UITC ABSTRACTS 2018

Wednesday morning

1. TISSUE PARAMETERS 1

1.1 **Quantitative ultrasound and texture predictors of breast-tumor response to chemotherapy prior to treatment,** Gregory Czarnota, Hadi Tadayyon, Mehrdad Gangeh, Lakshmanan Sannachi, Ali Sadeghi-Naini, William Tyler Tran, Sonal Gandhi, Maureen Trudeau, [1]*Department of Radiation Oncology, and Physical Sciences, Sunnybrook Health Sciences Centre,* [2]*Division of Medical Oncology, Sunnybrook Health Sciences Centre,* [3]*Division of General Surgery, Sunnybrook Health Sciences Centre,*[4]*Departments of Medical Biophysics, University of Toronto, Toronto, ON, Canada,* G*regory.Czarnota@sunnybrook.ca*

Background: Previous studies have demonstrated that quantitative ultrasound (QUS) is an effective tool for monitoring breast cancer patients undergoing neoadjuvant chemotherapy (NAC). Here, for the first time, we demonstrate the clinical utility of pre-treatment QUS texture features in predicting the response of breast cancer patients to NAC.

Methods: Using a 6 MHz center frequency clinical ultrasound imaging system, radiofrequency (RF) breast ultrasound data were acquired from 100 locally advanced breast cancer (LABC) patients prior to their NAC treatment. QUS Spectral parameters including mid-band fit (MBF), spectral slope (SS), and spectral intercept (SI), and backscatter coefficient parameters including average acoustic concentration (AAC) and average scatterer diameter (ASD) were computed from regions of interest (ROI) in the tumor core and its margin. Subsequently, employing gray-level co-occurrence matrices (GLCM), textural features including contrast (CON), correlation (COR), energy (ENE), and homogeneity (HOM), and image quality features including core-to-margin ratio (CMR) and core-to-margin contrast ratio (CMCR) were extracted from the parametric images as potential predictive indicators. QUS results were compared with the clinical and pathological response of each patient determined at the end of their NAC.

Results and Discussion: Results from the 100 patients indicate that a combined QUS feature model demonstrated a favorable RECIST-based response (sensitivity=83%, specificity=79%, and AUC=82%), Miller-Payne based response (sensitivity=88%, specificity=71%, and AUC=83%), and were linked to patient survival (sensitivity=71%, specificity=92%, and AUC=82%) predictions. Best results were obtained using a radial-basis –function support vector machine) RBF-SVM machine learning algorithm. Only four features were selected in each binary response group classification.

Conclusion: The findings of this study suggest that QUS features of a breast tumor are strongly linked to tumor responsiveness. The ability to identify patients that would not benefit from NAC would facilitate salvage therapy and a clinical management that has minimum patient toxicity and maximum outcome (and a better quantity/quality of life). Future work will include investigations into the ability of a QUS model in predicting patient survival upon completion of chemotherapy and surgery, and the effect of including (i.e., estrogen/progesterone/human epidermal growth factor receptor 2 receptor status and histological grade) in the QUS-based predictive model.

1.2 **Comparing machine learning classifiers in breast cancer treatment response monitoring using quantitative ultrasound,** Lakshmanan Sannachi[1], Mehrdad Gangeh,[1] Ali Sadeghi-Naini[1], William Tran[1], Sonal Gandhi[2], Frances Wright[3], Gregory Czarnota,[1,4] [1]*Department of Radiation Oncology, and Physical Sciences, Sunnybrook Health Sciences Centre,* [2]*Division of Medical Oncology, Sunnybrook Health Sciences Centre,* [3]*Division of General Surgery, Sunnybrook Health Sciences Centre,* [4]*Departments of Medical Biophysics, University of Toronto, Toronto, ON, Canada, Gregory.Czarnota@sunnybrook.ca*

Objective: Pathological response of breast cancer to chemotherapy is a prognostic indicator for long-term disease free and overall survival. Responses of locally-advanced breast cancer in the neoadjuvant chemotherapy (NAC) settings are often variable and the prediction of response is imperfect. The purpose of this study was to detect tumor responses early after the start of neoadjuvant chemotherapy using quantitative ultrasound (QUS) technique with machine-learning algorithm in patients with locally-advanced breast cancer.

Methods: A total of 100 LABC patients treated with neoadjuvant chemotherapy were included in the analysis here. Breast tumors in patients were scanned with an Ultrasonix-RP clinical ultrasound system prior to chemotherapy treatment,

during the first, fourth and eighth week of treatment, and prior to surgery using a L14-5 transducer with a central frequency of 7 MHz. QUS parameters were calculated from ultrasound radiofrequency (RF) data within tumor regions of interest. Additionally, texture features were extracted from QUS parametric maps. Patients were classified into two treatment response groups based on identified Miller-Payne score: responders, and non-responders. QUS and texture parameters estimated from tumor regions were used to train a machine-learning algorithm. The resulting algorithm was utilized in identifying unseen individual subjects as either "responders" or "non-responders". Three machine learning algorithms namely, linear discriminant, *k*-nearest-neighbors, and support vector machine algorithms were implemented and evaluated.

Results and Discussion: All algorithms distinguished responders and non-responders with prediction accuracies ranging between 68% and 92%. In particular, the support vector machine was found to be the best classifier in differentiating responders and non-responders with accuracies of 78%, 90% and 92 % at week 1, 4 and 8 after treatment, respectively. The most relevant features in separating the two response groups at early stage (week 1 and 8) were texture features and at a later stage (week 8) were quantitative ultrasound parameters, particularly ultrasound backscatter intensity parameters.

Conclusion: Early stage treatment response of breast cancer can be predicted at an individual subject level by quantitative ultrasound technique with advanced machine learning algorithms. Future studies should examine the performance of this type of response-monitoring model in other populations and its subsequent utility in facilitating critical decisions of changing the treatment for refractory patients early during treatment.

1.3 **Quantitative ultrasound characterization of breast- cancer hyperthermia treatment response *in vivo*,** Deepa Sharma[1], Lakshmanan Sannachi[1], Holliday Cartar[1], Wentao Cui[1], William Tyler Tran[1,2], Gregory J. Czarnota,[1,2,3] *[1]Physical Sciences, Sunnybrook Research Institute, [2]Department of Radiation Oncology, Sunnybrook Health Sciences Centre, [3]Departments of Medical Biophysics, University of Toronto, Toronto, ON, Canada. Gregory. Czarnota@sunnybrook.ca*

Background: Quantitative ultrasound (QUS) is an important noninvasive imaging method that allows treatment effects of various potential therapies to be readily detected. QUS can be easily employed to distinguish between healthy functioning cells and damaged cells depending on the quantitative ultrasound features such as signal intensity, scatterer size, and the concentration of microscopic scatterers. In the present study, tumor responses to ultrasound-stimulated microbubble vascular disruption and hyperthermia treatments were monitored *in vivo* using QUS.

Methods: Tumor-bearing mice (*n*=85), with breast cancer xenografts (MDA-MB-231) were exposed to ultrasound-stimulated microbubbles (USMB) at a concentration of 3% (v/v) and hyperthermia at different exposure times (0, 10, 20, 30, 40, 50 min). Treatment effects were examined using quantitative ultrasound with center frequency of 25 MHz (bandwidth range: 16 – 32 MHz). Ultrasound parameters such as midband fit (MBF), spectral slope (SS), 0-MHz intercept (SI), scatterer spacing (SAS), scatter diameter (ASD) and acoustic concentration (AAC) were determined 24 hours prior to and after treatment. Additionally, texture features: contrast (CON), correlation (COR), energy (ENE), and homogeneity (HOM) were extracted from QUS parametric maps. Finally, all estimated parameters were compared with histology. *Results and Discussion:* The results demonstrated significant increases in QUS parameters with treatment: hyperthermia-only 20 minutes heat exposure) and combined hyperthermia plus USMB and finally reaching a maximum at 50 minutes of heat exposure (hyperthermia only: ΔMBF = +5.40 ± 1.03 (±SD) dBr; SI= +6.44 ± 2.08 dBr and AAC = 5.19 ± 0.93 dB/cm^3, and combined: ΔMBF = +5.93 ± 2.09 dBr; SI= +5.07 ± 2.22 dBr and AAC = 5.92 ± 0.75 dB/cm^3). Furthermore, histological data revealed differences in microstructure, nucleus size and their orientation when compared between hyperthermia only and combined treatment. Texture based QUS parameters were found to be linked to biological changes in accordance with microstructural changes obtained from histological data (hyperthermia only: ΔSAS-CON= -0.031 ± 0.050 %; ΔASD-ENE = 0.006 ± 0.007 % and combined: ΔSAS-CON= 0.029 ± 0.027 % (p= 0.0317); ΔASD-ENE= 0.001 ± 0.006 % (p= 0.0159).

Conclusion: Quantitative ultrasound data demonstrated that specific markers can be used to detect hyperthermia treatment effects in breast cancer tumors *in vivo.* Data were linked to the extent of histological damage in tumor specimens after treatment.

1.4 **Application of robust short-lag spatial-coherence beam- forming to breast-ultrasound data,** Alycen Wiacek,[1] Ole Marius Hoel Rindal,[2] Kelly Fabrega-Foster,[3] Susan Harvey,[3] Muyinatu A. Lediju Bell,[1,4] *[1]Department of Electrical and Computer Engineering, Johns Hopkins University, [2]Department of Informatics, University of Oslo, [3]Department of Radiology and Radiological Science, Johns Hopkins Medicine, [4]Department of Biomedical Engineering, Johns Hopkins University, awiacek1@jhu.edu*

Ultrasound imaging is a critical tool in the detection of breast lesions, particularly in patients with dense breast tissue where mammography alone is limited. Like many ultrasound imaging modalities, breast ultrasound images are plagued with clutter due to the heterogeneity of breast tissue. These artifacts obscure important diagnostic features, and

complicate clinical decisions. While short-lag spatial coherence (SLSC) imaging is effective at reducing clutter and improving the contrast of hypoechoic targets, the texture of SLSC images does not always follow the same speckle pattern seen in B-mode images, particularly at the higher lag values.

Two modifications to the lag summation step of SLSC imaging (i.e., M-Weighted SLSC and Robust SLSC) were recently implemented to provide SLSC tissue texture that is more familiar to clinicians.(1) The first modification applies a weighted summation of each coherence image (called M-Weighting), placing emphasis on low-lag regions, while enabling the incorporation of information from higher lag values. The second modification employs robust principle component analysis in order to identify and remove outliers in the displayed coherence values. Both modifications introduce additional robustness to the original SLSC imaging method, enabling enhanced tissue smoothing, boundary delineation, and hypoechoic target visibility at higher lag values.

This work is the first to apply SLSC, Robust SLSC, and M-Weighted SLSC to breast ultrasound data. Three patients who exhibited one of three benign targets in breast tissue (i.e., cyst, hematoma, fibroadenoma) were included in our preliminary study. Channel data were acquired with an Alpinion Research Ultrasound Scanner (Alpinion, Seoul, Korea) as approved by the Johns Hopkins Medicine Institutional Review Board. These channel data were used to create matched B-mode, SLSC, M-Weighted SLSC, and Robust SLSC images for each breast mass. Contrast improvements up to 9 dB were achieved in hypoechoic regions when comparing the original B-mode image to the Robust SLSC image. In addition, Robust SLSC consistently provides an option to match B-mode speckle signal-to-noise ratio by varying a sparsity parameter called λ. We also show that the cyst and fibroadenoma appear similarly hypoechoic in ultrasound images, but they have largely different coherence values in the three types of SLSC images. This finding highlights the potential of SLSC imaging to distinguish between fluid-filled cysts and solid lesions, perhaps even malignancies, that appear similarly hypoechoic in traditional B-mode ultrasound images.

(1) Nairet, AA et al. in *IEEE Trans. Ultrason. Ferroelectr. Freq. Contr* (2018, in press).

2. TISSUE PARAMETERS 2

2.1 **Comparison of human and nonhuman primate cervix: summary of quantitative ultrasound findings and implications for future research**, Timothy Hall,[1] Helen Feltovich,[1,2] Ivan Rosado-Mendez,[1] Lindsey Drehfal,[1] Quinton Guerrero,[1] Andrew Santoso,[1] Mark Palmeri,[3] *[1]Medical Physics, University of Wisconsin-Madison, Madison, WI; [2]Maternal Fetal Medicine, Intermountain Healthcare, Provo, UT;[3]Biomedical Engineering, Duke University, Durham, NC, tjhall@wisc.edu*

Objective: To compare findings from studies using quantitative ultrasound (QUS) biomarkers and nonlinear optical microscopy to study the cervix.

Methods: We use QUS techniques to study the extracellular matrix (ECM) microstructure and associated biomechanical properties of the *ex vivo* and *in vivo* cervix of humans and nonhuman primates (Rhesus macaque; NHPs). Specifically, we use shear wave elasticity imaging (SWEI) to evaluate cervical softness, and acoustic backscatter to evaluate ECM microstructural organization. We compare those findings to observed structure in second harmonic generation (SHG; multiphoton) microscopy images of *ex vivo* cervix.

Results: We found similar decreases in SWS in humans and NHPs from early to late pregnancy, suggesting greater cervix softness in late pregnancy. Similarly, backscatter anisotropy, parameterized using the mean backscatter power difference (mBSPD), was significantly greater in the non-pregnant and early pregnant cevix, as compared to the late pregnant cervix, suggesting decreased microstructural organization in late pregnancy – a finding consistent with invasive terminal studies of rodent cervix SHG images. There are, however, some significant differences in the anatomy and structure of the human versus NHP cervix and those difference have a significant impact on QUS scanning methods and spatial heterogeneity of QUS parameter values. A new prototype transducer, recently implemented in a longitudinal study of human cervix during pregnancy, considerably improves visualization of the cervix and improves confidence in sampling the same location in the cervix in longitudinal studies.

Conclusions: These biologically plausible results suggest that a combination of QUS biomarkers that simultaneously assess various facets of cervical change may be an effective way to evaluate the *in vivo* pregnant cervix. Supported by NIH grants T32CA009206, R01HD072077, R21HD061896 and R21HD063031 and the Intermountain Research & Medical Foundation. We are also grateful to Siemens Healthcare Ultrasound division for an equipment loan and technical support.

2.2 **Correlation length ratio as a parameter for determination of fiber-like structures in soft tissues**, Mohammadreza Kari[1], Andrew P. Santoso[1], Quinton W. Guerrero[1], Helen Feltovich[1,2], Timothy J. Hall,[1] [1]*Medical Physics, University of Wisconsin-Madison, Madison, WI,* [2]*Maternal Fetal Medicine, Intermountain Healthcare, Provo, UT,* *mkari@wisc.edu*

Objectives: Quantitative ultrasound techniques often assume the tissue is homogeneous, isotropic, and provides diffuse scattering. However, tissues-like skeletal muscle exhibit backscatter anisotropy because of elongated structure. This work compares the echo amplitude SNR and generalized spectrum (GS) analysis to a novel parameter named the correlation length ratio (CLR).

