountain Healthcare, Provo, Utah, qguerrero@wisc.edu*

Objectives: Acoustic attenuation has been proposed to quantify cervical change, specifically for predicting the risk of preterm birth. The role of spatial location and angle of interrogation in estimating attenuation in the cervix, though, is unexamined and could lead to significant estimate variance. In this work, we examined the effects of spatial location along the length of the cervix and angle of interrogation relative to the canal. It was seen that spatial location played a major role in the mean attenuation coefficient and its frequency dependence with respect to ripening status. In addition, the angle of interrogation affected the magnitude of attenuation.

Methods: Hysterectomy specimens (N = 14) were collected, bivalved, and pinned to sound-absorbing rubber. The samples were positioned so that the endocervical canal was parallel to the face of the transducer. Samples were scanned with a Siemens Acuson S2000 and an 18L6 linear array transducer. RF

frames were collected at 21 different angles, from -40° to +40° in steps of 4°. Reference phantom data was collected for the same angles and attenuation was calculated using the Reference Phantom Method. Attenuation estimate bias was minimized with respect to spectral estimation regions and parameter estimation regions using the multitaper method. The internal os and external os of the cervix were then used to group the attenuation measurements among cervix specimens based on a fractional distance along the canal.

Results: There was a statistically significant difference (p = 0.007) in attenuation estimates among spatial locations along the cervix. In addition, the mean variance of attenuation estimates decreased from the distal to proximal ends (1.45 ± 1.26 (dB cm^{-1} MHz^{-1})^2 vs. 0.65 ± 0.48 (dB cm^{-1} MHz^{-1})^2, respectively. Angle of interrogation played a role in the magnitude of attenuation estimates. After subtracting the attenuation estimate for 0° data, there was a monotonically-increasing attenuation progressing from negative to positive angles (-0.03 to 0.3 dB cm^{-1} MHz^{-1} at the mid-proximal location). These results are consistent with the presence of spatially-dependent aligned collagen in the cervix and care must be taken with regard to scanning angle and scanning position. Supported by NIH grants R01HD072077, R21HD061896 and R21HD063031 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and a grant from the obstetrician–gynecologists at Utah Valley Regional for providing access to their patients for this study. We are also grateful to Siemens Healthcare Ultrasound division for an equipment loan and technical support.

6.2 **Cervical ultrasonic attenuation and cervical length in pregnancy**, William D. O'Brien, Jr[1] and Barbara L McFarlin[2] , *[1]Bioacoustics Research Laboratory, Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, 405 N. Mathews, Urbana, IL 6180, and [2]Women Children and Family Health Science, University of Illinois at Chicago, Chicago, IL, wdo@illinois.edu*

Objective: Ultrasonic attenuation is a method to quantify tissue microstructure. The objective was to determine whether ultrasonic attenuation and cervical length were associated with preterm birth risk.

Methodology: Seventy-one pregnant African-American women were recruited for the study. Three women were unable to complete the study. The women agreed to undergo five transvaginal ultrasound (TVUS) examinations for cervical ultrasonic attenuation and cervical length at 20, 24, 28, 32, 36 weeks gestation (GA). Raw ultrasonic data of the cervix and a reference phantom (known attenuation) were obtained from the z.one, Zonare ultrasound system. Ultrasonic data were processed offline using a spectral log-difference technique. Descriptive statistics, mean plots over time and *t*-tests were conducted among groups and time points.

Results: Women were African-American, 79% multigravid and 32% had a history of at least one prior preterm birth. Mean GA at delivery was 39 (± 1) weeks for the term group, 35 (± 1) weeks for the medical indicated preterm group and 29 (± 6) weeks for the spontaneous preterm group. 239 TVUS were conducted for attenuation and cervical length. At 21 weeks, women who delivered preterm had a lower mean attenuation (1.08 dB/cm-MHz) than the women delivering at term (1.37 dB/cm-MHz), p = 0.10. Cervical length at 21 weeks was not significantly different between preterm and term groups. Compared to the SPTB group, the full-term group displayed consistent attenuation value with small errors. Attenuation risk of SPTB: Specificity = 71.4%, Sensitivity = 62.9% PPV = 91.7% & NPV = 27.8%. None of the women in the study had a short cervix at 20 weeks.

Conclusion: Cervical ultrasonic attenuation assessment has the potential to be an early noninvasive indicator of tissue-property changes associated with preterm birth. Supported by the Irving Harris Foundation, the University of Illinois College of Nursing Internal Research Support Program, NIH grant 1R21HD062790 and the University of Illinois Center for Clinical and Translational Science (NIH grant UL1TR000050).

6.3 **Effect of intervening tissues on backscatter measurements of bone**, Brent K. Hoffmeister, Mark E. Sellers and P. Luke Spinolo, *Department of Physics, Rhodes College, Memphis, TN 38112, hoffmeister@rhodes.edu*

Ultrasonic backscatter techniques are being developed to detect changes in bone density and strength caused by osteoporosis. A significant amount of tissue (skin, fat muscle and the outer bone cortex) can lie between the transducer and interrogated regions of cancellous bone, producing errors in backscatter measurements. The goal of this study is to evaluate a backscatter-difference technique that may be less susceptible to errors produced by intervening tissues. The technique is based on the power difference between two different portions of the same backscatter signal. Measurements were performed on 25 cube-shaped specimens of cancellous bone using a broadband 5 MHz transducer. Intervening tissues consisting of a thin layer of cortical bone (to simulate the outer bone cortex) and a soft tissue-mimicking phantom were positioned between the transducer and cancellous-bone specimen. Measurements were performed with and without intervening tissues. The intervening tissues reduced the overall power of the backscatter signal from the cancellous bone specimen but the power difference between different portions of the backscatter signal remained relatively unaffected. In addition, the power difference demonstrated moderate to strong ($R > 0.7$) linear correlations with bone density. These results suggest that backscatter-difference techniques may be useful for clinical bone-assessment purposes.

6.4 **Acoustic property measurement for rat organs using 250-MHz ultrasound**, Kenji Yoshida[1],Sou Irie[2], Kenta Inoue[2], Kazuyo Ito[2], Hitoshi Maruyama[3], Jonathan Mamou[4], Kazuo Kobayashi[5] and Tadashi Ymaguchi[1],*[1]Center for Frontier Medical Engineering, Chiba University, Chiba, Chiba, Japan, [2]Graduate School of Engineering, Chiba University, Chiba, Chiba, Japan, [3]Graduate School of Engineering Chiba University, Chiba, Chiba, Japan, [4]Frederic L. Lizzi Center for Biomedical Engineering, Riverside Research, New York, NY and [5]Honda Electronics Co., Toyohashi, Aichi, Japan, kenyoshi1980@chiba-u.jp*

Objectives: Ultrasonic microscopy can characterize acoustic properties of tissue such as speed of sound (SOS), attenuation and acoustic impedance. High-frequency ultrasound (>100 MHz), corresponding to spatial resolution smaller than 15 μm, enables us to measure properties of individual cells in tissue. Thus, acoustic microscopy can provide beneficial information from the perspective of histology and pathology. Our aim is to summarize acoustic properties of various organs focusing on tissue microstructure.

Methods: The acoustic properties of various organs (i.e., liver, kidney, spleen, lung and heart) of a normal rat were measured by using a modified scanning bioacoustic microscope (AMS-50SI; Honda Elec.) incorporating a 250-MHz center frequency transducer with ZnO membrane. The 2D image of acoustic properties could be obtained by scanning the transducer in 2-μm steps. The spatial resolution of the resulting 2D images was about 4 μm.

Results: The 2D image of SOS enabled us to discern morphology of tissue microstructure, e.g., kidney tubule and lung alveolus. The SOS of liver, kidney, red-pulp spleen, white-pulp spleen, lung and heart was 1650-1750 m/s, 1480-1610 m/s, 1550-1700 m/s, 1480-1600 m/s, 1540-1700 m/s and 1630-1830 m/s, respectively. Because of the fine spatial resolution, the contrast of SOS between organs could be attributed to the difference of biological composition (e.g., type of cell), not morphological structure.

Tuesday afternoon

7. SHEAR WAVES/ELASTICITY 1

7.1 ***In-vivo* ARFI visualization of prostate lesions: how effectively does ARFI see prostate cancer?**, Zachary A. Miller[1], Tyler J. Glass[1], Stephen J. Rosenzweig[1], Mark L. Palmeri[1], Andrew Buck[3], Thomas Polascik[2] and Kathryn R. Nightingale[1], *[1]Department of Biomedical Engineering, Duke*

University and Departments of [2]Urology and [3]Pathology, Duke University Medical Center, Durham, NC, zam4@duke.edu

The ability to target lesions during prostate cancer (PCA) biopsy is a significant unmet clinical need. Currently, PCA biopsy relies on random-core sampling for diagnosis because there are no real-time clinical imaging methods available that effectively visualize prostate lesions. This reliance on random-sampling results in both over-diagnosis and a high false-negative rate. In this study, Acoustic Radiation Force Impulse (ARFI) imaging was evaluated for its ability to visualize PCA lesions, potentially opening the door for an ARFI-based lesion-targeting system.

In-vivo ARFI prostate data was acquired for 32 patients with known PCA using an Acuson ER7B transducer coupled to a Siemens Acuson SC2000 Ultrasound scanner swept laterally through the prostate. ARFI raw data was processed and loaded into 3D Slicer, an open-source visualization program. Prostate capsules and central glands were then segmented in order to define the outer boundary of the prostate and focus attention on the peripheral zone, the region where 80% of PCA occurs. A reader, blinded to histopathology, segmented and modeled suspicious regions on the ARFI image stack assigning an index of suspicion based on a 4-tier scale. ARFI lesions were identified based on the GADDST algorithm: glassy appearance, asymmetric dark stiff regions disconnected from central gland boundaries and located in a prostate with a small and tapered central gland. The GADDST algorithm was derived from analysis of a 16-patient subset of this ARFI data compared to histopathology. The greater number of GADDST criteria fulfilled, the higher the index of suspicion assigned. Segmented suspicious regions were then compared to gold-standard histopathology when available and preoperative multiparametric MR, another imaging approach reporting success in PCA diagnosis, otherwise.

Prostate lesions were correctly identified 45% of the time. Sixty-nine percent of the correctly identified prostates were assigned a high index of suspicion (3 or 4) while lower indices of suspicion (1 or 2) accounted for 31% of true positives. The false positive rate was 28%. Eighty-eight percent of the false-positive lesions had a low index of suspicion. ARFI failed to identify lesions in 27% of cases.

Preliminary results suggest ARFI demonstrates the ability to identify prostate cancer lesions particularly in prostates with small and tapered central glands. As research on ARFI's use in the prostate has just begun, it is likely that technical improvements in the ARFI imaging setup will increase ARFI's true positive rate to the point where it becomes a clinically-useful device for lesion targeting during prostate cancer biopsy.

7.2 **Attenuation-measuring ultrasound shear-wave elastography and its application in liver transplant patients**, Ivan Z. Nenadic[1], Matthew W. Urban[1], Heng Zhao[1], William Sanchez[2], Paige E. Morgan[2], James F. Greenleaf[1] and Shigao Chen[2], *[1]Mayo Clinic Basic Ultrasound Research Laboratory and [2]Department of Medicine, Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, MN, nenadic.ivan@mayo.edu*

The basic principle of ultrasound elastography techniques is the use of an external vibrator or focused ultrasound to create waves in the tissue and pulse-echo ultrasound to measure the wave propagation and estimate the wave velocity. Assuming that the tissue is purely elastic, the wave velocity (c) is directly related to the elastic modulus (μ) of the tissue via $\mu = \rho c^2$, where ρ is the tissue mass density (close to that of water). All biological tissues are inherently viscoelastic and ignoring the viscous component not only biases the velocity-derived estimates of elasticity but also fails to report a potentially-important tissue parameter.

