UITC ABSTRACTS 2017

Monday morning

1. TISSUE PARAMETERS 1

1.1 **Preliminary assessment of cervical remodeling during pregnancy with speckle statistics: comparison between early and late pregnancy**, Ivan M. Rosado-Mendez,[1] Andrew Santoso,[1] Quinton Guerrero,[1] Lindsey Drehfal,[1] Helen Feltovich [1, 2] and Timothy Hall,[1] [1]*Medical Physics, University of Wisconsin - Madison, Madison, WI and* [2]*Maternal Fetal Medicine, Intermountain Healthcare, Provo, UT, rosadomendez@wisc.edu*

Objectives: Before parturition, the collagenous structure of the uterine cervix remodels to increase the organ's compliance and allow vaginal delivery. We are investigating Quantitative Ultrasound biomarkers to quantify these changes and potentially detect conditions that lead to spontaneous preterm birth. The link between ultrasound speckle and the spatial distribution of scatterers in tissue (collagen fibers in the cervix)[1], motivates the use of parameters describing the statistics of speckle. We present a cross-sectional comparison of speckle statistics parameters in the cervix of women in early and late stages of pregnancy.

Methods: In this IRB-approved study, 13 patients in early pregnancy (5-14 wk), and 20 in late pregnancy (37-41 wk) were recruited. Radiofrequency (RF) echo signals from the cervix were acquired trans-vaginally with a Siemens Acuson S2000 Ultrasound system (Siemens Healthcare, Ultrasound Business Unit, Mountain View, CA, USA) using a prototype catheter transducer attached to the clinician's finger. Parametric images were constructed by sweeping a 2×2 mm^2 parameter estimation region across each RF data frame. Three parameters were investigated: the point-wise echo amplitude signal-to-noise ratio (SNR),(1) the Nakagami shape parameter m,(2) and a Nakagami-based Generalized Likelihood Ratio Test statistic T.(3) Mean values of the three parameters were obtained from each parametric image within a 5×5 mm^2 region of interest (mimicking the region analyzed in previous shear-wave elasticity imaging studies). Summary values for each pregnancy group are reported in terms of the median [interquartile range]; statistical significance of their differences was assessed with a Kruskall-Wallis nonparametric test.

Results: No significant differences were observed between the early- (SNR=1.72[1.64-1.84], m=0.86[0.80-0.95], and T=16[12-19]) and late-pregnancy groups (SNR=1.70[1.63-1.79], m=0.84[0.81-0.90], and T=15[13-18]). Ranges of speckle statistic parameter values indicate scattering conditions are close to that of fully-developed speckle (SNR=1.91 and m=1.0) and the absence of coherent scattering.(2) These findings motivate the estimation of QUS parameters based on incoherent scattering, such as the effective scatterer diameter. Based on the link between m and scatterer concentration, our results agree with current theories that, during pregnancy, collagen reorganizes but the concentration remains approximately constant.(4)

Conclusions: QUS parameters based on speckle statistics provide insight on the collagen microstructure of the cervix. We are currently assessing the spatial heterogeneity and anisotropy of these parameters from beam-steered ultrasound data and correlating these findings to collagen structure assessed through second-harmonic generation optical microscopy. Supported by grants R01CA111289 and T32CA009206 from the NCI, and grants R21HD061896, R21HD063031, and R01HD072077 from the NICHD. We also thank Siemens HealthCare Ultrasound Division for technical support and equipment loan.

(1) Wagner RF et al. *IEEE Trans Ultrason Ferroel Freq Contr 30*,156-163 (1983). (2) Shankar PM. *IEEE Trans Ultrason Ferroel Freq Contr 50*, 339-343 (2003). (3) Rosado-Mendez IM et al. *IEEE Trans Ultrason Ferroel Freq Contr 63*, 1306-1320 (2016). (4) Yoshida et al. *PLOS ONE 9* :e112391 (2014).