Methods: An anisotropic phantom containing dense, randomly-spaced, aligned fibers (200 micron diameter) and an anisotropic tissue (bicep muscle) were scanned. RF echo signals were obtained with the 18L6 linear array on a Siemens S3000 system. Using MATLAB, we computed the echo amplitude SNR, the GS, and the CLR (ratio of lateral to axial envelope correlation length) from the backscattered RF echo signals. To account for the system point spread function, an empirical cumulative distribution function (CDF) of the CLR was obtained from a diffuse-scattering reference phantom. A one-sided threshold of 95% of the CDF was used to define the upper bound. A CLR greater than the threshold suggested elongated structures in the sample.

Results: The echo amplitude SNR and CLR for the reference phantom were 1.91±0.07 and 2.75±0.69, respectively. Analogous values in the anisotropic phantom were 2.04±0.13 and 4.02±1.65, suggesting the presence of randomly-spaced, elongated scattering sources. GS analysis did not show the presence of periodic scatterers in this phantom. Analogous SNR and CLR values in the bicep muscle were 1.24±0.29 and 7.50±3.22, showing the pre-Rayleigh scattering condition and strongly suggesting the presence of fiber-like structures in the bicep muscle, as expected. In addition, GS analysis showed that these scattering sources are periodically-spaced, as expected.

Conclusions: The CLR detected the presence of elongated structures in a phantom and tissue with anisotropic scatterers suggesting the potential for objective quantification of the presence of fiber-like structures in complex biological tissues without the need for beamsteering. Supported by NIH Grants T32CA009206 and R01HD072077. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. We are also grateful to Siemens Ultrasound for an equipment loan and technical support.

2.3 **Correlations between cervical smooth-muscle force generation and acoustic backscatter-coefficient parameters,** Andrew P. Santoso[1], Joy Vink[2], George Gallos[3], Helen Feltovich[1,4], Timothy J. Hall,[1] [1]*Medical Physics, University of Wisconsin- Madison, Madison, WI,* [2]*Dept of Obstetrics and Gynecology, Columbia University Medical Center, New York, NY,* [3]*Dept of Anesthesia, Columbia University Medical Center, New York, NY,* [4]*Maternal Fetal Medicine, Intermountain Healthcare, Provo, UT,* *apsantoso@wisc.edu*

Objectives: Smooth muscle cells in the human cervix may play a significant role in cervical function during pregnancy.(1) To date, noninvasive methods to evaluate cervical smooth muscle cell activity are lacking. This study demonstrates that parameters derived from the acoustic backscatter coefficient (BSC) correlate with force generation resultant from smooth muscle contractions in *ex vivo* uterine cervix samples.

Methods: After informed consent, whole transverse cervical slices (n=5) were obtained from nonpregnant women undergoing total hysterectomies for benign indications. Transverse slices were obtained from the internal os, attached to a force transducer recording muscle-force generation, and suspended in organ baths. Radiofrequency echo data were acquired every 2 s using a Siemens Acuson S3000 with a 14L5SP transducer for long durations (max of five hours). Bulk motion was assessed on B-mode images by computing center-of-mass deviation. The Reference Phantom Method was used to obtain BSC estimates before and after administration of 1μM of oxytocin. BSCs were parameterized in terms of frequency dependence and magnitude by calculating effective scatterer diameter (ESD) and average BSC (ABSC) within 4-9 MHz, respectively. Pearson correlation coefficients (r) were computed between muscle force and BSC parameters for the first 30 minutes post-drug delivery using a 1-minute moving average filter. Differences in coefficients of variation (COVs) pre- and post-drug delivery were analyzed using a Kruskal-Wallis H test.

Results: Bulk motion for all samples was less than 1.0 mm. Significant correlations were observed between muscle force and ESD for all samples (r = 0.40 – 0.91; p<0.0001), whereas correlations between muscle force and ABSC were more varied. All parameter COVs pre and post drug were significantly different (p<0.05).

Conclusions: These findings demonstrate ESD estimates correlate with increased muscle force generation in the cervix. Additional investigations (e.g., *in vivo* animal models) may elucidate mechanisms leading to parturition. Supported by National Institutes of Health Grants T32CA009206 from the National Cancer Institute and R01HD072077, 1R01HD082251-01A1, and K08HD088758 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. We are also grateful to Siemens Healthcare Ultrasound division for an equipment loan and technical support.

(1) Vink J et al. *AJOG*. 2016, 215(4):478.e1

2.4 **Quantitative ultrasound assessment of collagen fibers in *ex-vivo* human skin,** Masaaki Omura[1], Kenji Yoshida[2], Shinsuke Akita[3], Tadashi Yamaguchi,[2] *[1]Graduate School of Science and Engineering, Chiba University, [2]Center for Frontier Medical Engineering, [3]School of Medicine, Chiba University, Chiba, Japan, m.omura@chiba-u.jp*

Background: The goal of this study is to develop a quantitative ultrasound (QUS) method for diagnosing skin fibrosis or inflammation at the early stage of lymphedema. In skin tissues, it is recognized that collagen fibers are among the most dominant scatterers of the echo signal, so the characteristics of echo signals from normal or abnormal skin tissues may reflect the physical and acoustic properties of collagen fibers. We apply the signal analysis method using the echo amplitude envelope and the backscatter coefficient (BSC) to assess the conditions of collagen fibers.

Methods: We characterized *ex-vivo* normal skin (n=3) and lymphedema skin (n=1) samples from women patients at an abdomen. RF echo signals were acquired using a self-made ultrasonic scanner with a 25 MHz single element concave transducer (PT25, Toray) in three-dimension. The distance of the lower epidermis, dermis, and dermis-hypodermis junction was within 9 to 11 mm from the transducer, and QUS parameters were calculated in the above distance. QUS parameters were HKD clustering parameter μ (HKD-μ) related with scatterer number density in a medium, and integrated BSC (IBSC within 19-29 MHz) that indicates the intensity of backscattered echo signals. HKD-μ was computed using the log-moment method, and BSC was calculated with reflector method.

Results: The medians (25-75 percentiles) of calculated QUS parameters are as follows: HKD-μ=0.71(0.43-1.16), IBSC=4.32(2.20-10.3)$\times 10^{-3}$ sr^{-1} mm^{-1} in the normal skin, and HKD-μ=2.03(1.32-2.89), IBSC=13.0(6.49-23.4)$\times 10^{-3}$ sr^{-1} mm^{-1} in the lymphedema skin. It is considered that the number density of collagen fibers in the lymphedema dermis is higher, and its backscattered signal is more hyperechoic than normal dermis tissues due to skin fibrosis. These results were verified by computer simulation reflecting the macroscopic structure of skin analyzed with 250 MHz ultrasound. Partly supported by JSPS KAKENHI Grant Numbers JP17H05280, JP17J07762.

Wednesday afternoon

3. ELASTICITY 1

3.1 **Exploiting correlation and signal-to-noise ratio for delineating human carotid plaque components *in vivo* in ARFI imaging,** Gabriela Torres, Tomasz J. Czernuszewicz, Jonathon W. Homeister, Melissa C. Caughey, Benjamin Y. Huang, Ellie R. Lee, Carlos A. Zamora, Mark A. Farber, William A. Marston, David Huang, Timothy C. Nichols, Caterina M. Gallippi. *Joint Department of Biomedical Engineering, University of North Carolina at Chapel Hill and North Carolina State University, NC, cmgallip@email.unc.edu*

Background: Atherosclerosis is a slow progression disease that can remain asymptomatic until very late stages, making it difficult to identify and treat. Recent histological studies indicate that vulnerable plaques are most often not the largest or the most obstructive but an elusive range in the middle, with their relative risk governed by their composition and structure. Specific components distinguish a vulnerable plaque, including a thin or ruptured fibrous cap (TRFC), a large lipid-rich necrotic core (LRNC), and intra-plaque hemorrhage (IPH). A previous study demonstrated the capability of Acoustic Radiation Force Impulse (ARFI) imaging for delineating plaque features with histological validation.(1) In particular, collagen (COL) and calcium (CAL) deposits correlated with areas of decreased ARFI-induced peak displacement (PD), consistent with the expected response of stiff materials. Further, LRNC and IPH correlated with areas of increased PD, consistent with the expected response of soft materials. In this study, we aim to improve discrimination between soft and between stiff plaque components. We compare metrics exploiting ARFI-induced displacement, signal-to-noise ratio (SNR), and cross-correlation coefficient (CC) parameters in terms of their abilities to discriminate between soft and between stiff plaque features.

Methods: This study analyzed twenty human carotid plaques imaged *in vivo* by ARFI ultrasound in a previous clinical study involving patients undergoing carotid endarterectomy (CEA) (1). CEA specimens were harvested after imaging for histological validation of ARFI outcomes. Output parameters were systematically calculated as the variance of the n^{th} time derivate (n=0,1,2,3,4) for ARFI-derived displacement, SNR, and CC. For all the outcome parameters, images were normalized to the median value within the plaque ± two mean absolute deviations. The normalized parametric images were evaluated by a trained, unblinded reader who referenced the pathologist's markings on the spatially-matched histology to hand-delineate plaque features (COL, CAL, LRNC and IPH). Feature contrast-to-noise ratio (CNR) was

calculated between IPH and LRNC, between CAL and COL, between LRNC and COL, and between grouped "soft" plaque elements (LRNC and IPH) and grouped "stiff" plaque elements (CAL and COL). CNR coefficient of variation (CV) ratios were calculated as standard deviation over mean (σ/μ) for each parameter.

Results: Among all examined outcome measures, the base-10 logarithm of the variance of the second time derivative (LVD''), achieves the highest CNR between IPH and LRNC (1.45, CV: 0.61), between COL and CAL (2.30, CV: 0.42), between LRNC and COL (2.07, CV: 0.49), and between grouped soft and grouped stiff features (3.09, CV: 0.31). The second highest CNR between IPH and LRNC is achieved by the variance of the first time derivative of CC (1.40, CV: 0.67). The second highest CNR between CAL and COL was achieved using base-10 logarithm of SNR (1.35, CV: 0.62). Finally, PD achieves the second highest CNR between grouped soft and grouped stiff plaque features (1.92, CV: 0.28).

Conclusions: These results suggest that parameters exploiting signal correlation and SNR in ARFI imaging can improve discrimination between soft and between stiff plaque features in comparison to PD. The presented results also demonstrate that although LVD'' is influenced by both CC and SNR, evaluating CC alone or SNR alone does not differentiate between soft and between stiff plaque features as well as LVD'' does. Sensitivity and specificity of these ARFI-derived metrics for *in vivo* human carotid plaque feature delineation will be evaluated in a future blinded-reader study. Supported in part by NIH grants R01HL092944, K02HL105659, and T32HL069768.

(1) Czernuszewicz et al. *J. Vasc. Surg. 66*, 1749-1757 (2017).

3.2 **Normalized shear-deformation indicator for ultrasound strain elastography in breast tissues: *in vivo* feasibility study,** Jingfeng Jiang,[1] Bo Peng,[2] *[1]Department of Biomedical Engineering, Michigan Technological University, Houghton, Michigan 49931, School of Computer Science, Southwest Petroleum University, Chengdu, Sichuan, China, jjiang1@mtu.edu*

Shear deformation under load contains useful information for differentiation of benign breast lesions from malignant ones. In this study, we propose a normalized shear deformation indicator (NSDI) that is derived from the concept of principal strains. Particularly, NSDI ranges from 0 to 1 for easy interpretation.

Since the NSDI requires both high quality axial (parallel to the acoustic beam) and lateral (perpendicular to the beam) displacement estimates, a strategy combining high-quality speckle tracking with signal "denoising" was employed. Both techniques were previously published by our group. More specifically, a high-quality subsample speckle tracking algorithm was first used to accurately track both axial and lateral displacements from a sequence of ultrasound echo data following a multiple- compression manner. Then, these ultrasonically-estimated displacements were processed using a partial differential equation (PDE)-based signal "denoising" algorithm. The adopted PDE-based algorithm iteratively reduced noise contained in the raw displacement estimates by enforcing the tissue incompressibility. Finite element (FE) models were used to identify possible causes for elevated NSDI values in and around breast lesions, followed by an analysis of ultrasound data acquired from 26 biopsy-confirmed *in vivo* breast lesions.

Through the FE modeling work, we found that, theoretically, the elevated NSDI values could be attributed to three factors: significantly harden tissue stiffness, increasing heterogeneity and limited elevation deformation among breast cancers. The analysis of *in vivo* data showed that the proposed NSDI values were higher ($p < 0.05$) among malignant cancers as compared to those measured from benign ones. In conclusion, our preliminary results demonstrated that calculation of NSDI value is feasible and NSDI could add value to breast-lesion differentiation with current clinical equipment as a postprocessing tool.

3.3 **Characterization of local muscle-fiber anisotropy using shear-wave elastography in patients with chronic myofascial pain**, M. Bird[1], J. Shah[2], L. Gerber[1], H. Tandon[2], S. DeStefano[1], S. Sikdar,[1] *[1]George Mason University, Bioengineering, Fairfax, VA. [2]National Institute of Health, Physical Medicine and Rehabilitation, Bethesda, MD, mbird2@masonlive.gmu.edu*

Background and Aims: Myofascial trigger points (MTrPs) are a common finding in soft tissue musculoskeletal pain conditions, but their etiology and pathophysiology are poorly understood. Previous work has shown that MTrPs appear hypoechoic on ultrasound imaging. The objective of this study was to characterize the muscle fiber architecture in the neighborhood of MTrPs through the use of ultrasound Shear Wave Elastography (SWE) in an attempt to better understand the nature of MTrPs. We hypothesized that muscle containing MTrPs have disorganized fiber architecture.

Methods: Twenty-four participants (14 women) who met criteria for chronic myofascial pain affecting the neck region were recruited. All underwent a standard clinical history and physical examination. A Supersonic Aixplorer ultrasound imaging system with an L10-4 ultrasound transducer was used to image the upper trapezius muscle. We utilized the property that externally-induced shear waves propagate faster longitudinally along muscle fibers compared to across the fibers. A custom transducer holder was used to image through a 20 mm diameter window placed over the palpable MTrP. The holder allowed rotation of the imaging plane to precise angles from 0° (along fibers) to 90° (perpendicular to fibers).

The primary outcome measure was the asymmetry in the change of the shear-speed profile with angle, which is a measure of fiber anisotropy.

Results: Muscles with active (symptomatic) MTrPs (N=24) exhibited higher anisotropy (14.25±11.01°), compared to normal, asymptomatic muscle tissue (N=12), which is more isotropic (7.16±6.70°) (p<0.05). There was a positive correlation between the maximum anisotropy and average pain (Pearson's r = 0.54).

Conclusions: Our findings suggest that muscle containing active MTrPs may demonstrate anisotropic fiber architecture compared to normal muscle tissue. These results may provide insight into underlying mechanisms of trigger point formation.