Attenuation Measuring Ultrasound Shear-wave Elastography, or AMUSE, is a novel method for measuring shear-wave velocity and attenuation independently to provide true model-free characterization of tissue mechanical properties. The 2D Fourier Transform of the shear wave motion in tissue yields the k-space with the coordinates of frequency (f) and wave number (k). The shear-wave velocity and attenuation can be calculated from the coordinates and the shape of the peak in the k-space.

The AMUSE method was used to measure shear-wave velocity and attenuation at 100 Hz and 200 Hz in six transplanted livers post-transplant with potential acute cellular rejection and the results were compared to clinical diagnoses made by liver biopsy in a blind study. During acute cellular rejection, the

number of lymphocytes in the liver increases while the overall fluid content of the liver remains relatively constant. At 100 Hz, the average and standard deviation for the shear-wave velocity and attenuation for patients with no acute rejections were $c = 1.59 \pm 0.03$ m/s and $\alpha = 126.03 \pm 8.98$ Np/m, and for patients with acute rejections were $c = 2.41 \pm 0.36$ m/s and $\alpha = 95.53 \pm 9.08$ Np/m. At 200 Hz, the average and standard deviation for the shear-wave velocity and attenuation for patients with no acute rejections were $c = 1.71 \pm 0.08$ m/s and $\alpha = 151.00 \pm 11.79$ Np/m and for patients with acute rejections were $c = 2.85 \pm 0.61$ m/s and $\alpha = 118.83 \pm 15.22$ Np/m. An explanation for these results may be that the increased cellular infiltration in the livers undergoing acute rejection could cause the shear waves to propagate faster because the cells are packed tighter together in a confined volume and the effective tissue stiffness increases. The attenuation decreases because the presence of additional cells in the liver displaces some of the interstitial fluid that may contribute to shear-wave attenuation.

To assess the value of these results for separating these results to obtain a reliable diagnosis, we conducted a statistical analysis based on the Hotelling trace criterion. At 100 Hz, the Hotelling trace criterion was 3.97 for the velocity, 4.27 for the attenuation and 15.18 for velocity and attenuation combined. At 200 Hz, the Hotelling trace criterion was 2.54 for the velocity, 2.09 for the attenuation and 23.17 for velocity and attenuation. These results show that using wave attenuation in addition to the velocity improves the ability to separate the two groups of patients. The AMUSE method can be used to assist in diagnosis of acute rejection in liver transplants. Supported by NIH grants DK082408 and EB002167 from the National Institute of Diabetes and Digestive and Kidney Diseases and National Institute of Biomedical Imaging and Bioengineering.

7.3 **Shear-wave vibrometry evaluation in transverse isotropic tissue-mimicking phantoms and muscle**, Sara Aristizabal[1], Carolina Amador[1], Randall R. Kinnick[1], Ivan Z. Nenadic[1], James F. Greenleaf[1] and Matthew W. Urban[1], [1]*Ultrasound Research Laboratory, Mayo Clinic College of Medicine, Rochester, MN, 55905, aristizabaltaborda.sara@mayo.edu*

Ultrasound radiation force-based methods have emerged in the last two decades with the ability of evaluating the viscoelastic properties of soft tissues, such as liver, kidney, prostate, myocardium, breast and others. Tissue viscoelasticity is an important physiological parameter for the assessment of the status of different body tissues under healthy and disease conditions. When evaluating the viscoelastic properties, these techniques assume that the tissues are isotropic and homogeneous; therefore the current ultrasound radiation force-based methods face a challenge in quantifying the tissue mechanical properties when the properties of the tissues under evaluation are directional dependent, a property known as anisotropy.

To investigate this phenomenon, we created two different phantoms designs with preferential orientations incorporating fibrous material and fishing-line material. The first set of phantoms were made in a cube-shaped mold using a fibrous material (polyester) arranged in multiple layers and embedded in porcine gelatin using two different concentrations of the gelatin (8%, 14%). The second set of phantoms were made in a cube-shaped mold using fishing-line material (arranged in a parallel arrangement with a spacing of 3 mm in between them and embedded in porcine gelatin using two different concentrations of the gelatin (8%, 14%). In a separate container, a control homogenous phantom was made from the same gelatin batch for all cases. The total number of phantoms that were designed and studied was four transversely-isotropic phantoms and four control phantoms. Additionally, in order to evaluate the efficiency of the designed phantoms, we evaluated the anisotropic characteristics of an ex vivo pork tenderloin.

Measurements were made in the phantoms and the pork muscle at different angles by placing each individual phantom and the excised pork tenderloin in a rotating platform with a rotation range ranging between 0˚ to 360˚ in 10˚ steps. The phantom and excised-pork muscle were rotated with respect to the transducer, where 0° and 180° were defined along the fibers and 90° and 270° were defined across the fibers. Shear waves were generated and measured by a Verasonics ultrasound system equipped with a linear-array transducer operating at 4.1 MHz center frequency. The shear-wave speed was evaluated from the distribution of particle motion, which was estimated by two-dimensional (2D) in-phase/quadrature

autocorrelation method with spatial and temporal averaging of the compounded echoes from three different angled plane waves detected at an effective frame rate of 4.16 kHz.

For the fibrous phantom, the mean and standard deviations of the shear-wave speeds for 8% and 14% gelatin along the fibers (0°) were (3.60 ± 0.03 and 4.10 ± 0.11 m/s) and across the fibers (90°) were (3.18 ± 0.12 and 3.90 ± 0.02 m/s), respectively. For the fishing-line material phantom, the mean and standard deviations of the shear-wave speeds for 8% and 14% gelatin along the fibers (0°) were (2.86 ± 0.20 and 3.40 ± 0.09 m/s) and across the fibers (90°) were (2.44 ± 0.24 and 2.84 ± 0.14 m/s), respectively. For the pork muscle, the mean and standard deviations of the shear-wave speeds along the fibers (0°) at two different locations were (3.83 ± 0.16 and 3.86 ± 0.12 m/s) and across the fibers (90°) were (2.73 ± 0.18 and 2.70 ± 0.16 m/s), respectively.

The shear-wave speed decreased progressively as the phantoms and pork muscle were rotated to an angle perpendicular to the fibers while the shear-wave speed increased gradually as the phantoms and pork muscle were rotated to an angle parallel to the fibers. Both phantom designs exhibited anisotropy that resembles that observed in pork muscle. Phantom anisotropy could be measured using quantitative shear-wave speed measurements. Increasing the gelatin percentage increased the shear-wave speed and anisotropic shear-wave speed. Supported in part by NIH grant DK092255 from the National Institute of Diabetes and Digestive and Kidney Diseases.

7.4 **On the potential for acoustic radiation force impulse (ARFI) imaging to measure fibrous cap thickness in carotid atherosclerotic plaque, *in vivo,*** Tomasz J. Czernuszewicz[1], Jonathon W. Homeister[2], Melissa C. Caughey[3], Mark A. Farber[4], Joseph J. Fulton[4], Peter F. Ford[4], William A. Marston[4], Raghuveer Vallabhaneni[4], Timothy C. Nichols[2,3] and Caterina M. Gallippi[1], *Departments of [1]Biomedical Engineering, [2]Pathology and Laboratory Medicine, [3]Medicine, and [4]Surgery, University of North Carolina at Chapel Hill, Chapel Hill, NC, cmgallip@bme.unc.edu*

Background: Acute cerebral ischemic events are associated with the rupture of vulnerable carotid plaque. An important characteristic of vulnerable plaque is the thickness of the fibrous cap; histological studies performed on carotid endarterectomy (CEA) samples suggest that plaques with a minimum cap thickness of <200 μm and a representative cap thickness of <500 μm are associated with higher probability for rupture. The objective of this study was to analyze the capability of ARFI imaging for transcutaneous measurement of fibrous cap thickness, *in vivo*. Data is presented in a case study format from three symptomatic patients.

Methods: In an ongoing clinical trial, patients undergoing clinically-indicated CEA were recruited from our hospital and imaged with ARFI implemented on a Siemens Acuson Antares modified for research. Imaging was performed pre-operatively by focusing on the carotid bifurcation. Imaging beam sequences were composed of excitation pulses at 4.21 MHz and tracking pulses at 6.15 MHz. After surgery, the extracted specimen was sectioned according to noted arterial geometry for spatial registration to the ultrasound imaging plane. The sections were stained and compared to parametric 2D ARFI images of peak displacement (PD). Average fibrous cap thickness was measured from both ARFI images and histology.

Results: In the common carotid artery of a 57 y/o male, ARFI imaging showed a plaque of almost homogeneous displacement (mean PD: 1.3 ± 0.7 μm) except for a higher displacing area located towards the right part of the plaque (3.7 ± 3.9 μm). The region separating the higher displacing area from the lumen was measured to be 1.37 ± 0.1 mm thick. Histological staining confirmed the presence of a necrotic core with extravascular erythrocytes, indicating mild intra-plaque hemorrhage, covered by a fibrotic cap measuring 1.26 ± 0.3 mm (8.7% difference compared to ARFI measurement). In the internal carotid artery (ICA) of a 52 y/o female, ARFI imaging showed plaque with a shoulder protrusion into the lumen. The area beneath the shoulder had higher displacement (mean PD: 2.6 ± 1.6 μm) than the rest of the plaque (1.2 ± 0.7 μm). The average thickness of the region separating the higher displacing area from the lumen was measured to be 0.92 ± 0.3 mm. Histological staining confirmed the presence of a cellular region of inflammation covered by a fibrous cap, 0.84 ± 0.3 mm thick (9.5% difference). Finally, in another ICA of a 55 y/o female, ARFI imaging showed an area of notably higher displacement (8.3 ± 2.8

μm) than the adjacent wall (4.7 ± 1.6 μm). The region of tissue between the higher displacing area and the lumen was measured as 0.80 ± 0.2 mm. Histological staining revealed a large necrotic core covered by a relatively thin fibrous cap, 0.48 ± 0.08 mm thick (66.7% difference).

Conclusions: In this case study, ARFI-derived fibrous cap thickness measurements were within ~10% error of those measured from histology when the cap thickness was ~1 mm. As the fibrous cap got thinner than 1 mm, the contrast of the cap decreased and made measurement increasingly more difficult and erroneous. There are a number of factors that may affect the ability of ARFI to accurately measure fibrous cap thickness, including correlation kernel length, mechanical coupling between the fibrous cap and necrotic core, and mechanical waves generated following the ARF excitation. The results of this case study merit further investigation in the limits of ARFI-derived fibrous cap thickness measurement.