1.2 **Quantitative ultrasound anisotropy of the *in-vivo* uterine cervix: early vs. late stage pregnancy,** Quinton W. Guerrero[1], Lindsey C. Drehfal[1], Andrew Santoso[1], Ivan Rosado-Mendez[1], Helen Feltovich[1,2], Timothy J. Hall,[1] [1]*Medical Physics Department, University of Wisconsin, Madison, WI 53706 and* [2]*Maternal Fetal Medicine Department, Intermountain Healthcare, Provo, Utah, qguerrero@wisc.edu*

Objectives: Quantitative ultrasound (QUS) biomarkers to quantify changes to the cervical extracellular matrix during pregnancy may lead to improved understanding of term and preterm labor. We have previously demonstrated that QUS parameters show significantly less anisotropy in the late pregnant cervix compared to the *ex vivo* non-pregnant cervix. The goal of this study was to compare backscatter parameter anisotropy of the first trimester cervix (the extracellular matrix of which is thought to be similar to the non-pregnant cervix) to that of the third trimester cervix (in which the microstructure has presumably undergone extensive remodeling in preparation for delivery).

Methods: Women presenting in the first (N=13) and third (N=20) trimester were recruited. Ultrasound data were acquired with a Siemens Acuson S2000 and a prototype phased-array transducer (128 element, 3 mm diameter, 14 mm aperture) operated in linear array mode. RF echo signals were collected at 15 different beamsteering angles, from -28° to +28° in steps of 4°. Data were similarly acquired from a phantom composed of isotropic Rayleigh scattering glass beads. The Reference Phantom method was used to test mean backscatter power differences (mBSPD) among beamsteering angles.

Results: mBSPD was significantly smaller in the third, as compared to the first, trimester cervix ($p < 0.01$; Wilcoxon Rank Sum Test). These results suggest that the extracellular microstructure of the early pregnant cervix has greater alignment/organization than that of the late pregnant cervix.

Conclusions: These data are consistent with the cervical microstructural disorganization that has been directly observed in animal models. We are currently applying this technique in tandem with others, such as shear-wave elasticity imaging (SWEI), to comprehensively study cervical microstructural change during pregnancy. While SWEI can demonstrate *that* a cervix is softening, integrating other biomarkers such as backscatter anisotropy parameters could explain *how* and *why* the cervix is softening. Supported by NIH grants T32CA009206, R01HD072077, R21HD061896 and R21HD063031 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the Intermountain Research & Medical Foundation. We are also grateful to Siemens Healthcare Ultrasound division for an equipment loan and technical support.

1.3 **Assessment of cervical softening during pregnancy in the Rhesus macaque using shear-wave speed: comparison of trans-abdominal vs. intra-cavitary approaches**, Lindsey C. Drehfal,[1] Ivan M. Rosado-Mendez,[1] Mark L. Palmeri,[2] Andrew Santoso,[1] Quinton Guerrero,[1] Helen Feltovich[1,3] and Timothy Hall,[1] [1]*Medical Physics, University of Wisconsin - Madison, Madison, WI,* [2]*Biomedical Engineering, Pratt School of Engineering, Duke University, Durham, NC and* [3]*Maternal Fetal Medicine, Intermountain Healthcare, Provo, UT, lcarlson2@wisc.edu*

Objectives: During pregnancy, dramatic microstructural remodeling allows the uterine cervix to shorten, soften and dilate to allow for vaginal delivery. It also causes the cervix to regain strength after birth. Appropriate timing of these events results in normal delivery. However, early softening can lead to spontaneous preterm birth (SPTB), the leading cause of neonatal mortality worldwide. SPTB could potentially be predicted and even prevented by objectively assessing cervical softening through noninvasive, quantitative methods. We are investigating use of shear-wave speed (SWS) as a biomarker of cervical softening. This work investigates the objectivity of those assessments by comparing SWS changes during pregnancy using different scanning approaches (trans-abdominal (TA) vs intra-cavitary (IC)) in a non-human primate (Rhesus macaque) model of the cervix.