3.4 **Longitudinal measurements of response to corticosteroid therapy in transplanted livers using attenuation-measuring ultrasound shear-wave elastography (AMUSE),** Ivan Z. Nenadic[1], Luiz Vasconcelos[1], Sara Aristizabal[1], Matthew W. Urban[1,2], William Sanchez[3], James F. Greenleaf[1] , Shigao Chen[1,2], *[1]Mayo Clinic Ultrasound Research Laboratory, [2]Department of Radiology, [3]Department of Medicine, Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, MN,* *Nenadic.ivan@mayo.edu*

The success of liver transplantation with good short-term and long-term survival rates has resulted in its widespread use for treatment of many patients with end-stage liver disease. The current 1-year, 5-year and 10-year survival rates are 84%, 68% and 54%, respectively. According to the American Liver Foundation, more than 6,000 liver transplants are performed each year in the United States. The most common complication in the early post-transplant period is acute cellular rejection (ACR), occurring in 20-40% of patients. Currently, clinical confirmation of ACR requires a liver biopsy, which is invasive and may cause hemorrhage and mortality. In this study, we compare shear wave velocity and attenuation to biopsy findings of acute cellular rejection in six transplanted livers. Measurements were made four times between days 7 and 14 post-transplant.

Focused radiation force was used to excite shear waves in the liver and pulse echo is used to track the wave motion. Two-dimensional (2D) Fourier Transform of the shear wave motion to obtain the k-space whose coordinates are the frequency (f) and the wave number (k). The shear wave velocity (c) at the given frequency is equal to f_0/k_0, where f_0 and k_0 are the coordinates of the peak at the given frequency. The shear wave attenuation is calculated using $\alpha = (\pi/\sqrt{3})$ x $FWHM$, where $FWHM$ is the full-width at half maximum of the peak along the wave number axis. Measurements of shear wave velocity and attenuation were made at 100 Hz in six patients with transplanted livers that were being evaluated for potential acute cellular rejection, and the results were compared to clinical diagnoses made by liver biopsy in a blind study.

Data were analyzed for shear wave velocity and attenuation on days 7 and 14 in patients following the treatment for ACR at 100 Hz. The biopsy based diagnoses for each patient (P1–P6) from day 7 to day 14 changed as follows: P1, mild ACR to mild ACR (no change); P2, mild ACR no ACR; P3, mild ACR to minimal/no ACR; P4, mild ACR to no ACR; P5, minimal ACR to no ACR; P6, mild ACR to no ACR. These results are consistent with our previous findings that shear wave velocity decreases and attenuation increases as the liver transitions from cellular rejection to no rejection. The shear wave velocity measurements are in good agreement with invasive biopsy findings

3.5 **Characterization of nonlinear brain elasticity with shear shock waves**, David Espindola, Bharat B. Tripathi, Gianmarco Pinton, *Joint Department of Biomedical Engineering, University of North Carolina at Chapel Hill and North Carolina State University, 109 Mason Far road, Room 348 Taylor Hall, Chapel Hill, NC 27599.* *gfp@unc.edu*

Introduction: Shear shock waves can easily form in the brain. A 30 g surface impact, which is quite common, can propagate deep into the brain where it becomes a shear shock with local acceleration of 255 g. The nonlinear elasto-dynamic parameters for shear waves are therefore a critical but previously unappreciated tissue property that is required to describe injury biomechanics. Here, we characterize the elastic beta, the nonlinear parameter that governs shear wave behavior, in brain. Experimental and numerical results are compared to estimate the nonlinear parameter of the brain.

Methods: An external electromechanical shaker was used to generate large amplitude nonlinear shear waves in the porcine brain. A programmable ultrasonic scanner and a conventional transducer that was placed on top of the brain acquired high frame rate RF data. An adaptive-tracking algorithm was then used to generate movies of the brain's motion. A custom simulation tool that we have developed specifically to capture the physics of the shear shock wave propagation was then fitted to the experimental data by sweeping across the elastic beta. The shear wave attenuation and dispersion, which has a strong influence on the nonlinear propagation dynamics, was also measured independently with linear plane

wave experiments. These frequency-dependent parameters are also presented and discussed for the 50-400 Hz range relevant to shear shock waves.

Results: The simulation tool closely matches the observed shear shock wave dynamics. The fitting procedure predicts a nonlinear elastic parameter of beta=13. This translates to a shear wave Mach number that is three orders of magnitude larger than typical acoustic Mach numbers.

Conclusions: The brain linear dispersion and attenuation, and nonlinear elastic properties of brain were characterized. A focused shear shock wave configuration increases the precision of the beta estimate.

4. ELASTICITY 2

4.1 **Strain-dependent corneal-elasticity measurement using high-frequency ultrasound,** Laurentius O. Osapoetra,[1] Dan M. Watson,[1] Stephen A. McAleavey ,[2] *[1]Dept. of Physics, [2]Dept. of Biomedical Engineering, University of Rochester, Rochester NY, losapoet@ur.rochester.edu*

Background, Motivation and Objective: The cornea is an optically-transparent tissue essential for vision. Structural alterations of corneal collagen fiber due to pathologies (e.g. Keratoconus) and refractive surgeries result in changes of corneal biomechanical properties. Ultrasound elasticity imaging is a potential tool for noninvasive characterization of corneal biomechanics. As corneal thickness is only five-hundred microns, implementation of ultrasound elasticity imaging using high-frequency ultrasound is required. In this work, we study strain-dependent effect of corneal wave speeds.

Statement of Contribution/Methods: We implement vibration elasticity imaging of the cornea using a 35 MHz single-element transducer of 19 mm focus and aperture number 3.500Hz harmonic vibrations are generated on corneal surface using an electromagnetic shaker. The vibrations are tracked at some lateral tracking locations by repeated vibrate and track sequence. The acquisition results in motion frames that span 8 mm laterally, with 75 μm A-line spacing. Slow-time RF is acquired using 10kHz PRF for 25.6 ms.

Ex-vivo porcine eyes were immersed in edema-inhibiting fluid (10% Dextran-40 in saline) at room temperature. A custom-made chamber was designed to position the eye. An insertion needle was inserted into the anterior chamber of the eye for IOP control. Corneal wave speeds were estimated from 8 porcine eyes at IOP values of 10, 20, 30, and 40 cm H_2O.

*Results, Discussion, and Conclusion***:** Measurement of corneal wave speeds at different IOP values confirms strain-dependent effect of corneal biomechanics. Using high-frequency ultrasound, we come up with depth-dependent corneal wave speed maps at different IOP values. This work demonstrates implementation of elasticity imaging using high-frequency ultrasound for nondestructive characterization of corneal biomechanics.

***In vivo* assessment of interstitial fibrosis in renal allografts using simultaneous estimation of shear wave speed and backscatter coefficient,** Roberto J. Lavarello[1], Gabriela Torres[2], Carolina Amador[3], Sara Aristízabal[4], Maria Luisa Montero[5], Andrew D. Rule[6], Naim S. Issa[6], Thomas D. Atwell[7], Matthew W. Urban[7], *[1]Laboratorio de Imágenes Médicas, Departamento de Ingeniería, Pontificia Universidad Católica del Perú, San Miguel, Lima 32, Perú, [2]Joint Department of Biomedical Engineering, University of North Carolina, Chapel Hill, NC, [3]Ultrasound Imaging and Interventions, Philips Research North America, Cambridge, MA, [4]Well Living Lab, Inc., Rochester, MN, [5]Laboratorio de Estadística, Sección Matemáticas, Pontificia Universidad Católica del Perú, San Miguel, Lima 32, Perú, [6]Division of Nephrology and Hypertension, Department of Internal Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota, [7]Department of Radiology, Mayo Clinic College of Medicine, Rochester, Minnesota, lavarello.rj@pucp.edu.pe.*

Background and motivation: Renal transplant is the preferred long-term treatment for end-stage renal disease. Graft survival and renal function are monitored over the course of the graft's life using blood tests, medical imaging and renal biopsy. While complication rates of renal biopsies are low, biopsies are invasive, costly, and only sample a small part of the kidney. Therefore, in this work the potential of multiwave quantitative ultrasound (QUS) for the noninvasive diagnosis of interstitial fibrosis was studied.

Methods: Data were obtained from 22 renal transplant patients scheduled for protocol biopsies. Experiments were performed using a General Electric Logiq E9 with a C1-6-D curvilinear array transducer operating in Comb-push ultrasound shear elastography mode. Both the shear wave speed (SWS) and the average backscatter coefficient (aBSC) from each patient's kidney was estimated from the same datasets. Kidney biopsies were obtained, and the degree of interstitial fibrosis was scored as absent (ci=0, N=14), mild (ci=1, N=7), and moderate (ci=2, N=1). Statistical differences in QUS parameters for patients with ci=0 and ci>0 were evaluated using two-sided Wilcoxon rank sum tests, and classification was performed using linear logistic regression.

Results: The median aBSC values were 3.77×10^{-4} and 7.12×10^{-4} $sr^{-1}cm^{-1}$ for the *ci*=0 and *ci*>0 groups, respectively, with a statistically-significant difference observed (p = 0.002). The median SWS values were 2.08 m/s and 2.21 m/s for the *ci*=0 and *ci*=1 groups, respectively, with no statistically significant differences observed (p = 0.92). The logistic regression model that uses both aBSC and SWS values improved the classification accuracy (i.e., 0.91 vs 0.82) and AUC (i.e., 0.98 vs. 0.9) when compared to the model that uses only the aBSC values.

Conclusion: **T**he results suggest that multi-wave QUS may be a useful tool for the noninvasive diagnosis of renal interstitial fibrosis. Supported by DARI-PUCP and grant 012-2014- FONDECYT-C1 from the Peruvian government. Also supported in part by grant R01DK092255 from the National Institute of Diabetes and Digestive and Kidney Diseases.

4.2 **Comparison of acoustic radiation force-based methods for characterizing mechanical anisotropy in *ex vivo* skeletal muscle: ARFI, VisR, SWE, SDUV**

Leela Goel, Md. Murad Hossain, Caterina M. Gallippi. *The Joint Department of Biomedical Engineering, The University of North Carolina at Chapel Hill and North Carolina State University, Chapel Hill, NC, cmgallip@email.unc.edu*

Background: Many biological tissues are mechanically anisotropic, including skeletal muscle. Previous studies have shown that skeletal muscles' elastic anisotropy can be assessed by Shear Wave Elastography Imaging (SWEI), Shear-wave Dispersion Ultrasound Vibrometry (SDUV) and Acoustic Radiation Force Impulse (ARFI) measurements. Further, viscous anisotropy in skeletal muscle may be interrogated using SDUV. The purpose of this study is to demonstrate the feasibility of Viscoelastic Response (VisR) ultrasound, an ARF-based method that estimates tissue elasticity and viscosity in the region of ARF excitation, for characterizing elastic and viscous anisotropy in pig *psoas major* muscle, *ex vivo.*

Methods: A Siemens S3000^{TM} and 9L4 linear array transducer with an F1.5 focal configuration at a focal depth of 15 mm was used for imaging. VisR, ARFI, SDUV, and SWEI measurements were taken along and across the axis of symmetry of excised pig *psoas major* muscle. Corresponding ratios of estimated longitudinal shear elastic modulus to transverse shear elastic modulus were taken to assess elastic anisotropy. Ratios of viscous moduli estimated using VisR and SDUV were also calculated. Finally, elastic and viscous anisotropy measures made by VisR, ARFI, SDUV, and SWEI were compared.

Results/Discussion: The following elastic anisotropy measurements were obtained: ARFI = 2.17±0.39, VisR = 1.60±0.18, SWEI = 1.56±0.27, SDUV = 1.75±0.46. The following viscous anisotropy measurements were obtained: VisR = 2.83±0.70, SDUV = 2.23±0.54. The VisR-derived elastic anisotropy measurements were in close agreement with those derived using SWEI and SDUV; ARFI-derived elastic anisotropy was about 25% higher. The VisR derived viscous anisotropy measurements agreed with those obtained using SDUV.

Conclusions: VisR is a relevant method for assessing shear elastic and viscous anisotropy in skeletal muscle. This result suggests that VisR is useful for monitoring changes in mechanical anisotropy associated with pathology in muscle and other mechanically anisotropic organs.

4.3 **Estimation of mechanical anisotropy from ARFI-induced peak displacements**, Md Murad Hossain, Caterina M. Gallippi, *Joint Department of Biomedical Engineering, The University of North Carolina at Chapel Hill, Chapel Hill, NC, cmgallip@email.unc.edu*

Background: Many soft tissues, like skeletal muscle, can be modeled as transversely isotropic (TI) materials, defined by an axis of symmetry (AoS) perpendicular to a plane of isotropy. In such materials, mechanical properties differ along versus across the AoS. Hossain *et. al* assessed directional differences in mechanical property (i.e., degree of anisotropy (DoA)) in TI materials as the ratio of peak displacement (PD) achieved when the long axis of an asymmetric acoustic radiation force (ARF) point spread function (PSF) was aligned along versus across the material's AoS. However, DoA assessed using the PD ratio was qualitative. The objective of this work is to quantitatively estimate DoA using an empirically derived relationship between DoA and PD ratio.

Methods: Using LS-DYNA3D, 21 TI elastic materials were modeled with the following elastic constants: E_T = 18.1, E_L= 18.2, μ_L = 6.3-36.0, μ_T = 6.0 kPa, ν_{LT} = 0.499 and ν_{TT} = 0.51, where E = Young's modulus, μ= shear modulus, ν = Poisson's ratio, L = direction along the AoS, and T = direction perpendicular to the AoS. The materials were excited with impulsive, asymmetrical ARF excitations, which were modeled using Field II as the 3D acoustic intensity fields associated with a Siemens VF7-3 linear array transducer centered at 4.21 MHz with F/1.5 focal configuration. The ARF excitations were aligned along (90^o) or across (0^o) the material AoS. The resulting displacements directed the motion of scatterers in Field II simulations of acoustic displacement tracking using the VF7-3 at 6.15 MHz with F/1.5 focal

configuration. White Gaussian noise was added to each RF line to simulate system SNR of 30 dB. Axial (1D) cross-correlation between sequentially acquired RF lines was used to estimate the ARF-induced displacements. The displacement data sets were then subdivided into 'train' and 'test' sets. The 'train' set was comprised of simulated materials with DoA (i.e. shear moduli ratio) varying from 1.05 to 6 in steps of 0.4, while the 'test' set included materials with DoA values from 1.25 to 6 in steps of 0.4. The 'train' set was used to empirically derive a model describing the relationship between shear moduli ratio (μ_L/μ_T) and PD ratio (PD_{90} / PD_0). The performance of the derived model was evaluated on the 'test' set materials.

Results and Discussion: The empirically derived relationship between shear moduli ratio and PD ratio was $\sqrt{(\mu_L/\mu_T)} = m \times (PD_{90} / PD_0) + b$. The slope ($m$) and intercept ($b$) in the 'train' set were 2.1 and -1.13 for focal depth at 25 mm and were 1.83 and -0.85 for focal depth at 20 mm. This relationship predicted the shear moduli ratio of the 'test' set materials from the PD ratio with average absolute percent error of 6.5% and 2.0% for 25 and 20 mm focal depths, respectively. We note that the slope and intercept values in the linear relationship, and error in the DoA estimate, differed slightly between 25 and 20 mm focal depths. We attribute these differences to variation in the degree of asymmetry in the ARF PSF with depth.

Conclusion: This FEM analysis demonstrates a linear relationship between the ratio of ARFI-induced PD and the square root of shear moduli ratio. Further, this analysis shows that the linear model can be used to predict the true shear moduli ratio from the PD ratio. Future work will systematically investigate the impact of ARFI PSF asymmetry on the coefficients of the linear relationship between shear moduli ratio and PD ratio.