7.5 **Spatial-continuity expectation applied to ASSH-detected hemorrhagic region through clustering**, Rebecca E. Geist[1], Timothy C. Nichols[2], Elizabeth P. Merricks[3] and Caterina M. Gallippi[1], *[1]Joint Department of Biomedical Engineering, [2]Department of Medicine and [3]Department of Pathology and Veterinary Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, regeist@ncsu.edu*

Background: For patients with deficient or inhibited plasma coagulation proteins, undetected bleeding can be frequent and deadly. In the case of peripheral vascular injury, current bleeding detection methods fail when no hemorrhage or hematoma is visible at the skin surface. Alternative bleeding detection strategies that delineate bleeding below the skin surface are needed to improve bleeding outcomes. We have developed ARFI Surveillance of Subcutaneous Hemostasis (ASSH) to noninvasively identify peripheral hemorrhagic areas using acoustic-radiation force. We now modify ASSH to include *a priori* information regarding the expected spatial continuity and density of hemorrhage. *We hypothesize that incorporating hemorrhagic spatial continuity and density constraints will refine ASSH bleeding rate (BR) and time to hemostasis (TTH) measurements.*

Methods: Both the original and modified versions of ASSH were performed in association with a standardized peripheral vascular injury involving puncture of a 2 mm diameter peripheral vein in the hind limbs of 13 dogs (n = 6 control and n = 7 hemophilia A). The hemophilia A dogs were each examined in the naïve state and with two treatments given prior to vascular injury: infusion of c.FVIII to approximately 10% of normal c.FVIII level and infusion of recombinant c.FVIII to approximately 100% of normal c.FVIII level. For each treatment type in each dog, ASSH data were acquired serially over a 30-minute observation period immediately following the vascular challenge, with two repeated measures separated by at least two weeks. Acquired ARFI data were processed with one-dimensional cross-correlation to measure axial displacement and hemorrhagic pixels were identified by evaluating axial displacement variance in response to ARFI excitation. For modified ASSH, hemorrhagic spatial continuity was imposed by restricting the allowable linear distance between any hemorrhagic pixel and the main hemorrhage cluster to 10 mm. Hemorrhagic density constraint was imposed by requiring that at least 20% of pixels in a 2 mm axial x 2 mm lateral kernel around a given pixel also be identified as hemorrhage. Original and modified ASSH BR and TTH were deduced from the time series of hemorrhagic area measures and compared between cohorts.

Results: Using the original ASSH methods, there was no significant difference found in BR between the normal control, naïve hemophilia A, and 10% c.FVIII treatment cohorts (unpaired t-test, $p>0.05$); however, the 100% recombinant c.FVIII treatment cohort statistically differed from both the naïve hemophilia A and the 10% c.FVIII treatment cohorts ($p<0.05$). Similarly for the modified ASSH method with hemorrhagic spatial continuity and density constraints imposed, there was no statistically-significant difference in BR between the normal control, naïve hemophilia A and 10% c.FVIII treatment cohorts ($p>0.05$). Further, the 100% recombinant c.FVIII treatment cohort statistically differed from both the naïve hemophilia A and 10% c.FVIII treatment cohorts ($p<0.01$). Finally, the original and modified ASSH methods consistently differentiated percentage of dogs within and between cohorts with abnormal TTH (> 25 min).

Conclusions: Applying *a priori* information regarding hemorrhagic spatial continuity and density does not alter the statistical distributions of ASSH BR and TTH metrics amongst normal and hemophilia A (naïve and treated) dog cohorts in a pilot, *in vivo* feasibility study.

7.7 **Vibration elastography to assess the effect of dry needling on myofascial trigger points in patients affected by myofascial pain syndrome,** Diego Turo[1], Paul Otto[2], Md Murad Hossain[2], William F. Rosenberger[3], Hui Shao[3], Jay Shah[4], Lynn H. Gerber[5] and Siddhartha Sikdar[1,2], *Departments of [1]Bioengineering, [2]Electrical and [3]Computer Engineering and Statistics, George Mason University, Fairfax, VA 22030, [4]Rehabilitation Medicine, National Institutes of Health, Bethesda, MD, 20814 and [5]College of Health and Human Services, George Mason University, Fairfax, VA, 22030, ssikdar@gmu.edu*

Objective: Myofascial trigger points (MTrPs) are palpable, tender nodules in taut bands of skeletal muscles that can be painful both spontaneously and on compression. MTrPs are characteristic findings in myofascial pain syndrome (MPS) and are the target for a number of different therapeutic modalities. However, the role of MTrPs in the pathophysiology of MPS is still unknown. Objective characterization of the properties of MTrPs before and after treatment can elucidate their role in MPS. In this study we investigated whether ultrasound vibration elastography is sensitive to changes in muscle tissue properties following dry needling treatment on patients with chronic MPS and symptomatic MTrPs.

Methods: Forty-eight subjects (18 male, 30 female, 35±13 years old, mean ± standard deviation) with chronic myofascial pain in the upper trapezius (> 3 months) and a spontaneously-painful (active) MTrPs were recruited for this study. The most symptomatic active MTrP was identified based on established clinical criteria. A team blinded to the physical findings performed ultrasound examination using a linear transducer (12-5 MHz). Qualitative elastography was performed using an external massager (~100 Hz) and color Doppler variance imaging with standardized settings. In previous work, we have demonstrated that these methods are sensitive for objectively documenting MTrPs. Stiffer regions with low vibration amplitude appear as voids in the color Doppler image. The ratio of the size of all these regions to the size of the upper trapezius muscle on the ultrasound image was used as measure of the proportion of the muscle that was affected by the MTrP.

The subjects then went through a three-week course of dry needle therapy targeting this active MTrP. A change of the status from active to non-painful or no palpable trigger point evaluated at baseline and follow-up visits was used for assessing the response of the dry needling treatment. A number of clinical measures, including pain and the pressure pain threshold (PPT) were also acquired. The change of the relative size of the MTrPs measured at baseline and follow-up visits was compared to the change of PPT score and status of the patient.

Results and Discussion: Based on the physical examination of each subject, MTrPs identified in the medial third of the right and left upper trapezius muscle were labeled as active MTrP (spontaneously painful), latent MTrP (painful to palpation), or normal myofascial tissue (no MTrP, no pain). Some patients had bilateral active MTrPs but only the most symptomatic one was treated. All active MTrPs were therefore in two groups: "Treated" (n=48) and "Untreated" (n = 23). At follow up, the "Treated" active MTrPs either changed to normal ("Active to Normal", n = 13), or changed to latent MTrPs ("Active to Latent", n = 25), or stayed active ("Active to Active", n = 10).

Relative size of "Treated" MTrPs was significantly lower at the follow-up visit ($p<0.008$) compared to the baseline. The relative size of "Untreated" MTrPs was unchanged ($p=0.38$) PPT significantly improved ($p<0.001$) after treatment for "Treated" MTrPs whereas it did not improve for "Untreated" MTrPs.

There was no direct correlation between the ultrasound scores and PPT or other clinical measures. However a stratified analysis revealed that: (1) the "Active to Normal" group had significantly smaller relative MTrPs size at baseline ($p<0.04$) compared to the other groups; (2) in the "Active to Latent" group, there were significant decrease in both relative MTrP size ($p<0.007$) and improvement of PPT score ($p<0.008$); (3) considering all the "Treated" sites, a significant decrease of the relative MTrP size always corresponds to a significant improvement of the PPT score, however an increase in relative MTrP size was not associated with any significant change in PPT.

This small study provides some evidence that the relative MTrP size on ultrasound elastography is a sensitive measure of muscle tissue property changes following dry needling therapy in MPS. Supported by NIH grant 1R01-AR057348.

7.8 **Bayesian estimation of small displacements using generalized Gaussian Markov random fields: a parametric analysis**, Douglas M. Dumont[1], Mark L. Palmeri[2] and Brett C. Byram[1], *[1]Department of Biomedical Engineering, Vanderbilt University, Nashville, TN and [2]Department of Biomedical Engineering, Duke University, Durham, NC, douglas.m.dumont@vanderbilt.edu*

Precise motion tracking is a critical task in ultrasound, particularly for elasticity-imaging techniques like acoustic radiation force impulse (ARFI) imaging, where tracking micrometer-order tissue displacements can be challenging in noisy environments. Previously, we proposed using Bayes' theorem to improve estimation of noisy, displacement data by incorporating prior knowledge of the estimation task, and showed that even for relatively simple prior information schemes, significant improvements in mean-square error (MSE) could be realized over traditional, unbiased normalized cross-correlation estimators.[(1,2)]

In this study, we present an improved Bayesian formulation that models both Gaussian noise and decorrelation in the likelihood function of the displacement data and uses a generalized Gaussian Markov random field model to incorporate prior information from spatially-adjacent regions to improve the current estimate.[(3)] We examine the impact of prior neighborhood size, shape, and weighting on estimator performance in both low- and high-noise environments and analyze performance of the proposed estimator using simulated ARFI displacement data in a 8.5 kPa homogeneous phantom (n = 100 realizations).

The simulation results demonstrate the importance of appropriately weighting the prior information, with estimates using inappropriately weighted priors showing either little improvement in MSE (overly-wide prior distributions) or significantly worse MSE performance (overly-narrow prior distributions) compared to normalized cross-correlation. For a Bayesian estimator using appropriately-selected parameters, significant performance improvements can be realized. For example, the MSE at the location of the peak displacement (20.3 mm ± 0.5 mm) when using a Gaussian shape with a prior lambda of 0.518 μm is 4.1 ± 0.6 μm^2 , 3.7 ± 0.5 μm^2 , 2.2 ± 0.16 μm^2 and 1.8 ± 0.4 μm^2 for no additive white Gaussian noise, 40 dB SNR, 20 dB SNR and 10 dB SNR, respectively, a noticeable improvement over the MSE---7.5 ± 1.8 μm^2, 8.2 ± 1.8 μm^2, 17.7 ± 9.9 μm^2 and 32.5 ± 12.4 μm^2 for no additive white Gaussian noise, 40 dB SNR, 20 dB SNR and 10 dB SNR, respectively ---achieved with normalized cross-correlation. Note that for this particular width, greater improvement in MSE is achieved at higher noise levels due to the overall lower quality of the data (and, thus, the likelihood function), allowing the prior to exert a greater influence on the final displacement estimate. We will also present strategies for emphasizing bias, variance or MSE performance through parameter selection and discuss tradeoffs between noise performance, image-feature preservation and computational overhead.

(1) Byram et al. *IEEE Trans UFFC 60*, 132-143 (2013). (2) Byram et al. *IEEE Tran UFFC 60*, 144-157 (2013). (3) Bouman et al. *IEEE Tran Image Proc 2*, 296-310 (1993).

8. LIGHT AND SOUND 2

8.1 **Expanding the clinical role of photoacoustic imaging: thermography and spectroscopy for guiding thermal ablation,** Katherine L. Dextraze[1,3], Joshua P. Gray[1,3], Christopher MacLellan[1,3], Trevor M. Mitcham[1], Marites P. Melancon[2,3] and Richard R. Bouchard[1,3], *[1]Departments of [1]Imaging Physics and [2]Interventional Radiology, University of Texas MD Anderson Cancer Center, Houston, Texas and [3]University of Texas Health Science Center at Houston Graduate School of Biomedical Sciences, Houston, TX, kldextraze@mdanderson.org*

Background: Photoacoustic-ultrasonic (PAUS) imaging, which utilizes an ultrasound transducer to provide coregistered pulse-echo ultrasound images, is capable of measuring temperature non-invasively while simultaneously providing anatomical images. The submillimeter resolution and centimeter-order penetration depths achievable with PAUS imaging allows for active monitoring of the target tumor microenvironment and of nearby healthy tissue during thermal ablation. Furthermore, spectroscopy can be performed by varying the laser source wavelength during photoacoustic (PA) imaging. Spectroscopic changes can serve as indicators of tissue changes that are consistent with the treatment endpoint (e.g., protein coagulation). The ability to concurrently monitor local changes in temperature, molecular composition and anatomy makes PAUS imaging a promising new technique for guidance and monitoring during photothermal ablations of solid tumors.