Methods: Pregnant primates (n=18) were scanned at weeks 4, 10, 16, 20, 23 and two weeks post-partum. Scanning was performed with a Siemens Acuson S-series ultrasound system (Siemens Healthcare, Ultrasound Business Unit, Mountain View, CA, USA), using a 9L4 linear array transducer in the TA approach, and a prototype catheter array transducer (128 elements, 14 mm aperture, 3 mm diameter) operated in linear array mode and used trans-rectally in the IC approach. For each approach, a 5x5 mm^2 region of interest was placed at the cervical isthmus at the anterior and posterior portions of the cervix. Five repeat shear-wave speeds measurements were made at each location (anterior and posterior) for both approaches and all time-points. Displacements were estimated using the Loupas' algorithm[(1)] and SWS was estimated using a RANdom SAmple Consensus (RANSAC) method.[(2)] Preliminary analysis was restricted to the posterior side and we are currently analyzing results for anterior. Summary values for specific time points are reported in terms of the median [interquartile range]; statistical significance of their differences was assessed with a Wilcoxon signed-rank nonparametric test.

Results: Results from both scanning methods demonstrated a reduction in SWS throughout gestation (from TA: 3.76 [3.03] m/s and IC: 5.04 [1.71] m/s at week 4 to TA: 1.79 [0.85] m/s (p = 0.049) and IC: 1.38 [0.70] m/s (p = 0.03) at week 20), and SWS increase after delivery due to structural recovery (TA: 2.79 [1.46] m/s and IC: 2.55 [1.16] m/s for at the post-partum scan).

Conclusions: Our preliminary results suggest that SWS can potentially assess cervical remodeling changes during pregnancy. However, differences were observed between SWS values from each scanning approach. We are currently studying the influence of possible confounders inherent to the different approaches (supine vs. prone postures), as well as other factors such as shear-wave bandwidth related to the different transducers. Nevertheless, it is encouraging that trends through pregnancy are comparable for the two scanning approaches. SWS estimation throughout pregnancy may be useful tool for developing methods of detection and prevention of preterm birth. Supported by NIH grants T32CA009206 from the NCI, and R21HD061896, R21HD063031, and R01HD072077 from the NICHD. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. We also thank Siemens HealthCare Ultrasound Division for technical support and equipment loan.

(1) Pinton GF et al. *IEEE Trans Ultrason Ferrorelectr Freq Contr 53*,1103-1117 (2006). [PMID: 26776146]. (2) Wang MH et al. *Ultrasound Med Biol 36*, 802-813 *(*2010). [PMID: 20381950].

1.4 **Cross-sectional study of backscatter-based quantitative ultrasound to assess cervical remodeling**, Andrew P. Santoso[1], Ivan M. Rosado-Mendez[1], Quinton W. Guerrero[1], Lindsey C. Drehfal[1], Helen Feltovich[1, 2] and Timothy J. Hall,[1] [1]*Medical Physics, University of Wisconsin - Madison, Madison, WI and* [2]*Maternal Fetal Medicine, Intermountain Healthcare, Provo, UT, apsantoso@wisc.edu*

Objectives: Backscatter-based quantitative ultrasound parameters have extensively been shown to track changes in tissue microstructure such as kidney, liver, and breast.[(1)] This motivates their use to detect and quantify microstructural remodeling and ripening of the uterine cervix during pregnancy. The ultimate goal is to use these parameters as biomarkers of abnormal changes that could lead to spontaneous preterm birth. This work presents a cross-sectional comparison quantifying changes in cervical microstructure *in vivo* using the acoustic backscatter coefficient (BSC) in early and late stages of pregnancy.