(1) Hossain, MM et.al. in. *IEEE TUFFC 3010*(c)

4.4 **Fourier-domain shift matching: robust time-of-flight approach for shear-wave speed estimation,** *David Rosen, Jingfeng Jiang, Michigan Technological University, Houghton, MI, jjiang1@mtu.edu*

The objective of this study was to develop a new time-of-flight method suitable for robust estimation of (group) shear wave speed (SWS) in relatively noisy shear wave data. Our proposed method was built around re-alignment of shear waveforms by coupling the concept of characteristic lines that result from the 1D elastic wave equation and the shift property of the Fourier Transform (FT). We develop this realignment process where the FT can be applied to either the temporal or spatial dimensions and refer to the method as Fourier-domain shift matching (FDSM).

The proposed method was evaluated using computer-simulated shear wave data as well as shear wave data collected from a commercial tissue-mimicking phantom and *ex-vivo* tissues. Signal quality was modulated by addition of Gaussian noise within the simulated data and through adjustment of the voltage applied during the exciting pushing pulse in phantom and tissue experiments. The proposed method was compared against three other time-of-flight methods: the Radon Sum transformation method, time-to-peak with random sample consensus fitting (TTP-RANSAC) and Cross-Correlation based arrival time estimation. Also considered for comparison was a 2D Fourier Transform (2D-FT) adapted to produce a (group) SWS through averaging of the phase shear wave velocity values.

The resulting comparisons suggests that FDSM with the FT applied to the temporal dimension performed most similarly to the established Radon Sum method at both high and low signal qualities. This was particularly apparent for SWS estimation within the *ex vivo* tissue data, where the correlation between the two methods was highest for high signal quality (correlation coefficient 0.99 at an excitation voltage of 60 volts) and relatively unchanged for intermediate-to-low signal quality (correlation coefficient of 0.98 for an excitation of 40 volts.)

5. PHOTOACOUSTICS

5.1 **Integrated optical-acoustic numerical model for simulation of photoacoustic-imaging systems for breast-cancer detection,** Nima Akhlaghi[1], William C. Vogt[1], Keith A. Wear[1], T. Joshua Pfefer[1], Brian S. Garra[1,2], *[1]Food and Drug Administration, Silver Spring, MD, [2]The Washington DC VA Medical Center. nima.akhlaghi@fda.hhs.gov*

Breast cancer is the second leading cause of cancer-related death in American women. Photoacoustic Imaging (PAI) is a hybrid imaging modality in which pulsed laser excitation is combined with ultrasound detection to produce images with contrast based on optical absorption, but resolution and penetration depth depend on ultrasound imaging. In recent years, PAT has been shown to be an attractive technique for breast cancer detection and classification due to its capability of visualizing abnormal vasculature and performing oximetry. Standardized methods for testing PAI performance are essential for system evaluation but are currently nonexistent. Computational simulation is a powerful tool to investigate transport phenomena such as laser-tissue interactions and acoustic wave propagation. We have developed a modeling framework that can elucidate key mechanisms governing PAI system performance. We coupled a previously-developed

3D Monte Carlo (MC) model of tissue light transport with a forward-time acoustic wave propagation model using an open-source Matlab toolbox (*k*-wave) to investigate how device and tissue parameter affect PAI system performance. This model simulates the optical energy deposition distribution, which determines the initial photoacoustic pressure wave generation. Simulated measurements of propagating acoustic waves were used to reconstruct *in silico* photoacoustic images of numerical tissue phantoms with varying properties and target inclusions such as blood vessels or thin filaments. Key device and tissue parameters studied include laser beam geometry, optical wavelength, acoustic transducer geometry and frequency response, and tissue optical absorption and scattering coefficients. We evaluated how these parameters affect image quality characteristics such as resolution, penetration depth, vessel detectability, and blood oxygenation measurement accuracy. Results highlight the broad utility of this multidomain modeling framework for improving understanding of PAI device operation, facilitating device optimization, and predicting real-world performance. Future work includes validation of model outputs against measurements in physical tissue phantoms with biologically-relevant geometries and optical-acoustic properties.

5.2 **Implications of theoretical photoacoustic spatial covariance for short-lag spatial coherence imaging**, Michelle T. Graham,[1], Muyinatu A. Lediju Bell,[1, 2] *[1]Department of Electrical and Computer Engineering, [2]Department of Biomedical Engineering, Johns Hopkins University, mgraha33@jhu.edu*

The spatial covariance of photoacoustic data forms the foundation of any coherence-based photoacoustic beamformer or coherence-based photoacoustic signal processing technique. We recently derived a new photoacoustic spatial covariance theory to support the application of short-lag spatial coherence (SLSC) beamforming to photoacoustic data. This theory confirmed previous experimental observations of contrast and resolution metrics that vary as a function of the short-lag value, *M*. In this work, we further develop our initial theory and explore additional implications for photoacoustic SLSC imaging performance with regard to target size and the illuminating beam profile.

Theoretical simulations and experimental channel data from vessel-mimicking phantoms with diameters 1.3 mm to 10 mm were used to generate SLSC images with a light sheet and narrow-beam Gaussian fluence profile. For each target size, theoretical and experimental spatial coherence curves agreed well in the short-lag region (< 30% of the aperture). These spatial coherence curves demonstrated that there is an inverse relationship between target diameter and coherence length, indicating that the optimal lag choice for image display depends on the target size. Similarly, for an infinitely wide light sheet beam profile, target contrast decreased from 19 dB to 5 dB as target diameter increased. For a narrow-beam Gaussian profile, target contrast decreased from 19 dB to 13 dB as target diameter increased, until the target size exceeded beam diameter, after which contrast reached a relatively steady state value of 13 dB.

Our results provide a new mathematical foundation for previous experimental observations where the choice of short-lag value was observed to depend on target size. Our newly-derived theory also demonstrates that physical optical parameters (e.g., the light beam profile size) can be adjusted to achieve optimal image contrast. These results are promising for building a new class of photoacoustic imaging systems that contains specialized optical hardware and customized signal processing software to deliver optimal coherence-based photoacoustic images.

5.3 ***In-vivo* imaging of neurotransmitter modulation of brain network activity using transcranial photoacoustic voltage-sensitive dye imaging**, Jeeun Kang[1,2], Haichong K. Zhang[1,2], Shilpa Kadam[2], Joshua Elmore[2], Heather Valentine[2], Adarsha P. Malla[2], Ping Yan[3], Jin. U. Kang[1], Arman Rahmim[2], Albert Gjedde[4], Leslie M. Loew[3], Dean F. Wong[2], Emad M. Boctor[1,2], *[1]Johns Hopkins University, Whiting School of Engineering, [2]Johns Hopkins University, School of Medicine, [3]University of Connecticut Health, [4]University of Copenhagen, kangj@jhmi.edu*

Noninvasive real-time monitoring of electrophysiological brain activities has been demanded in neuroimaging, which quantifies functional neuronal depolarization events without any need for invasive craniotomy. Here we present *in vivo* recording of neurotransmitter modulation of brain network activity in rat using transcranial photoacoustic imaging of fluorescence quenching-based near-infrared voltage-sensitive dye (VSD). The photoacoustic-based quantification of neural activity was cross validated with an extracellular neurotransmitter concentration change measured by concurrent microdialysis measurements. The experimental result presents a strong positive correlation of photoacoustic VSD imaging to an excitatory glutamate concentration change. In addition, further advanced validations were conducted with monocular visual stimulation (20-Hz white strobe light with 10 s of ON/OFF intervals) that evokes physiological neural perturbation under the glutamate-mediated signaling mechanism from retina to visual cortex. The photoacoustic VSD imaging outputs at posterior visual cortex (bregma -9.16 mm) presented a significant difference between contra- and ipsi-sided primary visual cortexes, i.e., 0.62 ± 0.02 vs. 0.54 ± 0.02, respectively ($p < 0.0001$). The results from these studies indicates that noninvasive photoacoustic imaging of near-infrared VSD is a powerful tool for a neurotransmitter modulation in deep brain. Supported by the NIH Brain Initiative under Grant No. R24MH106083-03 and the NIH National Institute of Biomedical Imaging and Bioengineering under Grant No. R01EB01963

5.4 **Deep neural networks for photoacoustic imaging using LED light source**, Emran Anas, Haichong K. Zhang, Emad. M. Boctor *Johns Hopkins U., Baltimore, MD, eboctor1@jhmi.edu*

Photoacoustic (PA) is an emerging technology for imaging of endogenous tissue chromophores and exogenous contrast agents in various clinical applications, including cancer detection, functional brain mapping and molecular imaging. The key concept of the PA imaging is based on the photoacoustic effect of generation of acoustic waves due to the light absorption in a soft-tissue sample. For excitation of the targeted tissue, the current standard technology uses heavy and complex laser system, in addition, there is a potential health hazard associated with the high intense laser source. Light emitting diode (LED), as an alternative, offers inexpensive, portable and safe light excitation. However, due to the limited output power of the LED elements, the PA signal of an LED-based system significantly suffers from low signal-to-noise ratio (SNR). The standard approach to improve the SNR is to increase the scanning time that could lead to motion artifacts in reconstructed images. To overcome the limitation, we present a deep neural networks-based approach to improve the PA image quality while reducing the scanning time. The proposed architecture consists of convolutional neural networks to extract the spatial features from noisy PA images. In addition, a recurrent neural network is used to exploit the temporal dependencies in PA image sequence. Moreover, we employ dense skip connections throughout the networks for an effective feature propagation, subsequently eliminating the vanishing gradient problem. We perform an end-to-end training of the networks using 33 sets of phantom experiments, where each experiment consists of a temporal sequence of 55 PA images. On an independent test set from 30 phantom experiments, we obtain a mean peak-signal-to-noise-ratio of 35.34 dB and a structural similarity index of 0.95 with an increase in the imaging frame rate of 8 times compared to the conventional approach.

5.5 **Feasibility of low-cost photoacoustic imaging using clinical ultrasound scanners without laser synchronization**, Yixuan Wu, Haichong Zhang, Emad M. Boctor, *Johns Hopkins U., Baltimore, MD, eboctor1@jhmi.edu*

Photoacoustic (PA) imaging is a burgeoning image approach that is nowadays widely applied among biomedical studies and shows promising potential in diagnostics. By pairing the pulsed laser source with the ultrasonic receiver, PA imaging combines high resolution of optical imaging and deep penetration of ultrasound imaging. If PA imaging can be transplanted directly onto clinical ultrasound scanners, its clinical transition will be conducted smoothly. However, there are two fundamental hardware requirements that clinical ultrasound platforms do not possess. First, a communication between the laser source and the ultrasound platform needs being established. Second, since the time of flight of PA signal is different from ultrasound signal, PA imaging acquires raw channel data for beamforming. Current PA systems are specialized with laser triggers to synchronize laser excitation and ultrasonic signal acquisition. Additionally, they use data acquisition (DAQ) hardware to acquire channel data. In previous work, a PA-beamforming paradigm that re-beamforms ultrasound post-beamformed (USPB) data was proposed. In this work, we focus on PA imaging in the absence of laser synchronization. When the laser trigger is not accessible, there will be asynchrony errors composed of frequency and phase information. First, the source positions in each channel is segmented from the USPB images of a point-target phantom. Since only when the system is synchronized will the aligned wave front appear in the USPB image, the frequency information is estimated by optimizing the compensation to the segmented source positions. Then, by iteratively compensating the depth of the aligned wave front and beamform it until a sharp focused spot is achieved, the phase information is retrieved. In simulation validation, the remaining errors in frequency and phase correction are 0.28% and 2.79% compared to the ground truth, which indicates the feasibility of PA imaging on clinical ultrasound platforms via a software solution.

Thursday morning

6. ELASTICITY 3

6.1 **Imaging of prostate cancer by combined quantitative ultrasound and acoustic-radiation-force-impulse imaging,** Daniel Rohrbach[1], Mark Palmeri[2], Thomas Polascik[3], Jonathan Mamou[1], Ernest Feleppa[1], Kathryn Nightingale,[2] *[1]Lizzi Center for Biomedical Engineering, Riverside Research, New York, NY, [2]Department of Biomedical Engineering, Duke University, Durham, NC, [3]Department of Surgery, Duke University Medical Center, Durham, NC*

Introduction: Definitive diagnosis of prostate cancer (PCa) is performed using core-needle biopsies guided by transrectal "B-mode" ultrasound imaging. Currently, no technology is available that reliably detects PCa regions in the prostate for guiding biopsies or targeting focal therapies, which results in high rates of false-negative diagnoses and

typically mandates treatment of the entire gland. Previously, classifiers based on quantitative ultrasound (QUS) demonstrated an encouraging ability to identify PCa-suspicious regions. Recently, acoustic radiation-force impulse (ARFI) imaging also demonstrated an encouraging ability to detect clinically-significant PCa lesions. The objective of this study was to investigate the ability of combined ARFI and QUS to detect PCa.

Methods: RF data were acquired over the full gland volume during ARFI imaging of a PCa patient scheduled for radical prostatectomy. Values of QUS parameters midband fit (Mf), spectral slope (SS), and intercept (I0) were computed from the RF data. Lesion location was specified by manual segmentation using 3D Slicer renderings of whole-mount histology slides and MRI image sets. ARFI-displacement and QUS-parameter values were computed for the cancerous and non-cancerous regions in 3D ultrasound data sets. 10-fold cross validation and ROC methods were used to assess the performance of a linear-discriminant classifier based on ARFI and QUS results.

Results: Scatter plots demonstrated good separation between positive and negative groups for ARFI and QUS results when used independently and improved separation when ARFI and QUS results were combined. The ROC AUC value of QUS parameters (i.e., Mf and SS) used alone was 0.88, of ARFI displacement used alone was 0.85, and of QUS (i.e., Mf and SS) and ARFI used in combination was 0.95.

Conclusion: These results suggest that combining QUS and ARFI parameters, which are sensitive to complementary and independent PCa-relevant tissue properties, can provide a low-cost, non-ionizing, well tolerated method for reliably detecting and imaging PCa.

6.2 **Improving shear-wave speed image quality in 3D prostate elasticity imaging,** Derek Y. Chan[1], Samantha L. Lipman[1], Ned C. Rouze[1], D. Cody Morris[1], Thomas J. Polascik[2], Mark L. Palmeri[1], Kathryn R. Nightingale[1], *[1]Department of Biomedical Engineering, Duke University, Durham, NC, [2]Department of Surgery, Duke University Medical Center, Durham, NC, derek.chan@duke.edu*

Introduction: Prostate cancer is the most common cancer and the second-leading cause of cancer death among men in the United States. A transrectal ultrasound-guided biopsy is the current technique used for diagnostic confirmation of prostate cancer. However, B-mode images often do not adequately distinguish lesions from surrounding healthy tissue, resulting in a high rate of missed cancer. We are developing a 3D ARFI/SWEI elasticity imaging system for screening the prostate for cancer-suspicious regions and providing imaging guidance for biopsies targeted to these regions in a single patient clinic visit. The combined sequence requires tradeoffs between spatial sampling and beam density and, to date, has been optimized for ARFI (on-axis) image quality. In this work, we implement a variation of multi-resolution[(1)] and multi-dimensional shear-wave tracking[(2)] to assess optimal SWEI image quality in phantoms and *in vivo* prostate data.