Methods: All PA images were acquired on a Vevo LAZR (FUJIFILM VisualSonics Inc., Toronto, Ontario) PAUS small-animal imaging system (21-MHz center frequency). In order to determine the potential clinical role of PA thermography, the technique was validated against the clinically-accepted magnetic resonance thermal imaging (MRTI) approach. To facilitate coregistration between modalities, the phantom had inclusions of gold nanoshells encapsulating super-paramagnetic iron oxide (SPIO) particles, where gold enhanced the PA signal and SPIOs provided negative contrast on MRI. Using the thermography phantom, PA images were acquired during localized heating and simulating photothermal therapy. This procedure was then repeated under MRTI. The spatio-temporal resolution and the accuracy of temperature estimation were compared across both modalities. To characterize spectral changes due to tissue ablation, multi-wavelength PA images (680-790 nm) were acquired of several agar-embedded tissue samples (bovine cardiac and liver) with ablated and nonablated regions. The field of view of these spectral images included both ablated and nonablated regions to allow for matched comparisons.

Results/Conclusions: PA thermography was thoroughly characterized for thermal therapy guidance and compared to clinically-accepted MRI techniques and "gold standard" fluoroptic probe measurements. The PA signal was shown to change linearly across a temperature range of 22°C–55°C, within the limits of typical ablation temperature. PA images demonstrated submillimeter axial and lateral resolution with a temporal resolution of 0.2 s, which will accommodate highly-precise real-time guidance and monitoring. In PA spectroscopy of ablated and nonablated tissues, a significant spectral shift was observed between thermally-treated and nontreated regions in excised tissue. These results indicate that a combined PA thermography and spectroscopy technique offers tremendous promise for real-time guidance and monitoring of thermal therapies.

8.2 **Modeling acousto-optic guided high-intensity focused ultrasound lesion formation**, Matthew T. Adams[1], Robin O. Cleveland[1] and Ronald A. Roy[2], *[1]Institute of Biomedical Engineering and [2]Department of Engineering Science, University of Oxford, Oxford, UK, adamsm2@bu.edu* (invited)

Real-time acousto-optic (AO) sensing has been shown to noninvasively detect changes in *ex vivo* tissue optical properties during high-intensity focused ultrasound (HIFU) exposures. The technique is particularly appropriate for monitoring noncavitating lesions that offer minimal acoustic contrast. Here, a model is presented that is used to improve the AO sensing of lesion formation during HIFU therapy, to develop treatment strategies for the ablation of large volumes and to assess the technique's viability and robustness in a clinical setting. The angular-spectrum method is used to model the acoustic field from the HIFU source and the temperature field, due to the absorption of ultrasound, is modeled using a finite-difference time-domain solution to the Pennes bioheat equation. Changes in tissue optical properties are calculated using a thermal-dose model, calibrated by experimental data. The diffuse optical field is modeled using an open-source GPU-accelerated Monte Carlo algorithm. The Monte Carlo algorithm is modified to account for light-sound interactions, using the acoustic field from the angular-spectrum method, and to account for AO signal detection. Supported in part by the Whitaker International Program.

8.3 **Flexible software framework for acquiring pre-beamformed photoacoustic rf data in real-time,** Hyun Jae Kang[1], Muyinatu A. Lediju Bell[1], Xiaoyu Guo[2], Alexis Cheng[1], Behnoosh Tavakoli[1] and

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Photoacoustic (PA) images represent the acoustic and optical properties of a target object based on the photoacoustic effect. For this research, acquisition of ultrasound (US) pre-beamformed radiofrequency (rf) data is essential. Therefore, many studies related to systems capable of generating PA images have been conducted. However, existing PA systems are incompatible with conventional clinical US systems and require specifically-designed motion stages, US scanner and data acquisition systems. In addition, these systems are difficult to reconfigure and generalize to other PA research.

To overcome the limitations of existing PA systems, we propose a flexible software framework for acquiring pre-beamformed rf data with a conventional US probe and a SonixDAQ device. This DAQ device is compatible with conventional clinical US systems and scanners. As a result, our framework is also compatible with conventional clinical US systems. Moreover, our software framework and its software modules are based on the concept of network-distributed modules. In this type of system, one module processes a single task and modules exchange their input and output data among themselves with network communication methods. Also, each module can support multiple-client network connections to simultaneously provide its output data to multiple modules. These aspects of our software framework allow us to easily reconfigure and generalize our system to other PA or US research.

To test the feasibility and flexibility of our framework, we applied our system to the following PA research: (1) spatial-angular compounding of PA images to improve image quality, (2) localization of *in vivo* brachytherapy seeds using PA images, (3) registration between video and 3D US using PA images and (4) predict tissue viscoelasticity using the time- and frequency-domain properties of the photoacoustic signal.

8.4 **Increasing the penetration depth of clinical photoacoustic imaging with interstitial irradiation**, Trevor Mitcham[1], Katherine Dextraze[1,4], Andrei Karpiouk,[2] Burapol Singhana[3], Marites Melancon[3,4] and Richard Bouchard[1,4], *[1]Department of Imaging Physics, University of Texas MD Anderson Cancer Center, Houston, TX 77030, [2]Department of Biomedical Engineering, University of Texas at Austin, Austin, TX 78712, [3]Department of Interventional Radiology, University of Texas MD Anderson Cancer Center, Houston, TX 77030 and [4]University of Texas Health Science Center at Houston Graduate School of Biomedical Sciences, Houston, TX, tmmitcham@mdanderson.org*

Background: Photoacoustic (PA) imaging has shown promise as an imaging modality capable of providing diagnostic and therapy monitoring information in clinical applications. Unfortunately, due to difficulty in delivering light deep into tissue, many of the pursued applications have been limited to superficial imaging techniques. Using an interstitial irradiation source would allow deeper imaging in tissue, thereby providing additional methods for PA imaging to be used clinically.

Objectives: The goal of this study was to use a local irradiation source in conjunction with a conventional external ultrasound (US) receive-array to extend the depth capabilities of future clinical PA imaging techniques.

Methods: PA imaging was achieved using a single optical fiber serving as a local irradiation source coupled to a Sonix RP US system with an external Ultrasonix L14-5/38 linear array. This setup was used to test for the ability to spectrally isolate the signal generated by endogenous and exogenous absorbers in tissue-mimicking phantoms as well as *ex-vivo* tissue by acquiring PA images at 730, 760, 800, 850 and 900 nm. Nanoparticle targets (HAuNS; absorption peak 760 nm) were imaged in a tissue-mimicking phantom and *ex-vivo* bovine prostate tissue, while hemoglobin (Hb) was imaged within *ex-vivo* bovine liver tissue. Characterization of fiber energy output was also accomplished to find the optimal energy delivery source.

Results: Using an interstitial optical fiber source with an average energy output of 10 mJ, PA imaging was able to spectrally isolate the tested absorbers within *ex-vivo* tissue. HAuNS targets were imaged and unmixed at a depth of 2.5 cm from the transducer face while Hb was isolated from surrounding absorbers in *ex-vivo* bovine liver up to a depth of 4 cm.

Conclusions: This work demonstrates the feasibility of using an interstitial source to provide sufficient local fluence to generate reliable PA images. Imaging techniques similar to those presented could be used in clinical applications, such as PA image-guided biopsies or thermal therapy delivered with an interstitial applicator. As demonstrated, the clinical role of PA imaging in the future can be further expanded by implementing local, interstitial irradiation for characterizing deeper tissues using conventional clinical US systems.

8.5 **Photoacoustic sensing for target detection,** Behnoosh Tavakoli, Xiaoyu Guo, Russell H. Taylor, Jin U. Kang and Emad M. Boctor, Johns Hopkins University, Baltimore, MD 21218, *btavako1@jhu.edu*

Photoacoustic (PA) sensing is a hybrid technique that combines advantages of ultrasonic deep-tissue imaging with the optical-absorption contrast. In this study, a miniature forward-sensing PA probe is investigated that can characterize target properties located inside a catheter. The probe includes an optical fiber to illuminate the target with pulsed laser light and a hydrophone to detect the generated PA signal. Numerical simulations are performed to model PA wave generation and propagation inside water-filled cylindrical tubes. The effect of boundary condition, tube diameter and target size on the detected signal are evaluated. A prototype of the probe is made and preliminary experimental results were consistent with the simulation. Our medical application for this miniature probe was detecting occlusion inside ventricular catheters of hydrocephalus patients. Unfortunately, the malfunction rate of these catheters due to proximal end blockage is very high. This sensing tool could locate the occluding tissue noninvasively and can potentially characterize occlusion composites by scanning at different wavelengths of light. For this application, we have also studied another approach based on illuminating the occlusion with a fiber and detecting the generated PA signal with an external US probe. We were able to image the target inside a catheter located 20 mm deep inside brain tissue through about 4 mm-thick skull bone. This study could lead to the development of a simple, safe and noninvasive device for percutaneous restoration of patency to occluded shunts. This will eliminate the need of surgical replacement of occluded catheters, which expose these patients to risks, including hemorrhage and brain injury.

8.6 **All-optical active ultrasound pattern injection system**, Xiaoyu Guo[1], Behnoosh Tavakoli[2], Hyun-Jae Kang[2], Jin U. Kang[1], Ralph Etienne-Cummings[1] and Emad M. Boctor[2,3], *Departments of [1]Electrical and Computer Engineering, [2]Computer Science and [3]Radiology, Johns Hopkins University, Baltimore, M*D, *xguo9@jhu.edu*

In recent years, several approaches have been developed to improve tool visualization and pose-recovery with ultrasonography. However, none of them has yet provided a solution that effectively solves the tool visualization and mid-plane localization accuracy problem and fully meets the clinical requirements. Our previous work has demonstrated a new active ultrasound pattern injection system (AUSPIS) that integrates active ultrasound transducers (active echo (AE) element) with the interventional tool, actively monitors the beacon signals and transmits ultrasound pulses back to the US probe with the correct timing. Tool-visualization enhancement and a mid-plane localization accuracy of 300 μm have been demonstrated in both *ex vivo* and *in vivo* experiments. In previous work, piezoelectric materials were used to make the AE elements. However, many interventional catheters have very small diameters, with some less than few hundred microns. Integrating a piezoelectric AE element and its electrical wire connections within that size is very challenging. Moreover, driving a piezoelectric element requires electrical pulses with a duration of hundred nanoseconds and a voltage of 20~50 V, which may raise safety concerns in some application. The piezoelectric material and the metal wires may also cause artifacts when used with CT and MRI systems.

In this work, we focus explicitly on developing an AE element based on fiber-optical components to overcome these issues. The all-optical AE element is composed of a US sensor and a transmitter. The sensor receives the ultrasound pulse and converts it to an optical signal, which is picked up by an external optical system and turned to an electrical signal to trigger the AUSPIS controller circuit. On the transmission side, AUSPIS drives a laser source to send laser pulses and generate US wave through the photoacoustic (PA) effect. AUSPIS requires the AE element being ready to fire at any time, capable to

run at a high repetition rate and adjustable pulse width, which cannot be achieved by Q-switch lasers. Diode lasers have merits of high repetition rate, flexible pulse duration and no pumping delay. In this system, we use a high-power pulsed laser diode (PLD) 905D3S3j09, with a customized laser-diode driver that can output a maximum voltage of 150 V and current of 300 A. The pulsed laser diode emission has a wavelength of 905±10 nm, a peak output power of 200 W, and a divergence angle of 20°. An aspherical lens pair is used to couple the laser beam to the 200 μm core Tx fiber. The major drawback of using a PLD as light source is its low pulse energy. To improve optical-to-acoustical energy conversion efficiency, we developed a fiber giant PA cell. In this device, the Tx fiber output is coupled to a highly-absorptive liquid target and the US pulse is generated through the liquid phase-change effect, which is significantly more efficient than the conventional thermal expansion mechanism. We developed the prototype AUSPIS and demonstrated the catheter tracking, pattern injection and mid-plane detection functions in the phantom experiments. In the fiber giant PA cell test, our design goal of generating a high-intensity US wave with driving laser pulse energy less than 50 μJ was also achieved.