Methods: An IRB-approved study was conducted with 33 recruited patients. Patients were classified based on gestational age: early (5-14 weeks, n=13) and late pregnancy (37-41 weeks, n=20). A Reference Phantom Method was used to estimate BSC parameters.(2) Radio frequency (RF) echo data were acquired transvaginally with a Siemens Acuson S2000 Ultrasound system (Siemens Healthcare, Ultrasound Business Unit, Mountain View, CA, USA) with a prototype catheter transducer attached to a clinician's finger. RF data from a reference phantom were collected under the same acquisition settings. BSCs were estimated by sweeping a 4×4 mm power spectral estimation region with 90% overlap across each RF frame. Frequency dependence and magnitude of the BSC were parameterized in terms of the effective scatterer diameter (ESD, estimated using a Gaussian form factor) and average BSC within 4-9 MHz.(2, 3) Mean values of the two parameters were obtained from each parametric image. Results are summarized in terms of the median [interquartile range] within a region of interest that included the cervix. Statistical significance of their differences was assessed with a Kruskall-Wallis H test.

Results: Statistically-significant differences were observed between early pregnancy (ESD=92 μm [72-106 μm] and ABSC=1.8×10^{-3} cm^{-1} sr^{-1} [$1.1\text{-}2.6\times10^{-3}$ cm^{-1} sr^{-1}]) and late pregnancy (ESD=48 μm [30-65 μm] and ABSC=1.95×10^{-4} cm^{-1} sr^{-1} [$1.2\text{-}3.3\times10^{-4}$ cm^{-1} sr^{-1}]) for both parameters ($p \ll 0.001$).

Conclusions: Physical interpretation of our results is nontrivial because we use a Gaussian model to characterize a continuously varying impedance distribution. While this model is too simple for direct interpretation, we observe that the spatial correlation function of the impedance distribution changes substantially between early pregnancy and term pregnancy. This suggests extracellular matrix remodeling. Future studies will address more complex models. Supported by grants R01CA111289 and T32CA009206 from the NCI, and grants R21HD061896, R21HD063031, and R01HD072077 from the NICHD. We also thank Siemens HealthCare Ultrasound Division for technical support and equipment loan.

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1.5 **Multi-QUS biomarker approach to evaluation of the pregnant cervix: summary of findings and implications for future research**, Helen Feltovich,[1, 2] Ivan M. Rosado-Mendez,[1] Lindsey Drehfal,[1] Quinton Guerrero,[1] Andrew Santoso,[1] Mark Palmeri, William Grobman[3] and Timothy Hall,[1] [1]*Medical Physics, University of Wisconsin - Madison, Madison, WI,* [2]*Maternal Fetal Medicine, Intermountain Healthcare, Provo, UT and* [3]*Maternal Fetal Medicine, Northwestern University, Chicago, IL, hfeltovich@gmail.com*

Objective: To integrate findings from our studies of quantitative ultrasound (QUS) biomarkers for evaluation of the pregnant cervix.

Methods: We have applied 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 (NHPs). Specifically, we use shear-wave elasticity imaging (SWEI) to evaluate cervical softness with shear-wave speeds (SWS), and acoustic backscatter to evaluate ECM microstructural organization.

Results: We have found that (1) SWS decrease from early to late pregnancy, suggesting greater tissue softness in late pregnancy; (2) backscatter anisotropy, parameterized using the mean backscatter power difference (mBSPD), is significantly greater in the non-pregnant and early pregnant, as compared to the late pregnant cervix, suggesting decreased microstructural organization in late pregnancy; (3) the spatial correlation length of backscatter, parameterized using the effective scatterer diameter, is significantly larger in early pregnancy than in late pregnancy, suggesting more organized scattering structure in early pregnancy; (4) the Nakagami M (a measure of scatterer number density) does not vary among the non-pregnant, first, and third trimester trimester cervix, suggesting little change in total collagen concentration throughout pregnancy; and (5) SWS is lower but mBSPD is not significantly different in cervixes ripened with a prostaglandin compared to untreated, suggesting no significant change in fundamental underlying microstructure despite increased softening.