Methods: In an ongoing study, ARFI and SWEI data have been obtained using a combined sequence pre-operatively in men expecting radical prostatectomy (29 subjects to date), on a Siemens SC2000 scanner with an Acuson ER7B side-fire transrectal probe. Shear-wave velocity signals were extracted from the raw data by computing the phase of the complex correlation coefficient between sequential time steps. For each native plane acquisition, shear-wave speed values at each pixel were estimated in both the lateral and axial directions using a 2D algorithm, and combined to give a single speed estimate per pixel. We incorporated estimates at different lateral positions from multiple push locations in the ARFI/SWEI sequence to produce a 2D elasticity map for each native plane, using a weighted-average approach based on the distance from each pixel and the normalized correlation coefficient from the calculation of the shear-wave speed. Scan conversion and display of the 3D SWEI volume were performed using 3D Slicer modules that were developed for visualization of the prostate during an ARFI/SWEI targeted biopsy.[(3)] Identified regions of suspicion in the *in vivo* data were validated with whole-mount histopathology.[(4)]

Results: Lesions were visible in the reconstructed SWEI volume for both phantom and *in vivo* data, with higher shear-wave speeds inside the lesion compared to the surrounding background. The 2D shear-wave speed calculation produced more homogeneous estimates compared to a conventional 1D algorithm, which had elevated biased estimates of shear-wave speed. These findings suggest that shear-wave elasticity data can be used to identify cancer-suspicious prostatic regions in a combined 3D ARFI/SWEI sequence without compromising the quality of the ARFI on-axis data.

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6.3 **Ultrasound elastography in skeletal muscle,** Fabrice Prieur[1], Oliver Seynnes[2], *[1]Department of Informatics, University of Oslo, Oslo, Norway, [2]Department of Physical Performance, Norwegian School of Sport Sciences, Oslo, Norway, fabrice@ifi.uio.no*

Elastography can assess *in vivo* tissue stiffness and is a noninvasive imaging technique with great diagnostic value. With shear wave elastography imaging, the acoustic radiation force produced by focused ultrasound generates a local

force that produces shear waves. By analyzing the propagation of these waves, one can estimate their propagation velocity and tissue stiffness. In a homogeneous isotropic medium, shear waves propagate mainly perpendicularly to the pushing force. Within the ultrasound image field of view, this corresponds to a horizontal propagation to the left and to the right of the generated downwards force. This is not the case in anisotropic media such as skeletal muscle. We show, both experimentally and theoretically, that, in striated muscle, shear waves tend to propagate along the orientation of the muscle fibers. *Ex vivo* experiments on porcine muscle show that the misalignment between the assumed direction of the wave propagation and their actual propagation direction along muscle fibers leads to an overestimation of propagation velocity. This bias can be reduced when using a correlation method in two dimensions that does not assume a propagation direction orthogonal to the ARF. We further conduct a theoretical study and use a transverse isotropic model to compute the Green's functions for the shear wave displacements. The ARF spatial distribution generated by the ultrasound probe used in our experiments is estimated by numerical simulations. We use this force distribution together with the Green's functions to estimate the displacements for our experimental setup when varying the angle between the ARF and muscle fibers. The simulation results confirm our observations: in striated muscle the displacement amplitude is largest along the fiber direction in contrast to a homogeneous medium where displacement is largest perpendicularly to the force. This can be seen as a "guiding effect" of the waves along the fiber direction.

6.4 **First-order parameters influencing median nerve shear-wave speed estimates**, Anna Knight, Samantha Lipman, Thammathida Ketsiri, Lisa Hobson-Webb, Kathryn Nightingale, *Duke University, Durham. NC, knightannae@gmail.com*

Introduction: With the addition of shear-wave measurement tools to commercial ultrasound scanners, there have been several studies measuring stiffness and shear-wave speed in structured media, such as the median nerve. These tools report a single group shear-wave speed but do not account for the complex geometry and material properties that can lead to dispersion in these structures. The goal of this work is to identify the first-order parameters that must be addressed to reach an accurate shear-wave speed estimate in the median nerve.

Methods: Shear-wave speeds were measured in the median nerves of six healthy volunteers and six clinical subjects diagnosed with carpal tunnel syndrome through standard electrodiagnostic testing, using a Siemens S3000 system and a 14L5 transducer. A custom STL SWEI (single track location shear-wave elasticity imaging) sequence with an adjustable focal depth of 0.7, 1.0, 1.5, or 2.0 cm based on median nerve depth was used to acquire 10 longitudinal measurements at 7 locations between the wrist and elbow in each subject. At each location, the appropriate focal depth was adjusted so that the focus of the push was located at the bottom edge of the median nerve and the shear-wave was imaged in the longitudinal dimension. In successful SW acquisitions, the tissue displacement and velocity-based group shear-wave speeds were calculated using a Radon Sum approach using data from a selected ROI (region of interest) of depths inside the median nerve. The Radon Sum algorithm considers all possible trajectories across the fixed lateral dimension with positive time steps ($t_{end} > t_{start}$), and sums the displacement or velocity under each trajectory to identify which trajectory corresponds to the peak sum, and thus the speed estimate. These Radon sums often incorrectly identified the shear-wave trajectory due to challenges from reverberation, low signal to noise ratio, or clipping the leading edge of the velocity wave. To rectify these challenges, an iterative convergence algorithm was implemented to identify which processing window removed the reverberation artifacts while preserving the velocity or displacement signals. For estimates from both the standard and iterative approaches, visual inspection was performed to verify that final Radon sum trajectories were aligned with the propagating shear waves.

Results and Conclusions: Using the iterative algorithm, 580 out of 1045 acquisitions were of a quality deemed to accurately represent shear-wave speeds in the median nerve, in contrast to the standard algorithm for which only 294 estimates were of sufficient quality. This represents a 97% increase in the ability to accurately reconstruct shear-wave speeds in the median nerve with novel processing methods.

6.5 **Subresolution displacement in tissue maps in ultrasound imaging simulation,** Sandhya Chandrasekaran[1], Bharat B. Tripathi,[2] David Espandola,[2] Gianmarco F. Pinton,[2] *[1]Mechanical and Aerospace Engineering, North Carolina State University, NC, [2]Joint Department of Biomedical Engineering, University of North Carolina at Chapel Hill and North Carolina State University, NC, gfp@unc.edu*

Objectives: Highly-realistic finite-difference simulations of acoustic wave propagation can be used to describe ultrasound imaging in soft tissue. Recently, it has been shown that they can also model subresolution displacement of scatterers using the impedance flow method. Here, this method is extended to model subresolution motion of human tissue maps. After validation, the proposed method is used to model a) tissue motion induced by shear shock wave propagation in maps of the human brain, b) the backscattered signal from an imaging pulse, and c) to estimate the shear shock displacement from the simulated RF data.

Methods: Brain maps from the Visible Human Project were converted to acoustical maps for the Fullwave ultrasound simulations. This simulation tool was used to propagate a 5.2 MHz imaging pulse, into a 3 cm x 8 cm domain with a grid spacing of λ /16. Known displacements, as small as 0.1 px, were imposed *in silico* by varying the impedance of scatterers and tissue layers at interfaces. These imposed displacements were estimated using a validated custom piecewise parabolic method that models the shear shock wave physics in the brain. Then, the resulting subresolution shift was measured from the beamformed RF data using a correlation-based tracking algorithm.

Results: Jitter and bias measurements were used to characterize the error between the imposed and tracked displacements. The displacement error, on average, is much smaller than the wavelength (λ /833). In contrast, applying the impedance flow method only at the scatterers, generates an error of λ /172 at the tissue interface.

Conclusions: The impedance flow method was extended to surface interfaces to model subresolution motion generated by shear shock wave propagation in brain tissue maps. This technique can be used to model any type of tissue motion, including acoustic radiation force. Supported by the NIH grant R01-NS091195.

6.6 **Feasibility of Synthetic Aperture Imaging (SAI) for parallel beamformed tracking of transient shear waves**, Rifat Ahmed, Marvin M. Doyley, *Electrical and Computer Engineering, University of Rochester, Rochester, NY, rahmed6@ur.rochester.edu.*

*Objectives***:** Ultrafast tracking of shear waves relies on unfocused plane or diverging ultrasound beams. The lack of transmit focus in these techniques is usually compensated by coherently compounding multiple steered angular beams. The quality of this synthetic focusing (the lateral width of the point spread function) depends on the maximum steering angle and number of steered beams. However, large beam steering angles can also produce grating lobes that can introduce strong artificial wave motion.[(1)] Ultrasound synthetic aperture imaging (SAI)[(2)] uses small diverging sub-apertures at different lateral positions to achieve synthetic transmit focusing without the use of beam steering. In this work, we have evaluated the feasibility of using SAI as an alternative to plane or diverging wave tracking of radiation force induced shear waves.

Methods: Small virtual sources with 15 elements were used at multiple lateral locations to track the shear waves. To overcome the power limitation of SAI, multiple virtual sources were encoded with a Hadamard matrix during transmission. A large number of virtual sources (8, 16 and 32) were distributed over multiple push-detect events with each push-detect event using four unique virtual sources. Benefits and tradeoffs of using chirp-coded excitation with and without Hadamard encoding were evaluated to further improve the transmit power.

*Results***:** Using 8, 16 and 32 virtual sources increased the push-detect frame rate by factors of 2, 4, and 8, respectively, compared to plane wave tracking with four angles. However, the elastographic signal-to-noise ratio (SNR_e) improved by 32, 90 and 109% respectively. Chirp-coded excitation with Hadamard encoding provided further improvement (85% SNR_e increase for eight virtual sources), but also increased the ultrasound exposure.

Conclusions: Synthetic aperture imaging can improve the transmit focusing quality of parallel beamformed shear wave tracking and improve the elastographic performance without the use of large beam steering angles.

(1) Hollender et al. in *IEEE Trans Ultrason Ferrorelectr Freq Contr*, pp. 1784-94 (2017). (2) Jensen et al. *Ultrasonics 44*, pp.e5-e15.

6.7 **Comparison of two- and three-parameter viscoelastic material models using measurements of phase velocities and group shear-wave speeds,** Courtney A. Trutna, Ned C. Rouze, Mark L. Palmeri, Kathryn R. Nightingale, *Department of Biomedical Engineering, Duke University, Durham NC. courtney.trutna@duke.edu*

Introduction: Shear wave ultrasound elastography is used to noninvasively characterize tissue properties. Many commercial scanners use elastography to report a metric of elasticity, usually a single group speed. However, tissue is viscoelastic, and higher order characterization may be beneficial for disease diagnosis. Viscoelastic characterization is often performed using Fourier transforms to determine the phase velocities of the material, but these methods can be subject to low SNR. A more robust method of characterizing viscoelastic materials would be beneficial for accurate, repeatable characterization.

Methods: Shear wave data were collected in three viscoelastic CIRS phantoms and processed in two ways. First, group speeds were calculated for each of 21 fractional derivatives of the shear wave data, with orders ranging from 0 (displacement) to 2 (acceleration). A nonlinear fitting algorithm was used to determine the best fit parameters for an assumed material model based on an analytic model of shear wave propagation. Six different material models were investigated. The estimated parameters from each material model for each phantom were then used to analytically calculate the corresponding phase velocity curves. Second, phase velocities were directly calculated from the shear wave data using a 2D Fourier transform, and material model parameters were estimated for a given model by directly fitting

each model's analytic dispersion curve to the phase velocity data. Both the phase velocities and material property values were compared for each model and method of fitting (group speed or phase velocity).

Results: Results from three 2-parameter models and three 3-parameter models were compared. For most material models, the parameters through fractional derivative fitting are more repeatable across repeat acquisitions than for parameters determined by phase velocity. Additionally, comparing the consistency between the phase velocity and group speed methods suggests some models are more appropriate than others for these phantoms. Particularly, the commonly-used Voigt model does not give consistent results and does not appear to be an accurate model for these phantoms.

Conclusions: This fractional derivative group speed method determines material parameters with higher repeatability than material parameter determination based on phase velocity and can be used to identify appropriate material models for experimental data.

7. TISSUE PARAMETERS 3

7.1 **Identifying cancerous thyroid nodules by means of quantitative ultrasound,** Daniel Rohrbach[1], Jason Smith[1], Poorani Goundan[2], Harshal Patel[2], Ernest J. Feleppa[1], Stephanie L. Lee[2] *[1]Lizzi Center for Biomedical Engineering, Riverside Research, New York, NY, [2]Section of Endocrinology, Boston University School of Medicine, Boston Medical Center, Boston, MA, drohrbach@RiversideResearch.org*

Introduction: Thyroid cancer is the most-common endocrine malignancy. Most thyroid cancer occurs in nodules and the standard diagnostic method is a fine-needle aspiration biopsy (FNAB) of a thyroid nodule with cytological evaluation. Unfortunately, 20 to 30% of FNABs cannot differentiate benign from malignant thyroid nodules. Many of these patients require an additional surgical procedure for definitive histological diagnosis; however, only about 25% of those patients will have thyroid cancer. The objective of this study is to develop a noninvasive diagnostic approach using quantitative ultrasound (QUS) to detect thyroid cancer.

Methods: RF data were acquired from 12 patients using a GE Logiq E9 research ultrasound system equipped with a 10-MHz, ML6-15 linear probe. QUS-estimate values, such as effective scatter diameter (ESD), effective scatter concentration (ESC), and spectral parameters (i.e., midband fit, slope, and intercept) were derived using a reference-phantom method. The phantom consisted of 60-µm borosilicate beads. Additional QUS estimates were derived including envelope statistics employing a Nakagami distribution. Estimate values were used to train linear-discriminant (LD) and support-vector-machine (SVM) classifiers, and performance was assessed using area-under-the-curve (AUC) values obtained from receiver operating characteristic (ROC) analyses based on 10-fold cross validation.

Results: Five patients had cytologically-confirmed thyroid cancer. A combination of ESD and EAC produced an AUC value of 0.77 and 0.80 when a LD or SVM was used, respectively. Classification performance of envelope statistics (i.e., AUC_{LD}~0.75, AUC_{SVM}~0.78) and spectral parameters (i.e., AUC_{LD}~0.78, AUC_{SVM}~0.79) were similar. The best classifier performance was obtained by combining envelope statistics, ESD and EAC, which produced an AUC of 0.87 when a SVM classifier was used.

Discussion and Conclusion : Our initial results with AUC values of 0.87 are very encouraging for developing a new tool for thyroid-cancer detection. These initial results suggest that QUS has promising potential to improve non-surgical evaluation of thyroid nodules.

7.2 **Ultrasound sensing-based intuitive proportional control: evaluation study with upper-extremity amputees,** Ananya Dhawan[1], Biswarup Mukherjee[2], Shriniwas Patwardhan[2], Joseph Majdi[2], Rahsaan Holley,[3] Wilsaan Joiner,[2] Michelle Harris-Love, Siddhartha Sikdar,[2] *[1]Department of Computer Science, [2]Department of Bioengineering, George Mason University, Fairfax VA, [3]MedStar National Rehabilitation Hospital, Washington DC, adhawan2@masonlive.gmu.edu*

Background and aims: Recent studies have shown that unintuitive control is a key factor leading to upper-extremity, myoelectric prostheses abandonment. We have developed a novel approach for extracting proportional control signals in the residuum using ultrasound imaging. In this study, we investigate the performance of this technology in upper-extremity amputees.