8.7 **Noninvasive liver biopsy by photoacoustic spectrum analysis**, Guan Xu[1], Cheri Deng[2], Paul Carson[1] and Xueding Wang[1], *[1]Department of Radiology, University of Michigan Medical School and [2]Department of Biomedical Engineering, University of Michigan, guanx@umich.edu*

To provide more information for classification and assessment of biological tissue, photoacoustic spectrum analysis (PASA) moves beyond the quantification of the intensities of the photoacoustic (PA) signals. Following the method of ultrasound spectrum analysis, PASA quantifies the linear-fit to the frequency-domain power distribution of the PA signals with three parameters, including intercept, midband-fit and slope. Intercept and midband-fit reflect the total optical absorption of the tissues whereas slope reflects the heterogeneity of the tissue structure. This study investigates the capability of PASA in identifying liver steatosis and fibrosis in a mouse model by taking advantage of the optical absorption contrasts contributed by lipid and collagen at 1220 and 1370 nm, respectively. Mouse livers with conditions of normal, steatosis and fibrosis were examined by *ex vivo* experiments. Each condition group includes 12 samples. Mice with the aforementioned liver conditions were also examined noninvasively and *in situ*. The results support our hypotheses that the PASA has the potential to provide quantitative measures of the histological features in the normal, fatty and fibrotic livers to facilitate non-invasive liver biopsy.

8.8 **Assessment of osteoporosis with optoacoustic imaging,** Behnoosh Tavakoli, Javza Natsag, Xiaoyu Guo, Shadpour Demehr, John Carrino and Emad M. Boctor, *Johns Hopkins University, Baltimore, MD 21218, btavako1@jhu.edu*

Osteoporosis is the most common metabolic bone disorder. Monitoring micro-architectural deterioration of bone tissue and decrease of bone mineral density are necessary for early detection of osteoporosis. Previously, it was shown that broadband attenuation of ultrasound signal is correlated with bone mineral density and its microstructure. In this study, we have evaluated the possibility of using an optoacoustic method for assessing osteoporosis. Optoacoustic (OA) signal generation is governing by target optical and mechanical properties and its propagation depends on the intrinsic elastic properties of the medium and its mass density. In addition OA spectroscopy is capable of identifying the absorbing components of a target. Therefore this hybrid functional method, which combines both ultrasound and optical information, can be a promising technique for determination of osteoporosis in early stages. We have evaluated the optoacoustic spectrum of quantitative ultrasound calcaneal phantoms of normal and osteoporotic bone and also *in-vitro* iliac crest biopsy bone specimens. Our optoacoustic system includes a tunable Q-switch Nd:YAG laser followed by an OPO system generating pulses at the wavelength range 0f 690 nm-950 nm. The OA signals were detected with the FDA approved Sonix Touch ultrasound system, including a data acquisition device for recording the raw data. The resulted signals are analyzed in both time and frequency domains. Preliminary experiment results revealed a general decrease in the intensity, center frequency and bandwidth of osteoporotic samples compared to normal ones.

8.9 **Coregistered photoacoustic perfusion assessment and targeted nanoparticle tracking in a prostate cancer model**, R. Bouchard[1,3], M. Thornton[2], K. Dextraze[1,3], T. Morgan[2], J. Grant[4] and S. Krishnan[4], *[1]Department of Imaging Physics, University of Texas MD Anderson Cancer Center, Houston, TX, [2]Endra Inc., Ann Arbor, MI, [3]University of Texas Health Science Center at Houston Graduate School of Biomedical Sciences, Houston, TX and [4]Division of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, rrbouchard@mdanderson.org*

Background and Objective: The use of targeted gold nanoparticles (AuNPs) has shown tremendous promise in the early detection and improved therapy of cancer. Successful development and implementation of these new theranostic approaches, however, depends on specific accumulation of AuNPs to extravascular tumor tissue. This study utilized photoacoustic (PA) imaging to correlate – in three dimensions and through 24 hours – the accumulation of targeted AuNPs to indocyanine green (ICG)-based tumor perfusion in a subcutaneous murine model of prostate cancer.

Methods: AuNPs (nanorods; 800-nm peak) targeting the Luteinizing-hormone-releasing hormone receptor were systemically injected into three mice bearing PC-3 human prostate cancer tumors; as a control, three additional mice were injected with PEGylated AuNPs. For all particle-tracking studies, multiwavelength (680, 760, 800, 920 and 940 nm), volumetric (spherical volume with 3-mm diameter) PA imaging was conducted at pre-injection, post-injection, 15-min, 60-min, 240-min, and 24-hr time points; the imaging volume contained the tumor and the spleen (control). Following imaging, tumors were excised and inductively-coupled plasma mass spectrometry (ICP-MS) of samples was performed. Volumetric PA perfusion assessment was then conducted by monitoring the wash-out of ICG in near real-time (0.33 Hz for 180 s post-injection). All PA imaging studies were performed on the Nexus 128 preclinical imaging system (Endra Inc., Ann Arbor, MI). Accumulation data of the targeted AuNPs in the tumor were then compared to tumor perfusion data, PEGylated AuNP accumulation data in the tumor, AuNP accumulation data in the spleen and ICP-MS analysis.

Results: This study establishes that volumetric PA imaging is able to track nanoparticle accumulation throughout an *in vivo* tumor model. The location and relative degree of particle accumulation was also found to correlate with PA-based perfusion and vascularity assessment. This study demonstrates that volumetric PA imaging has the spatiotemporal resolution and sensitivity to correlate AuNP accumulation with perfusion in an *in vivo* tumor model. This *in-vivo* tracking ability along with concurrent PA-based perfusion could be of significant benefit in understanding and improving nanoparticle targeting for the diagnosis and treatment of cancer.

8.10 **Real-time transurethral photoacoustic imaging of prostate brachytherapy seeds**, Muyinatu A. Lediju Bell[1,2], Hyun-Jae Kang[1], Xiaoyu Guo[3], Danny Y. Song[4] and Emad M. Boctor[1-3], *Departments of [1]Computer Science, [2]Radiology, [3]Electrical Engineering and [4]Radiation Oncology, Johns Hopkins University, Baltimore, MD, mledijubell@jhu.edu*

Brachytherapy is a treatment option for prostate cancer that requires implantation of radioactive seeds according to a defined treatment plan. Intraoperative seed localization is currently limited by suboptimal ultrasound image quality. We introduce a transurethral light-delivery method for a novel photoacoustic imaging approach to seed detection.

Two canine prostates were surgically implanted with brachytherapy seeds under transrectal ultrasound guidance. One prostate was imaged in the native tissue environment shortly after euthanasia. The second prostate was imaged *in vivo*. In both cases, a urinary catheter was inserted in the urethra and a 1-mm optical fiber coupled to a 10 Hz, 1064 nm, Nd:YAG laser was inserted into the catheter. The fiber tip was modified to direct light 90º from the fiber axis. The average energy per pulse through this side-firing probe measured 6-8 mJ. A SonixTouch ultrasound scanner (Ultrasonix, Richmond, BC, Canada), transrectal ultrasound probe with curvilinear (BPC8-4) and linear (BPL9-5) arrays and a SonixDAQ were utilized for synchronized laser light emission and photoacoustic signal acquisition. Prebeamformed photoacoustic data were displayed at a rate of approximately 3.75 frames per second on a computer workstation that was synchronized with the DAQ. Postoperative CT images and ultrasound images co-registered with photoacoustic images were acquired to confirm seed locations.

The real-time image display enabled visual optimization of photoacoustic signals with subtle rotational and translational adjustments to the fiber and ultrasound probe. The side-firing fiber offered selective imaging of seeds that were 6-9 mm from the urethra. In addition, this method correctly identified seeds that were slightly outside of the image plane as well as a reverberation artifact that appeared to be a seed in the ultrasound image. Results are promising for intraoperative photoacoustic imaging of prostate brachytherapy seeds utilizing the urinary catheter that is routinely inserted during human procedures.

Wednesday morning

9. TISSUE PARAMETERS 3

9.1 **Towards histology-based simulation: ultrasound modeling in diffractive fields using a spatial map of acoustic bulk modulus,** Jeremy Kemmerer[1], Miklós Gyöngy[2] and Michael Oelze[1], *[1]Bioacoustics Research Laboratory, Department of Electrical and Computer Engineering, The University of Illinois at Urbana-Champaign and [2]Faculty of Information Technology and Bionics, Pázmány Péter Catholic University, H-1083 Budapest, Práter utca 50/a, Hungary, kemmere1@illinois.edu*

Relating the amplitude and frequency dependence of backscattered ultrasound to tissue morphology remains an open research question in quantitative ultrasound. Better modeling tools would serve to complement the existing body of experimental data in ultrasound tissue characterization. In this study, weakly-scattering spheres and cylinders were simulated using a novel modeling approach based on work by Mari et al.(1) The scattering domain was broken into a grid of subscatterers in order to relate the amplitude and frequency dependence of the response to sample morphology. Sample time-domain backscattered responses were simulated for a specified single-element transducer (2.25 MHz, f/2.666) for single sphere and single cylinder sample configurations and the response was compared to measurements of a single capelin fish egg acting as a spherical scatterer and a water cylinder, respectively, both in an agar background. The simulated and measured frequency-domain responses agreed to within 2 dB over the measurement bandwidth.

Moving towards simulation of tissues, simulations of monodisperse collections of spheres, spheroids and cylinders were compared to the response for a single object. In order to speed up processing, an approximate approach assuming a locally-uniform spatial-impulse response was also used to simulate these same collections of scatterers. The response for the approximate approach agreed with the explicit approach to within 2 dB over the simulation bandwidth while showing a potential for speed-up by a factor of 50.

In summary, a new modeling technique incorporating diffraction effects for simulating the response from weakly-scattering, arbitrarily-shaped objects and collection of objects was tested and validated with experiments. Supported by NIH Grant R01-EB008992 and F31-CA174308, and Hungarian state grant TÁMOP-4.2.1.B-11/2/KMR-2011-0002.

(1) Mari et al. *JASA* (2009).

9.2 **Two-dimensional impedance maps for studying weak scattering in tissues**, Adam C. Luchies and Michael L. Oelze, *Bioacoustics Research Laboratory, Department of Electrical and Computer Engineering, The University of Illinois at Urbana-Champaign, Urbana, IL 61801, luchies1@illinois.edu*

An impedance map (ZM) is a computational tool for studying weak scattering in soft tissues. Currently, three-dimensional (3D) ZMs are created from a series of adjacent histological tissue slides that have been stained to emphasize acoustic impedance structures. The slides are digitized using a camera, a realignment process is applied to the series of images, and each pixel is assigned an impedance value

based on color. The result is an estimation of a 3D spatial map of acoustic impedance. The 3D volume power spectrum of the 3DZM can be related to quantitative ultrasound parameters such as the backscatter coefficient.