Conclusions: These results suggest that a combination of QUS biomarkers that can simultaneously assess various facets of cervical change may be an effective way to evaluate the *in vivo* cervix during pregnancy. Further, although these results are preliminary, together they suggest that perhaps changes in cervical biomechanical properties in early pregnancy are due to alterations in collagen crosslinking, while in late pregnancy they are due to changes in collagen fiber/bundle size and orientation. This would be consistent with molecular studies in humans and mice.[(1,2)] Supported by NIH grants T32CA009206, R01HD072077, R21HD061896 and R21HD063031, R01HD072077, and the Intermountain Research & Medical Foundation. We are also grateful to Siemens Healthcare Ultrasound division for an equipment loan and technical support.

(1) Myers KM et al. *J Biomech 48* 1511-1523 (2015). (2) Yoshida K et al., PLOS ONE 2014, 9(11):e112391.

1.6 **Compressive sensing for quantitative acoustic microscopy images using approximate message passing,** J-H Kim[1], A. Basarab[2], P.R. Hill[1], N.Canagarajah[1], D. Kouamé[2], J. Mamou[3*] and A. Achim,[1*] [1]*Visual Information Laboratory, University of Bristol, Bristol, BS8 1UB, UK,* [2]*IRIT UMR CNRS 5505, University of Toulouse, CNRS, INPT, UPS, UT1C, UT2J, France and* [3]*Frederic L. Lizzi Center for Biomedical Engineering, Riverside Research, New York, NY 10025,* [*] *Joint last authors, alin.achim@bristol.ac.uk*

This paper introduces a novel approach to enhance the efficiency of data acquisition in quantitative acoustic microscopy (QAM) using a dedicated compressive-sensing (CS) scheme. During the last decade, CS has been intensively studied as an alternative to using the Nyquist sampling theorem for sampling signals. Under particular conditions, *CS* offers theoretical guarantees of perfect image reconstruction from undersampled data, i.e., below Nyquist rate. *CS* success is conditioned on the choice of the sensing procedure and the use of nonlinear recovery algorithms. In this work, an approximate message passing (AMP)-based algorithm was designed to reconstruct QAM images from spatially-undersampled measurements. Unlike classical reconstruction methods, AMP uses an iterative process performing sparse representation-based image denoising at each iteration. The first contribution of this study was the appropriate choice of a transform able to sparsify QAM images and of the denoiser to be embedded in AMP. The second contribution concerned the choice of the sensing matrix (i.e., the 2D spatial sampling scheme) that should simultaneously meet the *CS* requirements and be practical for QAM radio-frequency acquisition. More precisely, three different sensing patterns well adapted to QAM data were investigated. The proposed methods were tested on 250 MHz simulated and experimental QAM data. The simulated data were obtained from three histological images while experimental images were acquired from cancerous human lymph nodes and human cornea. Reconstruction results showed that the best performance was obtained using a spiral-sensing pattern combined with a Cauchy denoiser in the wavelet domain. Using the spiral-sensing matrix, which reduced the number of spatial samples by a factor of 2, on the QAM speed-of-sound images of a human lymph node, an excellent *PSNR* of 43.21 dB was obtained. These results demonstrate that the *CS* approach could significantly improve scanning time, while reducing costs of current QAM systems.

2. IMAGING 1

2.1 **Principal component short-lag spatial coherence imaging (PC-SLSC)**, Arun Asokan Nair, Trac D. Tran and Muyinatu A. Lediju Bell, *Johns Hopkins University, Baltimore, MD, anair8@jhu.edu*