Methods: We recruited 4 amputee participants with varying amputation and myoelectric prosthetic use backgrounds: 3 transradial unilateral amputees, one of whom had a congenital amputation, and 1 bilateral amputee with a wrist disarticulation and a shoulder disarticulation. Participants were instrumented with a portable ultrasound system, with the transducer on the volar aspect of their residuum. Ultrasound images were processed in real-time to extract a graded activity signal in response to volitional user-intended motions (UIMs). Participants iteratively performed each motion

while being provided with visual feedback. They then controlled an on-screen cursor that responded proportionally to an extracted muscle-activity signal, to reach targets at different levels of motion completion. Control steadiness (cursor standard deviation) and control error (difference between the mean cursor position and target) were computed.

Results: All participants completed the training phase within 15 minutes (25 iterations or 90% accuracy) for at least 4 degrees-of-freedom (DoF), with an average leave-one-out validation accuracy of 93.1%. 3 participants participated in the motion control task. The congenital amputee participant performed 2 motions and the rest performed at least 4 motions with control errors between 1.15% and 9.36% (avg 4.2%) and control steadiness between 2.96% and 17.23% (avg 10.49%).

Conclusions: We demonstrate direct proportional position control using ultrasound-based muscle activity sensing in amputees with varying backgrounds. Our approach is based on measurements of muscle deformation and thus strongly related to the users' innate proprioceptive sense. We believe this enables us to provide more intuitive control compared to currently pervasive methodologies, namely surface electromyography.

7.3 **Quantitative analysis of 3D ultrasound images for assessing pelvic floor muscle injury,** Qi Wei, Qi Xing, Parag Chitnis, Siddhartha Sikdar, Seyed A. Shobeiri, *George Mason U., Fairfax, VA, qwei2@gmu.edu*

3D ultrasound imaging is the diagnostic standard for evaluation of injury to the levator ani (LA) muscle, which is one of the key factors causing pelvic floor disorders. Current ultrasound-based examination of LA muscles involves subjective assessment conducted by clinical experts. In this study, we investigated the utility of quantitative ultrasound analysis for providing objective assessment of LA muscle injury and potentially elucidate the underlying changes of tissue composition associated with the injury and recovery process. We performed quantitative analysis on 3D endovaginal ultrasound data from eight patients (age range: 19-68, mean age ± SD: 50 ± 17) subject in different stages of pelvic floor prolapse. Levator ani defect (LAD) scores that characterize the severity of muscle defect were determined by a physician using 3D ultrasound data. Three statistical models including the Nakagami distribution (ND), gamma distribution (GD) and mixture of gamma distribution (MGD) were retrospectively fitted to histogram of the LA muscle gray-scale pixel intensity. Our preliminary analysis shows a positive correlation between the shape parameters of the three distributions and the subjective LAD score (R^2_{ND} = 0.59, R^2_{GD} = 0.56, R^2_{MGD} = 0.88). Our results demonstrate the potential use of QUS as an objective diagnostic tool for levator ani muscle injury

7.4 **Inferring micro-architecture parameters from the ultrasonic attenuation in cortical bone,** Omid Yousefian[1,2], Rebekah White[2], H. T. Banks[2], Marie Muller,[1,2] *[1]Mechanical and Aerospace Engineering Department, North Carolina State University;[2]Center for Research in Scientific Computation, North Carolina State University, Raleigh, NC 27606, oyousef@ncsu.edu*

Osteoporosis changes the microstructure of both cortical and trabecular bone, which leads to fragility fractures, higher morbidity and mortality and reduction of life expectancy by 1.8 years. The microarchitecture of cortical porosity impacts the macroscopic mechanical properties of cortical bone. It is therefore highly relevant to develop methods for the quantitative assessment of the microarchitecture of cortical porosity. We hypothesize that tracking the microstructural changes in cortical bone could benefit the diagnosis of osteoporosis and may enable treatment monitoring. The correlation between microarchitectural and ultrasonic parameters could be a key factor for the ultrasonic characterization of the micro-architecture of cortical bone.

The overall goal of this research was to investigate a phenomenological relationship between parameters of the porosity (pore density and diameter) and frequency-dependent attenuation. In order to do this, we developed a phenomenological model that describes the attenuation of ultrasonic waves in cortical bone. We changed the microstructure of the bone models by changing the pore size and pore density. We numerically generated data using a finite-difference, time domain SimSonic research freeware, which simulates elastic waves propagating in heterogeneous media. We then fit the developed phenomenological model to the simulated data using an ordinary least squares framework for the inverse problem. With the resulting estimates, we performed local sensitivity analysis and calculated confidence intervals for the parameters estimated.

With this we could propose a model as $\alpha(f) = a(\phi, \rho) f^{b(\phi,\rho)} + c$, where the sensitive model parameters ("*a*" and "*b*") are themselves a function of the microarchitectural ones. With a model of this form, one could infer pore diameter (ϕ) and density (ρ) from the estimates of "*a*" and "*b*". We determined via analytical partial derivatives that the model is not sensitive to "*c*". We also determined that the model sensitivity to the parameter estimates depends on pore diameter and density. Namely, for small diameters (20 – 40 micron) the model is sensitive mainly to estimates of "*a*"; whereas for large diameters, (100 micron) the model is sensitive mainly to estimates of "*b*". For intermediate diameters (60-80 micron) sensitivity depends on pore density, where the model is more sensitive to "*a*" at low densities and more sensitive to "*b*" at

high densities. In general, the 95% confidence intervals for these estimates were wider at high densities $(\rho \geq 14^{pore}/_{mm^2})$.

7.5 **Simultaneous estimation of attenuation and backscatter coefficient with Dynamic Programming**, Zara Vajihi,[1] Ivan M. Rosado-Mendez,[2,3] Timothy J. Hall,[3] Hassan Rivaz,[1] [1]*Electrical and Computer Engineering, Concordia University, Montreal CA,* [2]*Instituto de Física, Universidad Nacional Autónoma de México, Mexico City, Mexico,* [3]*Medical Physics, University of Wisconsin-Madison, Madison, WI, irosado@fisica.unam.mx*

Objectives: The performance of the backscatter coefficient s(*f*) and related parameters have had limited success as quantitative imaging biomarkers due to the need to accurately estimate and compensate for the total attenuation $a_T(f)$ from intervening tissues. We propose a dynamic programing approach (DP) to improve the accuracy and precision of simultaneously-estimated $a_T(f)$ and s(*f*).

Methods: The DP algorithm is based on a minimum least-squares (LS) approach previously proposed by our group,(1) which assumes a linearly frequency-dependent $a_T(f) = a_{0,T}f$ and a power-law $s(f)=bf^n$. DP incorporates into the least-squares minimization a depth-regularized cost function assuming piecewise homogeneity of tissue. The performance of the original LS and the DP algorithms was tested on a three-layer tissue mimicking phantom with uniform s(*f*) but a central layer with attenuation 1.5 times larger than the other two layers. The phantom was scanned with a 9L4 linear array transducer on a Siemens S3000 system. Expected values of $a_{0,T}$, *b* and *n* from each tissue layer were obtained from narrow-band substitution and broad-band pulse-echo techniques, respectively. Performance was quantified in terms of the percent bias ($B_{\%}$) and standard deviation ($SD_{\%}$) of the estimated value of either $a_{0,T}$, *b* and *n*.

Results: $B_{\%}$ with the LS and DP were comparable: in the three layers of the phantom, It ranged from 3.8-9.6% and 1.2-7.5% for $a_{0,T}$, 28.8-42.8% and 25.2-37.8% for *b*, and 3.6-8.3% and 3.1-9.1% for *n*, respectively. $SD_{\%}$ with the LS method ranged from 3.6-8.1% for $a_{0,T}$, from 5.6-28.6% for *b*, and from 1.9-5.0% for *n*. With the DP method, the $SD_{\%}$ ranged from 0.03-6.5% for $a_{0,T}$, and was below 0.01% for *b* and *n*.

Conclusions: Although similar bias was attained with both algorithms, DP significantly reduced variance, thus improving the precision of simultaneously estimated total attenuation and backscatter coefficients. Supported in part by Natural Science and Engineering Research Council of Canada (NSERC) Discovery grant RGPIN-2015-04136 and NIH grant R01HD072077. We also thank Siemens HealthCare Ultrasound Division for technical support and equipment loan.

(1) Nam K et al. *Ultrasound Med. Biol 37*, 2096-2104 (2011).

Thursday afternoon

8. IMAGING 1

8.1 **Comparison of time-delay spectrometry and pulse-echo ultrasound imaging systems,** Biswarup Mukherjee,[1] Ananya S. Dhawan,[2] Elizabeth Tarbox[1], Nima Akhlaghi,[2] Paul Gammell,[3] Parag Chitnis,[1] Siddhartha Sikdar,[1] [1]*Department of Bioengineering,* [2]*Department of Computer Science, George Mason University, Fairfax,* [3]*Gammell Applied Technologies LLC, ssikdar@gmu.edu*

Background and Aims: Clinical ultrasound systems utilizing pulse-echo imaging require high voltage and short-duration transmit pulses along with electronics that operate in the MHz frequency range. We have developed an imaging method based on time-delay spectrometry (TDS) that employs a low-voltage, wideband, chirp transmit signal to establish a relationship between time of flight of the signal, thus depth, and transmit frequency. In this work, we compare the performance of a single-channel TDS system to pulse-echo imaging.

Methods: The TDS system consists of an AD5930 swept-frequency source (250 kHz/ms , $\pm 4.5\ V_{\blacksquare}(P-P)$) , a custom RF transmit amplifier to boost the chirp signal, a diode-based passive demodulator for TDS mixing, and a receive amplifier/ low-pass filter. The resulting down-mixed signal is digitized by a data acquisition system and processed in MATLAB. An Olympus 5073PR pulser-receiver was used for comparison with pulse-echo. A commercially available 7.5 MHz 6 mm dual element probe (Olympus D721- RP) was used for contrast phantom imaging, single-point scattering and complex media imaging tests.

Results: Lateral and axial full-width half-maximum (FWHM) resolutions obtained from point spread functions for TDS was found to be 13.45 mm and 0.444 mm respectively while that of pulse-echo were 15.5 mm and 0.440 mm respectively. Worst-case CNR for the highest graphite concentration phantom was found to be 0.99 dB for TDS and -2.44

dB for pulse echo. CNR measured from complex media B-mode images was found to be 13.7 dB for TDS and 2.3 dB for pulse-echo.

Conclusion: Time-domain spectrometry has been demonstrated as an alternative to pulse-echo paradigm with low-voltage signaling, comparable resolution and improved CNR. Furthermore, TDS involves simplified receive electronics operating in the audio frequency range, therefore, lends itself well to miniaturization for use in wearable and point-of-care applications.

8.2 **Speckle reduction using neural networks,** Dongwoon Hyun[1], Leandra L. Brickson[2], Kevin T. Looby[2], Jeremy J. Dahl,[1] *Departments of [1]Radiology and [2]Electrical Engineering, Stanford University, Stanford, CA 94305, dongwoon.hyun@stanford.edu*

Ultrasound B-mode images represent the echogenicity of the imaged media. However, traditional beamforming methods produce B-mode images containing speckle, a noise that degrades the visibility of imaging targets and is difficult to remove. While some beamforming methods such as spatial compounding are used, most speckle-reduction techniques are image processing methods that apply filtering to already-beamformed images. In this work, we developed and trained a neural network to beamform channel data into speckle-reduced B-mode images and compared its performance against the conventional delay-and-sum (DAS) and spatial compounding beamformers and against a nonlocal means-based image processing method.

A deep convolutional neural network was designed to accept focused and demodulated subaperture signals as input and to produce B-mode images as output. Using 20,000 image patches from Field II simulations of diffuse ultrasound scattering, the network was trained to minimize the error between its output and the co-registered ground truth echogenicity that was used to weight the scatterers. The neural network was evaluated using channel data from simulations, a calibrated phantom, and the liver of a healthy volunteer. The simulated dataset was acquired using Field II, and the phantom and *in vivo* datasets were acquired using a Verasonics system. In all three imaging cases, the speckle signal-to-noise ratio (SNR) of the neural network (simulation: 5.8, phantom: 5.7, *in vivo*: 3.4) was higher than those of DAS (simulation: 1.9, phantom: 1.9, *in vivo*: 1.9) and spatial compounding (simulation: 2.5, phantom: 2.6, *in vivo*: 2.7). While NLM yielded better speckle suppression than all other methods (simulation: 11.2, phantom: 11.6, *in vivo*: 4.6), many image details were lost at the expense of speckle reduction. This work establishes that ultrasound beamforming and speckle reduction can be performed with neural networks and demonstrates that networks trained only using simulated data can be generalized to real-world imaging applications. Supported by the National Institute of Biomedical Imaging and Bioengineering grants R01-EB015506 and R01-HD086252.

8.3 **Deep-learning alternative to beamforming ultrasound images,** Arun Asokan Nair, Trac D. Tran, Austin Reiter, Muyinatu A. Lediju Bell, *Johns Hopkins University. Baltimore, MD, anair8@jhu.edu*

Traditional delay-and-sum beamforming with plane wave transmits requires multiple insonification angles to obtain images with good image quality and sufficient resolution, which, in turn, reduces achievable frame rates. We propose a novel alternative to beamforming by applying data-driven, deep learning to investigate our ability to achieve sufficient information from a single plane wave transmit. We focus on the task of delineating anechoic cysts from surrounding tissue. The beamforming step is presented as a segmentation task, and a fully convolutional neural network was trained to solve this task using 25,989 raw radiofrequency plane wave data created with the Field II ultrasound simulation software package. For each simulation, a plane wave was transmitted with a single insonification angle of 0° in order to image an anechoic cyst surrounded by scatterers. For each simulation, one of four parameters was varied: (1) sound speed (1440 m/s to 1640 m/s in increments of 10 m/s), (2) cyst radius (2 mm to 8 mm in increments of 1 mm), (3) the lateral position of the cyst center (-15 mm to 15 mm in steps of 2.5 mm), and (4) the axial position of the cyst center (35 mm to 75 mm in steps of 2.5 mm). The mean Dice coefficient was calculated to quantify the overlap between true cyst locations and cyst locations determined by the network, resulting in a value of 0.98. The pixel-wise recall score was 0.99. Images were then displayed in a new format that consists of a segmentation mask extracted directly from the raw radiofrequency data, enabling us to ignore common degradations like acoustic clutter and speckle. Results indicate that we can potentially bypass the need for multiple insonification angles that are required for delay-and-sum beamforming with plane wave transmits, which enables increased frame rates. This holds promise for imaging tasks that require fast, accurate and low-noise estimation of target locations, such as robotic tracking tasks. In addition, as the output is in the form of a segmentation mask, it is more interpretable compared to the delay-and-sum beamformed image created with a single plane wave insonification and requires less expert training to understand. It can also serve as a supplemental opinion to experts in the case of difficult-to-judge tissue features in traditional beamformed images.