The goal of this study was to demonstrate the ability to estimate 3D volume power spectra from two-dimensional (2D) ZMs. The strategy for doing so is based on the following result from random field theory. For an n-dimensional isotropic random field, the correlation function for any (n-k)-dimensional slice is preserved with respect to the original n-dimensional random field. To estimate a 3D volume power spectrum from a 2DZM, the correlation function was estimated as a one-dimensional function of lag and inserted into the 3D Fourier Transform equation that assumes radial symmetry.

Simulations were conducted on collections of spheres having different volume fractions. The error between power spectra estimated using 2D slices and using the entire volume was less than 3.5% over the examined *ka* range. The power spectra estimated using the entire volume. Simulations were also conducted to determine how many slices from a sphere were needed to approximate the power spectrum for a sphere, or equivalently how many spheres need to be in a slice. The results indicated that 4-5 slices per radial length of the sphere were required. Results from the study suggest that it is possible to estimate the 3D volume power spectra from 2D slices without having to reconstruct a 3D volume from histology slides.

9.3 **Empirical decision algorithm for estimating quantitative parameters from coherent and incoherent scattering**, Ivan M. Rosado-Mendez, Timothy J. Hall and James A. Zagzebski, *Medical Physics, University of Wisconsin - Madison, Madison, WI, rosadomendez@wisc.edu*

Objectives: Estimation of spectral-based, quantitative ultrasound parameters relies on two important assumptions: (1) backscattered echo signals are from a stationary random process and (2) a large number of randomly-distributed scatterers is present within the resolution cell. However, sources of coherent scattering, such as specular reflectors or organized scatterers often are present *in vivo*, violating these assumptions. This work presents an empirical decision algorithm to determine the presence of significant coherent contributions to echo signals and to discern the nature of their source. The algorithm provides a parameter most representative of the scattering conditions within a parameter estimation region.

Methods: Beamformed rf echo signals are recorded from samples and processed offline. The processing algorithm first classifies signals as nonstationary or stationary by using an optimized multitaper estimator of the generalized spectrum. If nonstationary, the shape of the generalized spectrum is analyzed to decide on the presence of specular reflectors or quasiperiodic scatterers with spacing larger than the resolution cell. If the generalized spectrum indicates stationarity, an optimized envelope-SNR analysis is used to detect the presence of quasiperiodic scatterers with spacing smaller than the resolution cell. Decisions are made by comparing the values of test parameters to those computed for a reference material with diffuse scattering conditions. When quasiperiodic scatterers are detected, the algorithm uses a harmonic-search method applied to the generalized spectrum or to a χ^2 statistic determined from the echo signal phase to estimate the mean spacing of resolved or unresolved periodic spacing, respectively. When no significant source of coherence is identified, attenuation and backscatter coefficients and parameters derived from them are estimated.

Results: When applied to a custom-made computational phantom with regions of diffuse scattering and regions with different sources of coherent scattering, the algorithm correctly classified each scattering condition (with a misclassification rate of 7%). Mean scatterer spacing estimates were unbiased down to a spacing of 0.3 wavelengths. This algorithm is currently being applied to analyze breast tissue-mimicking phantoms and to classify *in vivo* breast lesions. Supported, in part, by NIH (grants R21HD061896, R21HD063031, and R01HD072077) and the Consejo Nacional de Ciencia y Tecnologia of Mexico (Reg. 206414).

9.4 Quantitative ultrasound analysis of structural variations in HT-29 spheroids, Lauren A. Wirtzfeld, Elizabeth S. L. Berndl and Michael C. Kolios, *Department of Physics, Ryerson University, Toronto, Ontario, Canada, mkolios@ryerson.ca*

Background: The ability to study cancer cells arranged in three-dimensions in an *in vitro* setting is imperative in cancer research and, in particular, for the development of medical imaging techniques for monitoring changes within the cells as well as their spatial heterogeneity. Spheroids provide a three-dimensional *in vitro* model of cell-to-cell interaction and basic structure. Studies with high-frequency ultrasound of spheroids have shown good contrast between rim and core but have not analyzed spectral variations that offer the potential to monitor subwavelength changes in cellular structure or collective arrangement.

Objectives: To determine the changes in spectral and quantitative ultrasound parameters in HT-29 spheroids using high-frequency ultrasound as a function of imaging frequency, numbers of days of growth, original seeding numbers and location (core vs. rim).

Methods: HT-29 human colorectal adenocarcinoma cell spheroids were produced by the hanging-drop method. Initial drops were seeded with 2000 to 10000 cells at 0 hours. Spheroids were imaged on day four or day seven post seeding, with the day seven spheroids being fed by full media exchange on day four.

Spheroids were imaged at 55 MHz with a VisualSonics Vevo770 preclinical imaging system and at 80 MHz with a custom acoustic microscope. For both systems, raw rf data was collected from several imaging planes through the spheroid. Offline the attenuation, spectral slope, midband fit and effective scatter diameter (ESD) were computed for the segmented spheres. With the exception of attenuation, all parameters were estimated separately for the rim and core, when two distinct regions are visible in the reconstructed image.

Results: Variations in spectral parameters were observed between the core and rim of spheroids, and across the seeding size. N-way ANOVAs show statistically-significant differences in the midband fit, spectral slope and effective scatter diameter (ESD) estimates. Histology and ESD estimates correspondingly show larger cell size in the rims and smaller cell size in the core of the spheroids, with an increase in distinct cores with increased seeding size.

Conclusions: The demonstrated sensitivity of high-frequency ultrasound spectral parameters to changes within spheroids -- including differences between the central core and the outer rim --will allow this model to be used for more detailed experiments, such as evaluating changes in cell viability or in response to drug treatments.

9.5 **Diagnosis of keratoconus using combined ultrasound layered pachymetric maps and scanning Scheimpflug tomography**, Ronald H. Silverman[1,2], Raksha Urs[1], Arindam RoyChoudhury[3], Timothy Archer[4], Marine Gobbe[4] and Dan Z. Reinstein,[4] *Departments of [1]Ophthalmology and [3]Statistics, Columbia University Medical Center, New York, NY, [2]F.L. Lizzi Center for Biomedical Engineering, Riverside Research, New York, NY and [3]London Vision Clinic, London, UK, rs3072@cumc.columbia.edu*

Keratoconus (KC) is progressive, noninflammatory corneal dystrophy in which the cornea thins and deforms to assume a conical shape. These conformational changes result in irregular astigmatism and myopia and may ultimately require treatment by corneal transplantation. Early KC diagnosis is needed to avoid corneal refractive surgery (which would accelerate the disease process) and to take advantage of corneal crosslinking therapy, which can halt the disease process before irreversible damage has occurred.

Tomographic methods such as Scheimpflug scanning slit systems (e.g., the Oculus Pentacam) provide information regarding corneal thickness and two-surface topography that are useful in identification of KC. This technique, however, cannot resolve the corneal epithelium, which remodels in response to deformation of the underlying corneal stroma. High-frequency ultrasound methods allow depiction of the thickness of the epithelium and stroma, which provide independent information associated with KC. Our aim was to determine if combination of data from both techniques could be accomplished and provide an improved classifier compared to either method alone.

We obtained Artemis-1 and Pentacam scan data on 126 normal and 28 KC subjects. Artemis pachymetric maps were analyzed to produce a set of 126 variables related to epithelial and stromal thickness and gradients. Pentacam analysis software produced a set of 114 variables characterizing corneal thickness, two-surface topography, and KC risk indices. After selecting one random eye per

subject, we performed stepwise linear discriminant analysis (LDA) to obtain classification models based on Pentacam alone, Artemis alone and both methods in combination. ROC curves were produced for each model.

LDA analysis resulted in a 7-variable model based on Artemis data, a 4-variable model using Pentacam data and a 6-variable model using combined Artemis and Pentacam data. The combined model selected 3 Artemis- and 3 Pentacam-derived variables. ROC area-under-curve values were at or near 100% in all cases.

Both Pentacam and Artemis models were able to distinguish normal from advanced KC. Pooling variables from both devices produced a model composed of 3 variables from each. This result indicates that each technique contributes independent information for discriminating normal from KC. Thus, this approach may allow reduced uncertainty in diagnosis of subclinical KC. Supported in part by NIH grants EY019055, P30 EY019007 and an unrestricted grant to the Department of Ophthalmology of Columbia University from Research to Prevent Blindness.

10. SHEAR WAVES/ELASTICITY 2

10.1 **Micro-Elasticity (μ-E): a comparison of Acoustic Radiation Force Impulse (ARFI) Imaging with Single Track Location (STL) and Multiple Track Location (MTL) Shear Wave Elasticity Imaging (SWEI) for visualizing small targets,** Peter J. Hollender, Stephen Rosenzweig, Kathy Nightingale and Gregg E. Trahey, *Department of Biomedical Engineering, Duke University, Durham, NC, peter.hollender@duke.edu*

A number of techniques have arisen in recent years that use acoustic radiation force to transiently displace tissue and high frame rate ultrasound to monitor and characterize the mechanical response, with the goal of measuring local tissue elasticity. Acoustic Radiation Force Impulse (ARFI) imaging measures the magnitude of the induced displacements while Shear Wave Elasticity Imaging (SWEI) detects the incremental time-of-flight of a propagating shear wave away from the excitation using either Multiple Track Locations per excitation (MTL), or, as more recently proposed, a Single Track Location (STL) with multiple offset excitations. Beamforming of both the excitation and tracking beams affects each imaging mode differently. This work uses matched datasets for all three techniques in a phantom experiment, comparing contrast, resolution and contrast-to-noise ratio (CNR) for cylindrical inclusions with diameters between 1.5 mm and 10 mm and with nominal Young's moduli between 3 and 36 kPa. ARFI demonstrated the highest resolution while STL SWEI had the best CNR. Supported by NIH Medical Imaging Training Grant EB001040, NIH 5R37HL096023 and NIHR01EB01248.

10.2 **Comparison of single- and multiple-track location shear-wave speed estimates**, Stephen McAleavey[1], Laurentus Ostopoeta[2] and Jonathan Langdon[1], *Departments of [1]Biomedical Engineering and [2]Physics, University of Rochester, Rochester, NY, stephen.mcaleavey@rochester.edu*

Shear-wave elastography techniques employing acoustic radiation force as the excitation mechanism enjoy a great deal of flexibility in the shear wave source properties – sources may be modulated in both space and time. This ability allows shear-wave speeds to be estimated either by moving the shear- wave source and using a single tracking location (STL), or by keeping the source fixed and gating the shear-wave time-of -flight through multiple tracking locations (MTL). In this talk, we compare the performance of STL and MTL shear-wave speed estimation using transient ARFI shear-wave excitation. The two techniques are compared in targets with fully-developed speckle and targets with strong point scatterers. In targets with fully-developed speckle, both simulation and phantoms, the STL method shows significantly lower variance. In targets with a strong point-scatterer embedded in speckle, MTL estimates demonstrate a biased shear-wave speed estimate dependent on the relative location of the point target and the tracking beams; STL estimates are comparatively unbiased. Estimates in uniform phantoms as a

function of tracking window size demonstrate equivalent mean shear-wave velocity, with variance decreasing more rapidly for STL with increasing tracking window length.