Short-lag spatial coherence (SLSC) imaging is an alternative to delay-and-sum (DAS) beamforming that displays the spatial coherence of backscattered ultrasound echoes at different short lag values rather than displaying signal amplitudes. We propose to improve the tissue texture of SLSC imaging based on the observation that images formed with different short-lag values do not produce equivalent tissue texture. Instead of directly integrating spatial coherence curves as in traditional SLSC imaging, we form images created from a single lag value and extract their first principal component (PC-SLSC) in order to obtain images with smoother tissue texture. Improvements to the signal-to-noise ratio (*SNR*), contrast-to-noise ratio (*CNR*) and contrast with PC-SLSC were 2.32, 0.82, and 16.4 dB, respectively, when compared to traditional SLSC images and 4.76, 3.7 and 8.9 dB, respectively, when compared traditional B-mode images. Our new PC-SLSC algorithm is a promising alternative to spatial compounding, as it reduces tissue texture without requiring independent speckle realizations.

2.2 **Spatial coherence as a predictor of image quality**, Will Long[1], Gregg E. Trahey[1, 2], *Departments of [1]Biomedical Engineering and [2]Radiology, Duke University, Durham, NC, willie.long@duke.edu*

Ultrasonic image quality is traditionally assessed using contrast and contrast-to-noise ratio (*CNR*). However, the reliability of such metrics is often compromised by a strong dependence on ROI selection. This is especially the case for *in vivo* images, where intrinsic tissue contrast is unknown and the identification of adjacent hyperechoic and hypoechoic tissue regions can be made difficult by suboptimal image quality, poor imaging windows and/or tissue nonuniformity.

Spatial coherence is a measure of the similarity between received ultrasound echoes for array elements of varying separation or lag. The van Cittert-Zernike (VCZ) theorem predicts characteristic behavior of the spatial coherence curve in response to different sources of image degradation. Previous simulation studies have validated this behavior and demonstrated its high sensitivity to phase aberration, electronic noise, and reverberation clutter. Based on theory and previous results, spatial coherence shows promise as an alternative, more robust means to predict image quality without substantial *a priori* knowledge of the imaged structure.

In this study, we investigate the use of spatial coherence as a predictor of image quality. Coherence, contrast and *CNR* are measured from *in vivo* liver and fetal datasets of varying image quality. Calculated metrics are compared to simulation, models derived from VCZ theory and clinician scores for target conspicuity.

Coherence values measured from *in vivo* data show positive correlations with contrast and *CNR*. Observed trends are largely consistent with trends predicted by both simulation and theory. Metrics are evaluated against clinician scores to examine the predictive power of each metric with regards to expert-assessed image quality. The accuracy and variability of each metric, along with their associated trade-offs, are discussed.

2.3 **Assessment of ADMIRE in the presence of random noise and limitations of the conventional Hilbert transform envelope detection with decluttered signals**, Kazuyuki Dei and Brett Byram, *Department of Biomedical Engineering, Vanderbilt University, Nashville, TN, kazuyuki.dei@vanderbilt.edu*

To mitigate ultrasound imaging artifacts and increase its usefulness, we developed a nonlinear, model-based beamforming algorithm, which is called aperture-domain-model image reconstruction (ADMIRE). In our previous studies using conventionally focused beam sequences, we demonstrated that the algorithm suppresses reverberation artifacts, off-axis clutter and wavefront phase aberration. Recently, we reported that ADMIRE can be adapted to full-field insonification sequences, such as plane-wave imaging, to improve image quality in challenging high-clutter environments. Based on the findings, we have established that ADMIRE is an effective tool to reduce sources of clutter in ultrasound images. However, we have not yet evaluated the impact of thermal noise (i.e., white Gaussian noise) on ADMIRE model decomposition and reconstruction.