8.4 **Size manipulation of ultrasound contrast agent and its impact on subharmonic emissions and delayed onset,** Jeff Rowan, James McGrath, Marvin Doyley, *University of Rochester, jrowan@ur.rochester.edu*

Introduction: Ultrasound contrast agents have a growing number of applications in medical diagnostics and theranostics. Of particular interest have been super resolution techniques and sonoporation. While current research has shown promising results within these applications, they are still limited by the properties of the microbubble agents, in particular, their size distribution. Previous efforts at modifying contrast agent distributions have relied either on single bubble generation from microfluidics or post production filtration. The former suffers from concentration issues, while the latter is not suitable for clinical applications in the case of centrifugation, or throughput issues in the case of cloth filters. The current work presents a solid silicon-based ports chip for filtration of contrast agent, and shows the change in subharmonic properties that results.

Methods: Modified centrifuge cups were used to hold microchip filters with 1.5 micron slits. The agents were centrifuged at 500 g for 1 minute in order to filter out larger bubbles. Following filtration, the contrast agent was imaged using two orthogonally-aligned transducers, with 10 MHz transmit, 5 MHz receive, to maximize subharmonic response.

Results: Filtered populations saw an overall increase in subharmonic amplitude. In addition, the delayed onset phenomena were completely eliminated, going from a two-hour delay to instantaneous emission. The threshold for acoustic emission was also decreased in the filtered population by over 100 kPa.

Conclusions: A high throughput, highly-reproducible filter for ultrasound contrast agents has been presented. In addition to improved SNR. The proposed method also eliminates delayed onset and lowers the acoustic threshold for subharmonic emission, making low coherence methods, super resolution, and sonoporation much more feasible.

9. PHOTOACOUSTICS/ INTERVENTIONAL IMAGING

9.1 **Listening to cell membrane potential: a new diagnostic and interventional imaging approach** (invited), Emad A, Boctor, *Johns Hopkins U,. Baltimore, MD, eboctor1@jhmi.edu*

9.2 ***In vivo* demonstration of spectroscopic photoacoustic molecular imaging of prostate cancer**, Haichong K. Zhang, Ying Chen, Jeeun Kang, Ala Lisok, Il Minn, Martin G. Pomper, Emad M. Boctor, *Johns Hopkins U., Baltimore, MD, eboctor1@jhmi.edu*

Prostate cancer is the second leading cause of cancer-related death among men in the United States. Prostate cancer has its high survival rate when it is localized due to slow tumor growth, but the initiation of metastasis and accelerated tumor growth triggers the drop of the survival rate. There is an unmet need of developing a noninvasive method to detect localized prostate cancer and repetitively monitor its growth. We propose a spectroscopic photoacoustic (PA) imaging system that depicts molecular targeted prostate-specific membrane antigen (PSMA). PSMA has been used as imaging and therapy targets with its advantage of showing the expression in neovascular endothelium of solid tumors, and is also known for showing high affinity with aggressive tumors. In this talk, we evaluate the PSMA-targeted fluorescence agent, YC-27, in *in vivo* differentiation of PSMA-expressing tumor from nonexpressive tumor type (i.e., PSMA+ PC3 and PSMA- PC3, respectively) using tumor xerographs on mice. As a result, the PA agent contrast showed a statistically significant enhancement on the PSMA+ tumor comparing before injection and after 24-hour, and the PA agent contrast difference was observed by comparing PSMA+ and PSMA- tumors at 24-hour post-injection. These results demonstrate the potential of PA imaging to characterize prostate tumors for early detection and active surveillance. It can be further effective for other indications at a localized prostate tumor and other cancerous diseases that express PSMA.

9.3 **Deep learning for photoacoustic source detection and reflection artifact removal**, Derek M. Allman, Austin Reiter, Muyinatu A. Lediju Bell, *Department of Electrical and Computer Engineering, Johns Hopkins University, Baltimore, MD, dallman1@jhu.edu*

Many interventional applications of photoacoustic imaging rely on visualization of point-like targets, like the cross-sectional tips of needles, catheters, or brachytherapy seeds. When these point-like objects are imaged in the presence of highly echoic structures, like bone or subcutaneous fat, reflections artifacts are generated. Reflection artifacts are problematic, as they may occur as a true signal in the resultant beamformed image and cause uncertainty for a clinician tasked with reading this artifact prone image. In previous work, we showed that a deep network is capable of distinguishing between sources and artifacts in simulated photoacoustic channel data generated in k-Wave. Simulations initially contained one source and one artifact with various medium sound speeds and 2D target locations. Based on 3,468 test images, we achieved a 100% success rate in classifying both sources and artifacts. After adding noise to assess

potential performance in more realistic imaging environments, we achieved at least 98% success rates for channel signal-to-noise ratios (SNRs) of >-9dB, with a severe decrease in performance <-21dB channel SNR.

Expanding on this work, we then explored training with multiple sources and two types of acoustic receivers and achieved similar success with detecting point sources. Networks trained with simulated data were then transferred to experimental water bath and phantom data with 100% and 96.67% source classification accuracy, respectively. The corresponding mean ± one standard deviation of the point source location error was 0.40 ± 0.22 mm and 0.38 ± 0.25 mm for water bath and phantom experimental data, respectively, which provides some indication of the resolution limits of our new CNN-based imaging system. We finally show that the CNN based information can be displayed in a novel artifact-free image format, enabling us to effectively remove reflection artifacts from photoacoustic images, which is not possible with traditional geometry-based beamforming.

9.4 **Photoacoustic sensing of bioelectric activity using quantum dots**, Nashaat Rasheed, Mara Casebeer, Okhil K. Nag, Michael H. Stewart, Alan L. Huston, James B. Delehanty, John R. Cressman, and Parag V. Chitnis, *George Mason University, Fairfax, VA 22030, pchitnis@gmu.edu*

We present a novel voltage-reporting nano-construct that can facilitate photoacoustic sensing and mapping of bioelectric activity. The nano-construct consists of a CdSe-CdS/ZnS core-shell quantum dot (QD) conjugated to a peptide-fullerene bioconjugate. Photoacoustic-based voltage sensing was demonstrated by tracking the cell membrane dynamics during KCl-induced depolarization of QD-tagged PC-12 cells. KCl-induced change in cell-membrane voltage was confirmed using independent patch-clamp measurements. In response to 532-nm excitation, the QD probes produced a photoluminescence (PL) signal as well as a photoacoustic (PA) signal. When cells depolarized (voltage increased), the QD-PL signal decreased. Conversely, the QD-PA signal increased with an increase with voltage. The QD-PL and the QD-PA exhibited qualitatively similar temporal profiles in response to KCl-induced depolarization. The QD-based voltage reporter potentially can be used for fluorescence sensing *in vitro* as well as photoacoustic sensing when probing brain activity in small-animal models

9.5 **Photoacoustic-based catheter tracking: simulation, phantom and *in vivo* studies**, Alexis Cheng , Younsu Kim, Yuttana Itsarachaiyot, Haichong K. Zhang, Clifford R. Weiss, Russell H. Taylor, Emad M. Boctor, *NIH and Johns Hopkins U., Baltimore, MD, eboctor1@jhmi.edu*

Catheters are commonly used in many procedures and monitoring their location is critical to patient safety and surgical success. The standard of care for monitoring the catheter during the procedure is with the use of fluoroscopy. Alternate approaches use conventional tracking and guidance technologies, such as electromagnetic trackers, have been previously explored. This work explores the use of an emerging imaging modality, photoacoustics, as a means for tracking. A piezoelectric (PZT) sensor is placed at the tip of the catheter and acts as an acoustic sensor, receiving the acoustic signals generated from photoacoustic markers due to the photoacoustic effect. The locations of these photoacoustic markers are determined by a stereo-camera and the received acoustic signals are converted into distances between the PZT element and the photoacoustic markers. The location of the PZT sensor can be uniquely determined following a multilateration process. This work validates this photoacoustic-tracking method in phantom, simulation, and *in vivo* scenarios using metrics including reconstruction precision, relative accuracy, estimated accuracy, and leave-out accuracy. Submillimeter-tracking results were achieved in phantom experiments. Simulation studies evaluated various physical parameters relating to the photoacoustic source and the PZT sensor. *In vivo* results showed feasibility for the eventual deployment of this technology.

10. NIH PROGRAM FUNDING

(Discussion) Houston Baker, *NCI; +TBD* ; and James G. Miller, *Washington U. in St. Louis* (Moderator)

Friday morning

11. IMAGING 2

11.1 **Comparison of ultrasonic image quality metrics: theory, simulation and *in vivo* results,** Will Long[1], Gregg E. Trahey[1,2], *Departments of [1]Biomedical Engineering and [2]Radiology, Duke University, Durham, NC, willie.long@duke.edu*

Measurement of *in vivo* image quality is essential for the optimization of ultrasonic imaging parameters and sequence design. Traditionally, this has been performed using measurements of contrast, contrast-to-noise ratio (CNR), and frame-to-frame or temporal correlation, which together capture information about the contrast and sensitivity of an imaging system. Although widely used, existing metrics suffer from several drawbacks that limit their overall utility and accuracy in realistic imaging conditions.

Studies have shown that the spatial coherence, describing the correlation between array element signals, is sensitive to all major forms of ultrasonic image degradation. Accordingly, we have developed a novel image quality metric derived from the average spatial coherence between nearest-neighbor elements, namely the lag one coherence (LOC) which is a single region-of-interest (ROI) measurement that shows promise as a reliable metric of *in vivo* image quality.

To better characterize the behavior of LOC, this work presents the theoretical framework relating LOC to conventional metrics for ultrasonic image quality. We validate this theory in Field II simulation for the specific case of fully incoherent noise, modeling thermal noise and incoherent clutter from reverberation and high frequency aberrations, and compare the sensitivity and variability for matched measurements of LOC, contrast, and CNR for different levels of channel signal-to-noise ratio (SNR) and intrinsic contrast across multiple speckle realizations.

Simulations are in strong agreement with theory. Results indicate that LOC has significantly lower variability than either contrast or CNR for a wide range of clinically relevant channel SNRs. The benefit of a single ROI measurement is clearly demonstrated by changes in the sensitivity and variability of contrast and CNR across different targets. The effects of focal degradation and varying ROI size will be discussed and examples of metrics calculated from *in vivo* liver images acquired at varying transmit powers will also be examined.

11.2 **Pilot study of adaptive fetal imaging based on lag-one coherence**, Katelyn Flint[1], Will Long[1], James Long[1], David Bradway[1], Sarah Ellestad[2], Patricia McNally[2], Gregg Trahey[1,3], *Department of Biomedical Engineering, [2]Division of Maternal-Fetal Medicine, [3]Department of Radiology, Duke University, Durham, NC, katelyn.flint@duke.edu*

Several studies have found that most physicians and sonographers do not use patient exposure metrics such as Mechanical Index (MI) and Thermal Index (TI) to inform their choice of transmit power during a scan and, furthermore, they do not know what these values mean. We are investigating automated selection of transmit power based on feedback from image quality. We have developed a novel image quality metric, Lag One Coherence (LOC). LOC is the correlation coefficient between dynamic-receive-focused RF data from pairs of neighboring elements. Previous work indicates that the LOC is highly predictive of local signal-to-clutter level (i.e., image quality).

We collected B-Mode fetal ultrasound images from three volunteers. Each acquisition included a sweep of 18 transmit voltages that correspond to MIs ranging from 0.08 to 1.40. LOC as a function of MI was assessed in three image sequences from each patient. Three regions of interest, centered at approximately 4 cm, 6 cm (the focus), and 8 cm, were selected from each image. Overall, the average LOC asymptote was at 0.65 (+/- 0.10). The asymptote occurred, on average, at MI = 0.56 (+/- 0.15). For the regions shallow to the focus, the average LOC asymptote was 0.59 (+/- 0.10) and the corresponding MI was 0.53 (+/- 0.08). For the regions near the focus, the LOC asymptote was 0.68 (+/- 0.09) and the corresponding MI was 0.55 (+/- 0.13). For the regions deep to the focus, the LOC asymptote was 0.67 (+/- 0.10) and the corresponding MI was 0.62 (+/- 0.21).

These results suggest that maximum image quality can be achieved with lower exposure levels than are currently used clinically. Though fetal ultrasound imaging that adheres to FDA output guidelines has no known bioeffects, automated achievement of the ALARA (As Low as Reasonably Achievable) principle concerning patient acoustic exposure is a potentially useful tool for obstetric ultrasound.

11.3 **Short-lag Spatial Coherence imaging in 1.5-D and 1.75-D arrays: performance and implications for array design**, Matthew Morgan[1], Dongwoon Hyun[2], Gregg Trahey[1,3] *[1]Department of Biomedical Engineering, Duke University, Durham, NC, [2]Department of Radiology, Stanford University School of Medicine, Stanford, CA, [3]Department of Radiology, Duke University, Durham, NC, mrm63@duke.edu*

Introduction: Conventional ultrasound transducers contain a one-dimensional (1-D) array of elements with an acoustic lens to control slice thickness and provide a fixed focus in elevation with a reasonable depth of field. Transducers have also been developed which contain multiple rows of elements in the elevation dimension, which can improve elevation focusing. These elements can be mirrored about the elevation centerline (1.5-D) or individually connected (1.75-D).

Short-lag spatial coherence (SLSC) imaging is a beamforming method that forms images based on the spatial similarity of received echoes across the aperture. SLSC imaging has demonstrated significant improvements in contrast and contrast-to-noise ratio (CNR) over conventional delay-and-sum beamforming.

While SLSC imaging has been extensively studied using 1-D and 2-D arrays, its use with 1.5-D and 1.75-D geometries has not been thoroughly evaluated. This work seeks to characterize the performance of SLSC imaging in a variety of elevation geometries and suggest potential array design strategies.

Methods: Field II simulations of cyst targets of varying native contrasts (anechoic, -12, -6, 6, 12 dB) were performed using a 3 MHz linear array with 96 lateral elements. Array configurations with 3, 5, 7 and 9-element Fresnel-style elevation arrays were compared to a conventional 1-D array, as well as matrix arrays with wavelength and half-wavelength element spacing. Contrast and CNR were measured as a function of simulated acoustic clutter through the inclusion of spatially incoherent noise over channel signal-to-noise ratios between -20 and 20 dB.

Results: SLSC images were formed using 1.5-D and 1.75-D arrays; the short-lag region for each element was defined based on the predicted inter-element correlation when imaging diffuse scatterers. Elevation symmetry in 1.5-D arrays forced the inclusion of additional long-lag pairs into the short-lag region. Contrast and CNR were characterized in the presence of simulated acoustic clutter. Implications and tradeoffs associated with SLSC imaging in 1.5-D and 1.75-D arrays will be discussed. Potential array design constraints will be considered with regard to elevation element size, symmetry, and Fresnel-style geometries

11.4 **Cardiac image quality reflected by spatial and temporal coherence**, Nick Bottenus[1], Vaibhav Kakkad[1], Will Long[1], Katelyn Flint[1], David Bradway[1], Melissa Lefevre[2], Gregg Trahey[1,3] *Departments of [1]Biomedical Engineering, [2]Cardiology and [3]Radiology , Duke University, Durham, NC 27707, nick.bottenus@duke.edu*

Objectives: To test the hypothesis that temporal and spatial coherence can act as target-independent measures of image quality useful for image optimization.