10.3 **Modulation of acoustic-radiation-force-induced shear-wave spectral content by spatial beamwidths and excitation duration**, Mark L. Palmeri, Ned C. Rouze, Kathy R. Nightingale *Department of Biomedical Engineering, Duke University Durham, NC, mark.palmeri@duke.edu*

Introduction: Shear wave elasticity imaging methods, including Shear Wave Elasticity Imaging (SWEI), ShearWave Elastography™, Virtual Touch™ Quantification and Spatially-Modulated Ultrasound Radiation Force (SMURF), utilize acoustic radiation force (ARF)-induced shear waves to estimate liver stiffness, which is correlated to underlying fibrosis. First generation shear-wave elasticity systems have estimated shear-wave group velocities with an assumption that the tissue is predominantly elastic. It is known, however, that liver tissue can have appreciable viscosity, which could vary with different disease etiologies, thus motivating the investigation of the estimation of phase velocities. Shear-wave phase velocities are dependent on the frequency of the shear-wave particle velocities. The objective of this work is to characterize the modulation of shear-wave spectral content that occurs for different acoustic radiation force spatial beamwidths in the lateral and elevation dimensions, along with the dependence on the temporal duration of the shear-wave-generating focused ARF excitation.

Methods: Previously-validated Finite Element Method (FEM) simulations of elastic media with Young's moduli (E) ranging from 1-30 kPa with Gaussian-distributed ARF excitations were modeled in LS-DYNA3D (R6.1.1). Gaussian excitations widths (-6 dB power points) were modulated from 0.5 - 5 mm, spanning a realistic range of excitation beamwidths than can be achieved with standard diagnostic imaging transducers. ARF excitation durations were modulated from 50-1500 μs at a frequency of 2 MHz. Shear-wave particle velocities were calculated directly in the FE solver and the spectral content of these velocities was extracted using LS-PREPOST (v4.1), with signal processing performed with custom Python and Matlab (R2013b) functions.

Results and Conclusions: ARF excitations up to 500 μs do not affect shear-wave spectral content but axisymmetric modulation of the spatial extent of the ARF excitation indirectly modulates shear-wave spectral content, with tighter excitations yielding higher-frequency-content shear waves for 0.5-5.0 mm wide Gaussian excitations. Spatially-asymmetric ARF excitations, such as those that would occur with linear arrays that have fixed elevation lens focusing, lead to a more complicated relationship between the one-dimensional spatial (lateral) ARF distribution and resultant shear-wave spectral content. These results indicate that longer ARF excitations that are still impulsive (i.e., steady-state displacement responses are not approached) can be used without affecting the resulting shear-wave spectral content while ARF spatial distribution in lateral and elevation beamwidths do affect the passband of the resultant shear waves. Supported by NIH grants R01CA142824 and R01EB002132.

10.4 **Accounting for mass in Viscoelastic Response (VisR) ultrasound**, Mallory R. Selzo[1], Tomasz J. Czernuszewicz[1] and Caterina M. Gallippi[1], [1]*Joint Department of Biomedical Engineering, University of North Carolina at Chapel Hill, Chapel Hill, NC, mallory.selzo@unc.edu*

Background: Viscoelastic Response (VisR) ultrasound is a method for quantitatively assessing the viscoelastic properties of tissue. Using two successive ARF impulses and monitoring induced displacements in the region of excitation, VisR fits displacements to a mechanical model to measure the relaxation time constant, τ, given by the ratio of viscosity to elasticity. We have previously demonstrated VisR for characterizing the mechanical properties of gelatin phantoms and muscle by fitting displacements using the Voigt model; however, the Voigt model assumes a massless material. We hypothesize that a modified version of the Voigt model, consisting of an inertial component in series with the Voigt model, will more accurately model tissue displacement and better estimate VisR τ measurements.

Methods: Finite-element method (FEM) models of the dynamic response of a viscoelastic media in response to successive, focused, impulsive acoustic radiation force excitations were solved using LS–DYNA. Field II was used to characterize the three–dimensional acoustic-intensity field associated with a

VF7-3 linear-array transducer. VisR sequences were implemented using two, 100 μs ARF excitations administered to the same region of excitation and separated by 0.6 ms in time. VisR displacement profiles were fit to the Voigt model with added inertial component to calculate τ and compared to τ measurements derived from fitting displacement profiles to the classic Voigt model. Four different focal configurations of the ARF excitations were employed (F/1.5, F/3, F/4 and F/5) in order to vary the volume of displaced tissue and investigate the effect of material mass on calculations.

Results: The Voigt model with added inertial component was better able to predict displacement profiles than the classical Voigt model, given by the R^2 statistic. R^2 values for the Voigt model with added inertial component were 0.981 ± 0.014 for the four focal configurations whereas R^2 values for the classical Voigt model were 0.354 ± 0.050. Further, τ values for the different focal configurations were not significantly different when derived from the Voigt model with added inertial component (F/1.5: 0.4919 ms, F/3: 0 0.4876 ms, F/4: 0.4836 ms, F/5: 0.4876), but were significantly different when derived from the classic Voigt model (F/1.5: 0.8242 ms, F/3: 1.2399 ms, F/4: 1.7196 ms, F/5: 2.2847 ms).

Conclusions: Results showed good closeness of fit between the FEM displacements and the displacements predicted by the Voigt model with added inertial component. In addition, τ measurements derived using the Voigt model with added inertial component were not different for the different focal configurations despite an increase in the volume of the displaced tissue, suggesting that the model is able to compensate for differences in mass.

11. IMAGING 2

11.1 **Model extensions for chirp-based beamforming to aid direct *in vivo* differentiation of phase-aberration, off-axis scattering and multipath scattering clutter sources**, Kazuyuki Dei and Brett Byram, *Dept. of Biomedical Engineering, Vanderbilt University, Nashville, TN, kazuyuki.dei@ vanderbilt.edu*

Ultrasound is susceptible to propagation-based image degradation, which is often considered to be caused by phase aberration from sound-speed variations in the imaged media. Recent evidence suggests that energy from multiple scattering also causes image degradation. Distinguishing these two sources of degradation (plus bright off-axis scattering) during *in vivo* imaging is an open challenge. As part of characterizing image degradation, there exists a large amount of literature measuring *in vivo* "phase-aberration." Aberration profiles are often characterized by their autocorrelation full-width at half maximum (FWHM) and by their root mean square (RMS). Here, we show that literature values for aberration profiles may as well be described by multipath scattering as by sound-speed variation, which motivates the need for advanced signal-characterization schemes. We have previously presented a model for identifying and suppressing multipath scattering, resulting in significant improvements in ultrasound contrast. The original model had some inconsistent assumptions, which are eliminated in an extended model presented here. The new model is more appropriate for characterizing multipath scattering and eventually for differentiating various sources of *in-vivo* image degradation.

To mimic literature-based aberration measurements with multipath scattering, a simple pseudo-non-linear multipath clutter simulation is used, which is based on Field II. Scatterers were simulated at a 5 cm focus and at 1-4 scattering locations at 1cm axially and multiple azimuthal positions. From these simulations, "aberration" profiles could be formed with autocorrelation FWHM between 0 and 4.1 mm and RMS values between 9 and 36 ns. These values are consistent with literature values.

The previous model-based approach for differentiating scattering locations maintained Fresnel's small-angle approximation; however, multipath scattering can originate from near the surface of the transducer so the approximation is inconsistent. To avoid the inconsistency, an improved model is proposed. The new model uses spherical wavefronts (instead of parabolic wavefronts) and accounts for short-time Fourier transform, pulse-based windowing and element directivity. The new and old models were compared using Field II simulations. Results are reported as model error-to-signal power ratio. For a

scatterer at the focus (5cm) relative model error was -37.4 and -44.0 dB for the new and old model, respectively. However, for a scatterer at 1 cm axially and offset azimuthally by 1 cm, the error was -23.4 and -1.2 dB for the new and old model, respectively, a significant improvement for the new model. For an on-axis scatterer originating from 1 cm axially, -33.3 and -2.5 dB relative model errors were seen for the new and old models, respectively. This demonstrates the importance of the new model for correctly classifying *in-vivo* clutter sources.

11.2 **Time and aperture domain noise equivalence in coherence imaging**, Nick Bottenus[1] and Gregg Trahey[1,2], *Departments of [1]Biomedical Engineering and [2]Radiology, Duke University, Durham, NC, nick.bottenus@duke.edu*

Coherence imaging has been proposed as a method to reduce clutter in ultrasonic images created by off-axis scattering, reverberation and phase aberration. The wavefronts returned from diffuse media, after focusing, show similarity across a particular coherence length. The measured similarity of these signals can be used to augment a B-mode image or create a coherence image. Random temporal noise has been previously shown to degrade the measured coherence, compromising the quality of coherence-based imaging methods.

Uncorrelated temporal noise suppresses the measured coherence by superimposing a delta function on the tissue coherence signal. This effect can also be achieved in the aperture domain by using either uncorrelated phase or amplitude components. Each case is shown to produce an effective signal-to-noise ratio comparable to the traditional signal-to-noise ratio for temporal noise. Variations in element strength, scanner clock jitter and high-frequency aberration should therefore all reduce coherence in the same way as temporal noise. For example, these results can be used to explain the change in contrast with noise power previously observed in Short-Lag Spatial Coherence (SLSC) imaging. Optimum image quality in SLSC imaging is observed with a moderate noise level, so this new understanding of the properties of noise can be leveraged to reduce hardware requirements and increase frame rates while increasing quality.

11.3 **Coherent flow imaging: detecting slow flow signal with backscatter spatial coherence,** You Leo Li, Michael Cook, Nick Bottenus and Jeremy J. Dahl, *Department of Biomedical Engineering, Duke University, Durham NC, leo.you.li@duke.edu*

Power Doppler imaging is a common method for flow detection in various organs. Compared to color Doppler imaging, power Doppler imaging can provide higher sensitivity with small vessel and slow flow detection at the expense of direction information. It also requires a large ensemble, limiting the frame rate to a few frames per second, and may suffer from two major noise sources: thermal noise and clutter. Thermal noise is a white noise and thus cannot be removed with wall-filters, while slowly moving tissue and reverberation clutter may pass through the wall filter depending on the speed and strength of the echo. These two noise sources may degrade the quality of the power Doppler image. In order to circumvent these limitations, we have recently developed a coherent flow-imaging technique. This technique utilizes power Doppler techniques with the short-lag spatial coherence imaging method. Because coherent flow imaging is based on the spatial coherence of backscattered signal, spatially-incoherent signals such as thermal noise and reverberation clutter can be suppressed.

Simulations of blood flow with various flow speeds and vessel diameters were utilized to measure the performance of the coherent flow method. Coherent flow imaging yielded a 15-25 dB increase of SNR over conventional power Doppler imaging, particularly when thermal noise is high. Due to this improvement of SNR, the coherence flow method requires smaller ensemble lengths to produce high quality images, potentially yielding improvements in frame rate by a factor of 2, enabling high frame rate power Doppler imaging. Also, simulation of vessels with different diameters (0.6 to 2 mm) showed that the coherent flow method can provide 15-25 dB of improvement in SNR over the range of vessel diameters, enabling more sensitive detection than power Doppler on small vessels. In addition, simulations with flow speed varying from 1 mm/s to 30 mm/s demonstrated that coherent flow imaging detected slower rates flow, with a limit of detection ~30% lower than that of the power Doppler. Experimental studies with a 6-mm diameter flow phantom confirmed the superiority of the coherent flow

method, producing images with higher SNR and detecting flow with a velocity ~30% below limit of power Doppler. Application of the coherent flow imaging to *in vivo* thyroid demonstrated greater sensitivity to blood flow of small arteries compared to conventional power Doppler imaging.