Methods: We have implemented real-time visualization of temporal and spatial coherence as an overlay to B-mode imaging using the Verasonics research scanner. Receive channel data from temporal pairs of m-mode focused transmit lines are acquired immediately after conventional B-mode imaging. The coherence is estimated as the point-wise complex dot product of the delayed IQ data as an alternative to kernel-based normalized cross-correlation. Temporal coherence is calculated between the repeated transmissions and averaged over receive channels. The lag-one spatial coherence is calculated between pairs of adjacent receive channels and averaged across the aperture as well as across the repeated transmissions.

Our sonographer imaged the interventricular septum (IVS) of four healthy volunteers. We stored B-mode images and correlation estimates at roughly 15 frames per second for the 25 seconds leading up to the sonographer's determination that image quality has been optimized and 5 seconds afterwards. Optimizations include selecting an acoustic window and manipulation of the probe angle and pressure to improve the view of the IVS. The coherence overlays can be enabled at runtime to select whether the operator can use the coherence feedback information. In this study, we disable the overlays to allow the sonographer to perform her normal image optimization process.

Results: Our preliminary results indicate several interesting trends in the temporal and spatial coherence. We observe cyclical variation of both metrics throughout the cardiac cycle. Both metrics indicate some increase throughout the sonographer's optimization process and stability during the optimized hold period. The two metrics show differences at some time points, such as reflecting clutter from patient inhalation. Supported by grants R01EB017711 from the NIH NIBIB and R37HL096023 from the NIH NHLBI

11.5 **Visualization of the intensity field of a focused ultrasound (FUS) source *in situ***, Trong N. Nguyen, Minh N. Do, Michael L. Oelze, *Beckman Institute for Advanced Science and Technology, Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, tnnguyn2@illinois.edu.*

Background and Objectives : In some applications of Focused Ultrasound (FUS), the goal is not to heat tissues, but to cause a biological effect such as opening of the blood brain barrier (BBB) or collapsing microbubbles in a tumor. In such cases, what is needed is not temperature mapping but a visualization of the beam of the FUS source in the context of surrounding tissues. Real-time visualization of the field distribution of the FUS source during treatment would allow the localization of the intersection of the FUS beam with the tissue. Furthermore, real-time visualization of the FUS beam in the context of the tissue would allow proper positioning of the FUS beam for therapy especially during tissue motion.

Methods: A 6-MHz single-element transducer (f/2) was used as the FUS source and aligned perpendicular to the field of a linear array (L9-4). The 6-MHz FUS source was pulse excited and the fields scattered from a sample, i.e., tissue-mimicking phantoms or a chicken breast, were received by each element of the linear array. Bistatic beamforming was applied to the channel data to focus the receiving array at each point in the field and reconstruct the intensity field pattern from the FUS source. The intensity field pattern was then superimposed on a registered B-mode image of the sample acquired using the same linear array. To quantify the quality of the FUS beam reconstruction, the field pattern was mapped using a wire target. The intensity field pattern reconstructed from the homogeneous phantom was compared to the field characteristics of the FUS source characterized by the wire technique. A visualization of the beam was also constructed when scanning a two-layered phantom with an intensity contrast between the layers of 10 dB. A correction to the FUS beam visualization using the B-mode image was applied to account for the intensity difference. *Results:* The beamwidth estimates at the FUS focus using the *in situ* reconstruction technique and the wire technique were 1.5 mm and 1.34 mm, respectively. The depth of field estimates for the *in situ* reconstruction technique and the wire technique were 11.8 mm and 11.75 mm, respectively. The visual quality of the FUS beam visualization when intersecting a layer with higher intensity improved by using the B-mode to account for the intensity variations in the reconstruction. Therefore, we conclude that the novel reconstruction technique was able to accurately visualize the field of an FUS source in the context of the interrogated medium.

11.6 **Comparative study of CT-US registration performance with DAS and SLSC ultrasound beamforming techniques**, Eduardo Gonzalez,[1] Michelle Graham,[2] Muyinatu A. Lediju Bell,[1,2] *[1]Department of Biomedical Engineering, [2]Department of Electrical and Computer Engineering, Johns Hopkins University, Baltimore, MD, egonza31@jhmi.edu*

Registration of multimodal images is a powerful tool for transferring preoperative plans into an intraoperative environment, thereby enhancing the surgeon's accuracy to localize instruments in the operating room. Intraoperative ultrasound (US) to preoperative Computer Tomography (CT) registration is often a challenging task due to multiple factors, including the low signal-to-noise ratio of the US images and the presence of artifacts. This work explores Short Lag Spatial Coherence (SLSC) beamforming as an alternative to traditional Delay-And-Sum (DAS) ultrasound images to increase contrast and resolution for US-to-CT registration tasks.

We compared intensity-based registration of a volumetric CT of the human skull to US images created using both DAS and SLSC beamformers. CT data was obtained with a Phillips CT scanner. US channel data was acquired at the posterior base of the vomer bone from a human skull submerged in ionized water, using an ECUBE-12R US system and a 64-element phase array probe at 3.8 MHz transmit frequency, 12cm depth. Fuzzy C-means was used with an overlapping coefficient of 2 to segment all US images into three differentiated regions: bone, water, and regions outside scanning boundaries. Contrast enhancement for DAS was controlled with the dynamic range of log compression (D), while contrast enhancement for SLSC was controlled with the cumulative summed lag value (M).

Registration accuracy was measured as the Mean Square Error (MSE) between the normalized pixel intensities in CT and beamformed US images after contrast enhancement. The MSE for registration with DAS images was $\leq$0.014 when D $\geq$ -14 dB. Similarly, the MSE for registration with $\leq$0.014 for SLSC images when M $\geq$ 20. One limitation of DAS with D $\geq$ -14 dB was the absence of the complete structure of the posterior base of the vomer bone, which was consistently present in SLSC images regardless of the chosen lag value for image display. These preliminary results suggest that SLSC beamforming has the potential to achieve similar registration accuracy to DAS beamformed images with the additional benefit of maintaining bone boundary information in the registered US images,

12. IMAGING 3

12.1 **Temperature imaging in real time with 1^{o}C accuracy and 2x2 mm^{2} resolution using a conventional ultrasonic imaging system**, R. Martin Arthur, *Electrical & Systems Engineering, Washington University in St. Louis, St. Louis, MO 63130, rma@ese.wustl.edu*

Background: Magnetic resonance is the *de facto* standard for volumetric temperature imaging (TI). Ultrasound is a noninvasive, safe, inexpensive and convenient alternative modality for TI. Agreement among predicted, simulated and measured ultrasonic changes in backscattered energy (CBE) from both our *in-vitro* and *in vivo* experiments has shown that CBE can be used for temperature imaging (TI) at frequencies from 2 to 32 MHz in 1D, 2D and 3D during nonuniform heating. Previously we demonstrated 1^{o}C accuracy using CBE in 2D images of turkey phantoms in real time. Images were sent from the imaging system to a second system for non-rigid motion compensation and TI generation. We also compared the results of this system to MRTI results using the same tissue fixture and hot-water heating methods. Using

our stochastic-signal framework, we maintained 1°C accuracy over 2x2 mm^2 regions of interest. Our CBE TI accuracy and spatial resolution matched MRTI performance *in vitro*.

Methods: In this study, we optimized the use of our 7.5 MHz phased-array Terason 3000 ultrasonic imaging system to perform CBE TI with it alone, while maintaining 1°C accuracy and 2x2 mm^2 spatial resolution. Our previous studies showed that motion compensation was not necessary *in vitro* for frame intervals below 15 seconds during heating with 75°C water through the center of tissue specimens. To operate the Terason 3000 at the highest frame-rate for further processing, we used the SDK to save bitmap images, which were then read by Matlab® routines to calculate CBE values and convert them to TIs.

Results: Our 2006 vintage Terason 3000 with an XP operating system collected 7.56±0.14 frame/sec over 1000 images. CBE calculation and conversion to TI took 0.016 sec. At this frame rate the image system generated about 1 GBytes of data in a typical 600 sec hearting experiment.

Conclusions: We expect contemporary hardware to perform better than the 7 Hz frame rate we observed. Even so, this rate is expected to minimize tissue motion between frames to allow accurate CBE TI *in vivo*. Supported by R21-CA90531, R01-CA107558 and the Wilkinson Trust at Washington University in St. Louis, St. Louis, MO.

12.2 **Ultrasound thermal monitoring using external ultrasound elements: CNN approach**, Younsu Kim, Chloe Audigier, Emran Anas, Jens Ziegle, Michael Friebe, Emad M. Boctor, *Johns Hopkins U., Baltimore, MD, eboctor1@jhmi.edu*

Thermotherapy treatment is a clinical procedure to induce a desired biological tissue response using thermal energy. To operate the procedure accurately, temperature monitoring during the treatment is important. Ultrasound propagation speed in biological tissues changes with induced thermal energy. An external ultrasound sensor was used with a bipolar ablation device to acquire time-of-flight. Due to the sparse time-of-flight information acquired from limited angle, tomographic reconstruction approach confronts ill-posed problems. We propose a machine learning approach to solve the ill-posed problems. We use a computational bioheat model for a bipolar radio frequency ablation to generate training temperature images. We tested the simulation data using a designed convolutional neural network. We compared results with a speed-of-sound reconstruction method. To validate the proposed temperature reconstruction method, *ex-vivo* experiments were also performed on porcine liver.

12.3 **Ultrasonic monitoring method for HIFU ablation using physics-based simulation**, Chloé Audigier, Younsu Kim, Nicholas Ellens, Emad M. Boctor, *Johns Hopkins U., Baltimore, MD, eboctor1@jhmi.edu*

12.4 **Developments in pulse-echo sound-speed tomography,** Anthony S. Podkowa[1,2], Michael L. Oelze[1,2], [1]*Beckman Institute,* & [2]*Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, Urbana, IL 61801, tpodkow2@illinois.edu*

Tomographic reconstruction of spatially-varying sound speed profiles has demonstrated the ability to produce images with comparable quality to that of X-ray CT and MRI. Most sound speed tomography approaches utilize customized hardware such as ring arrays, which limit applicability to tissues like the female breast. This is due to the conventional wisdom that such techniques require a full angular coverage for accurate reconstruction in the general case. However, recent results (Jaeger, 2015) have demonstrated that in the presence of diffuse scatterers, this limitation can largely be overcome. Using steered plane wave excitations of a standard linear array in pulse-echo mode, depth dependent maps of relative time lags can be generated using cross-correlation techniques. From these time lag maps, a linear inverse problem can be solved that reveals the presence of large scale sound speed inhomogeneities, producing speckle-free, baseband images that are complementary to traditional B-mode ultrasound.

Jaeger's original reconstruction algorithm was derived in the Fourier domain, where the 4D multilinear operator mapping of the slowness (inverse sound speed) to the lag maps is approximately diagonal, allowing for reconstruction on a single commercial PC. However, such an approach leads to significant edge artifacting, restricting analysis to a direct spatial matrix implementation, which is both memory and computationally expensive (>34 GB & 281 TeraFLOPs per time lag map for 256x256 pixel images). In order to mitigate this effect, we have reformulated the original model as a truncated convolution, allowing for an FFT-accelerated reconstruction via a matrix free iterative approach (BiCGSTAB-FFT). Using this approach, edge artifact-free reconstructions can be performed with $O(n\log(n))$ operations and $O(n)$ memory storage requirements (~1-10 MegaFLOPs & 100-1000KB per lag map at 256x256 pixels). Such an approach is significantly more scalable and is a better candidate for real-time pulse-echo sound speed imaging applications.

12.5 **Correlation of ultrasound tomography with pathology and MRI in localizing prostate cancer**, Reza Seifabadi, Alexis Cheng, Bilal Malik, Shun Kishimoto, James Wiskin, Jeeva Munasinghe, Ayele H. Negussie, Ivane Bakhutashvili

Murali Cherukuri, Peter Choyke, Peter Pinto, Arman Rahmim , Emad M. Boctor, Maria Merino, Mark Lenox, Baris Turkbey, Bradford J. Wood, *NIH, QTultrasound, Johns Hopkins U., Baltimore, MD, eboctor1@jhmi.edu*

B-mode transrectal ultrasound (TRUS) guided biopsies are the gold standard for prostate cancer detection. The surgeon uses TRUS guidance to obtain biopsy samples at various regions of the prostate. However, TRUS is incapable of visualizing most tumors within the prostate, making biopsy a blind procedure. Although MRI is more sensitive than TRUS in locating tumors, it is not feasible to apply across a broad population, and may be cost prohibitive as a cancer screening tool. Encouraged by the success of full-angle ultrasound tomography (UST) in breast cancer detection, we study if the speed of sound (SoS) map obtained using ultrasound tomography can correlate with T2-weighted MRI and pathology to detect prostate cancer in *ex vivo* human prostate tissue.

Method: A commercial breast full-angle ultrasound tomography scanner was used to image an *ex vivo* prostate. An echolucent mold with a prostate-specific cavity was designed to encapsulate the prostate during UST imaging, spatially correlating it with MRI. Similarly, a prostate-specific 3D printed mold was developed to align the histology slices of interest with the UST and MR images. These histology slices were then H&E stained and digital pathology images of these slides were acquired. A radiologist with 10 years of experience in using multiparametric MRI for prostate cancer diagnosis participated in labeling the suspicious regions in both MRI and UST images with a 3 month interval to eliminate the bias.

Results: Two slices were found to have prominent lesions in both MR and UST in the peripheral zone. The locations and slice numbers of the lesions matched among MR, UST, and pathology, although MR and UST underestimated the lesion size in one slice.

Conclusions: Full-angle UST has the potential to detect prostate cancer without reliance upon MRI. Additional *ex vivo* fresh prostate tissue is required to further validate this finding.

12.6 **Transrectal ultrasound tomography with plane-wave full-waveform inversion**, Lianjie Huang, Kai Gao, Yunsong Huang, and Wenyong Pan, *Los Alamos National Laboratory, Los Alamos, NM 87545; ljh@lanl.gov*

Ultrasound tomography was used to reconstruct tissue mechanical properties for cancer characterization. We built a new transrectal ultrasound tomography system using a 256-channel Verasonics Vantage system and a GE intracavitary curved linear array to acquire plane-wave ultrasound reflection data for ultrasound tomography. We developed a novel plane-wave full-waveform inversion algorithm for transrectal ultrasound tomographic reconstructions of the tissue sound speed and density of the prostate. The algorithm is based on fitting synthetic ultrasound waveforms with recorded ultrasound waveform data. We verify the algorithm using synthetic ultrasound data for a numerical prostate phantom consisting of multiple tumors and show some preliminary results of prostate phantom data. Our reconstruction results demonstrate that our new transrectal ultrasound-waveform tomography algorithm using plane-wave ultrasound reflection data has great potential to accurately reconstruct the sound-speed and density values of prostate tumors for cancer characterization.