11.4 **Swept Array Synthetic Aperture Imaging (SASAI)**, Gregg E. Trahey[1], Marko Jakovljevic[1], Nick Bottenus[1] and Emad Boctor[2], *[1]Duke University, Durham NC and [2]Johns Hopkins University, Baltimore, MD, gregg.trahey@duke.edu*

A moving array with precisely-known positions with respect to tissue could form an extended coherent synthetic aperture with concomitant increases in resolution. Precise positioning could be achieved by a passive position-sensing device or a motorized translation system. We discuss the requirements for these systems and the impact of positioning errors and tissue motion on image quality. We discuss beamformer requirements for SASAI systems and propose several clinical scenarios in which such a system could find application. We present simulation studies demonstrating the potential of SASAI systems for both 1D and 2D arrays under various imaging scenarios. We also present initial experimental results showing improved image resolution achieved with SASAI.

11.5 **Co-robotic ultrasound tomography,** Fereshteh Aalamifar, Rishabh Khurana, Russell H. Taylor, Iulian Iordachita and Emad M. Boctor, *Johns Hopkins University, Baltimore, MD, fereshteh@jhu.edu*

Ultrasound tomography enables 3D imaging and at the same time can provide more information such as attenuation or speed of sound estimations. Several systems have been proposed to enable ultrasound tomography; some of them use cylindrical arrays of ultrasound elements that are mechanically challenging to put together and calibrate and/or may require a water bath. Another way of enabling ultrasound tomography is to use one probe as transmitter and another one as receiver. The advantage of such system is that it enables soft tissue tomographic imaging using already-existing 2D systems and can take advantage of most recent developments. However, the challenge is how to keep the two probes accurately aligned during the scan given that ultrasound waves do not travel through the air and should always be in contact with the tissue. Here, we propose a robot-assisted ultrasound tomography (RAUT) system that includes one hand-held probe operated by a sonographer and another robot-held probe that mimics the sonographer's hand movement trying to maintain the alignment.

A prototype was developed to enable the RAUT system; a 6-DOF UR5 robotic arm (Universal Robots, Denmark) is used to operate the robot-held probe, which is a low-noise, low-weight robot with 0.1 mm precision and 80 cm radius reach. To enable tracking, the MicronTracker Sx60 (Claron Technology, Canada), which has 0.25 mm precision and can collect data with a speed of up to 48 Hz, is used. The advantages of MicronTracker for the RAUT system is that it is lightweight, has passive easily-printable markers and can show a live scene view. This can enable the RAUT system to use the tissue photographic image for later tomographic reconstruction purposes. For this reason, an end-effector is specially designed to hold the MicronTracker on the robot arm, thereby providing a live-scenery view of the tissue scanned by the robot-held probe. The rigid body for the hand-held probe and the position of the tracker on the robotic arm should be designed such that it is guaranteed that the marker attached to the hand-held probe will always be in the tracker's field of view, making the RAUT system more easily portable. A simulation study is done to create a sample design for scanning a cylindrical phantom.

After putting together all the system components, the main challenge is to calibrate them together. Two ultrasound calibrations and one hand-eye calibration are required. The ultrasound calibrations will calibrate the hand-held probe image to its marker and the robot-held probe image to the MicronTracker coordinate system. The hand-eye calibration will calibrate the robot tool tip to the MicronTracker coordinate system. The ultrasound calibrations are done through point calibration and a gradient decent algorithm. The reconstruction precisions of the ultrasound calibrations are [1.20, 0.97, 3.99] mm and [0.69, 1.25, 1.05] mm along axes for the handheld and robot-held probes, respectively. Hand-eye calibration is done by fixing the marker to a table and moving the end-effector (with the tracker rigidly attached) to different positions and angles. Again the gradient decent algorithm is used to calculate the unknown transformation with a reconstruction precision of [1.50, 1.54, 1.23] mm along the axes. The

calibrations' information is entered into the C program that interfaces the tracker readings with the robot controller. A preliminary experiment is carried out to measure the RAUT system repeatability. The goal is to see if the system will yield the same robot-held image plane position when the hand-held probe is fixed; the experiment showed a repeatability of [5.87, 5.16, 4.97, 5.73] mm for the four robot-held image corners. In addition, the system is evaluated qualitatively by moving the handheld probe and running the program, which shows a visually-accurate alignment of the two probes with the two image planes having at least 50% overlap.

Current results confirm the feasibility of such system and more extensive evaluations of the system performance are currently under investigation. In addition, other methods can be used to further fine-align the probes such as using the image planes or ultrasound beam-energy information.

11.6 **Effect of spatial low-pass filtering on numerical simulations of the continuous-wave KZK equation**, Xiaofeng Zhao and Robert J. McGough, *Department of Electrical and Computer Engineering, Michigan State University, Ann Arbor, MI, mcgough@egr.msu.edu*

The Khokhlov-Zabolotskaya-Kuznetsov (KZK) equation is commonly applied to simulations of medical ultrasound. For continuous-wave excitations, one approach employed in simulations of the KZK equation(1) combines implicit backward Euler finite-difference and Crank-Nicolson finite-difference methods. In this approach, the backward Euler finite-difference calculation is applied for several steps in the axial direction to prevent numerical oscillations in the computed solution and then the Crank-Nicolson finite-difference method is applied for the rest of the simulation. This combination has also been implemented in FOCUS, the 'Fast Object-oriented C++ Ultrasound Simulator,' to calculate continuous-wave nonlinear pressures generated by flat circular and spherically-focused ultrasound transducers. In these calculations, the implicit backward Euler finite-difference calculation is recognized as a spatial low-pass filter, where the spatial frequencies removed by the backward Euler finite-difference calculations otherwise cause oscillations in Crank-Nicolson finite-difference calculations. This suggests an alternative approach that replaces the repeated backward Euler finite-difference calculations with a single spatial low-pass filtering step. When the remaining calculations are performed with the Crank-Nicolson finite-difference approach, similar results are expected when the low-pass filter is implemented as a 2D Gaussian function convolved with the flat circular or spherically-focused aperture function. Simulation results are evaluated for the linearized KZK equation with flat circular and spherically-focused ultrasound transducer models, where the reference fields for these linear pressure calculations are provided by the fast nearfield method in FOCUS. The simulation results show that the fast nearfield method, the linear KZK results obtained with backward Euler and then Crank-Nicolson finite difference methods and the linear KZK results obtained with the single low-pass filter step followed by Crank-Nicolson finite difference calculations all yield approximately equivalent results in the far field of the paraxial region. In the nearfield region, some interesting differences are observed, which is expected because the KZK equation is only accurate in the farfield of the paraxial region and for transducers with large f/#. Supported in part by NIH Grant R01 EB012079.

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11.7 **High-resolution pressure waveform measurements using fiber-optic hydrophones and complex deconvolution of hydrophone sensitivity**, Keith A. Wear[1], Paul M. Gammell[2], Subha Maruvada[3], Yunbo Liu[4], and Gerald R. Harris[1], *[1]Food and Drug Administration, Silver Spring, MD and [2]Gammell Applied Technologies, Exmore, VA, keith.wear@fda.hhs.gov*

Objective: Fiber-optic hydrophones can have extremely small sensitive element size (10 μm) for high spatial resolution, the ability to withstand moderately high-intensity therapeutic fields and the ability to measure temperature as well as pressure. However, their frequency response can be very nonuniform, which can lead to inconsistent measurements. The objective of this work was to investigate the effectiveness of complex deconvolution of sensitivity from fiber-optic hydrophone measurements in order to improve accuracy and precision of acoustic-output measurements.

Methods: In the first set of experiments, a swept-frequency time-delay spectrometry system was used to measure magnitude and phase responses of (1) a reference membrane hydrophone with very uniform sensitivity and (2) six fiber-optic hydrophones.[(1)] Measurements were performed using four broadband source transducers in order to obtain hydrophone sensitivity over the band from 1 to 40 MHz. In the second set of experiments, the six fiber-optic hydrophones and the reference membrane hydrophone were used to measure a 4-cycle, 3.5 MHz pressure waveform. The voltage waveforms acquired in the second set of experiments were deconvolved with sensitivities measured in the first set of experiments[(2)] The effects of deconvolution on measurements of peak compressional pressure ($p+$), peak rarefactional pressure ($p-$, which is related to mechanical index), and pulse intensity integral (*PII*, which is related to thermal index) were measured.

Results: The reference measurements for ($p+$, $p-$, *PII*) in (MPa, MPa, mJ/cm^2) for the membrane hydrophone were (3.1, 1.1, 0.061), with precision better than 10% for all three parameters. The means and standard deviations for the six fiber-optic hydrophones were (6.6 ± 1.1, 2.4 ± 1.2, 0.136 ± 0.024) before deconvolution and (3.0 ± 0.4, 1.6 ± 0.2, 0.077 ± 0.012) after deconvolution.

Conclusion: Complex deconvolution results in substantial improvement in accuracy and precision of acoustic output measurements with fiber-optic hydrophones.

Wear et al. *IEEE Trans Ultrason Ferroelectr* Freq Contr *58*, 2418-2437 (2011). Wear et al. *IEEE Trans Ultrason Ferroelectr Freq Contr 61*, 62-75 (2014).

11.8 **Robotic 2D ultrasound calibration utilizing trajectory of moved phantom,** Haichong 'Kai' Zhang[1], Alexis Cheng[2], Fereshteh Aalamifar[3], Hyun-Jae Kang[4], Gregg Trahey and Emad M. Boctor[1], [1]*Johns Hopkins University, Baltimore, MD and* [2]*Duke University, Durham, NC, hzhang61@jhu.edu*

Accurate localization and pose information of an ultrasound probe has various applications for medical diagnosis. In image-guided surgery, e.g., a virtual ultrasound-image overlay enables a depth-penetration view while being noninvasive and real-time. In addition, a potential utilization of pose information with synthetic-aperture techniques is considered. Synthetic apertures improve the resolution of deep targets by expanding the aperture size and, knowing the precise orientation and location of an ultrasound transducer, can generate imaginary elements, which eventually further expand the aperture. Accurate tracking of ultrasound images requires knowing the position of the tracking device attached to the ultrasound probe as well as the rigid-body relationship between the attached sensor and ultrasound image. The process of acquiring the unknown rigid-body transformation is called ultrasound calibration. The strategy taken to get the transformation between the tracking device and image is solving the hand-eye calibration problem, also known as AX=XB problem.

The problem of the conventional approach based on segmentation is that the accuracy of choosing points strongly depends on image quality. The accuracy that is required is directly related to the potential application. For instance, the synthetic-aperture technique requires subwavelength localization accuracy (616 μm for 2.5 MHz transducer), which cannot be achieved in the segmentation-based approach. Therefore, a simple and accurate calibration technique is necessary. We propose a new ultrasound calibration method that does not rely on segmentation but utilizes the trajectory of a moved phantom. While fixing the position of the ultrasound probe, a line phantom is moved in a designated distance in the x and y directions from the phantom's coordinates. The amount of displacement of a target appearing in the image is compared to the actual displacement. Compared to the segmentation method, normalized cross-correlation involves information on the entire characteristic of the acoustic response, including shape and amplitude, and it is possible to obtain accurate displacement of the target. At the same time, a robotic-tracking system is implemented to further improve the accuracy of the reconstructed transformation.

We validate the proposed method through simulations. In simulations, the NCC noise was defined as 50 μm, which is the number confirmed though a preliminary experiment, and the tracking-system accuracy of 100 μm was set based on the accuracy of the robot (Universal Robot, UR5) used in the experiment. For 60 ultrasound simulations, we obtained a rotational error, compared to the ground-truth, of 0.15±0.10° and a translational error of 0.48±0.32 mm.