To investigate the effects on image quality when applying ADMIRE in the presence of uncorrelated noise, we employed simulated cyst phantoms with added white Gaussian noise with channel data signal-to-noise ratio (*SNR*) between -10 dB and 60 dB. We computed contrast and contrast-to-noise ratio (*CNR*) of anechoic cyst images obtained from delay-and-sum (DAS), DAS with coherent factor (*CF*) weighting and AMDIRE, respectively. Unsurprisingly, results demonstrate that ADMIRE always outperforms DAS itself and DAS with *CF*, but we find the improvements to be reduced in high-noise scenarios. For example, with an *SNR* of -10 dB, the improvements are at least 15 dB and 6 dB higher in contrast, respectively, but with an *SNR* of 30 dB, the improvements are over 30 dB and 20 dB higher in contrast, respectively. It can thus be suggested that the improvement from using ADMIRE is better with low noise. In evaluating post-ADMIRE data, we identified limitations associated with the conventional software envelope-detection method using the Hilbert transform. The enveloped signal shows much greater amplitude than the actual amplitude of the decluttered RF signal, indicating that in some cases, RF signals derived from ADMIRE are degraded in the postprocessing of image formation. To minimize the limitations, we implemented envelope detection using an optimum equiripple finite impulse response (FIR) Hilbert filter based on the Parks-McClellan algorithm, followed by a low-pass Butterworth filter. We then examined the proposed envelope detector using the same phantom data. We observed better image contrast when compared to images using the conventional method. Quantitatively, the improvement from better envelope detection was 7 dB when the channel data SNR is at least 30 dB or higher but there is no improvement for lower SNRs. The FIR-based envelope detector showed no improvement with DAS for any *SNR*. These findings suggest that the proposed method enables us to fully realize the benefits obtained from applying ADMIRE.

2.4 **Beamforming using nonlinear transfer functions**, Adam Luchies and Brett Byram, *Department of Biomedical Engineering, Vanderbilt University, Nashville TN, 37235, adam.c.luchies@vanderbilt.edu*

In the past, members of our group developed a model-based beamforming method called aperture-domain-model image reconstruction (ADMIRE). They tuned this beamformer to improve ultrasound image quality by suppressing sources of image degradation such as off-axis scattering, reverberation and phase aberration. In addition, the development of ADMIRE demonstrated that beamforming could be posed as a regularized nonlinear regression problem, which suggests that an artificial neural network (ANN) might be used to accomplish the same task. Compared to regularized regression methods, ANNs are fast, adaptive and fault tolerant.

Based on the success of ADMIRE, we trained feed-forward ANNs to suppress off-axis scattering. We employed FIELD II to construct the required training and validation data sets. Point scatterers were placed in the field of a simulated linear array transducer and their responses recorded. Similar to ADMIRE, we defined acceptance and rejection regions based on the characteristics of the array transducer. Backpropagation was used to train the ANNs and an extensive hyperparameter search was conducted to locate the best performing ANNs.

Our initial results show that we can train ANNs to suppress off-axis scattering and realize maximum side-lobe levels of -100 dB without sacrificing main-lobe width. We found ANNs behaving linearly in amplitude. The initial hyperparameter search took about one month of time on an 8-GPU computing cluster to find-high performing ANNs but we were able to use transfer learning to train new ANNs for different frequencies and depths using previously-trained ANNs in less than an hour. Our results suggest that ANNs have the potential to be trained to improve ultrasound image quality.

2.5 **Nonlinear beamforming approaches for imaging large calcifications**, Jaime Tierney, Siegfried Schlunk, Mark George, Pranav Karve, Ravindra Duddu, Ryan His and Brett Byram, *Department of Biomedical Engineering, Vanderbilt University, Nashville TN, brett.c.byram @vanderbilt.edu*

Standard B-mode imaging has poor sensitivity and specificity for detecting kidney stones. Additionally, B-mode imaging typically overestimates stone size. Because B-mode performs poorly, the acoustic shadow produced by the stone and twinkling artifacts seen with color Doppler have been used as substitutes for conventional imaging for stone sizing and detection. However, often neither a shadow nor a color Doppler artifact are present. In order to gain further insight into the problem of kidney-stone imaging, we investigated the use of several nonlinear beamforming strategies. These strategies included basic plane-wave synthetic aperture, aperture-domain-model image reconstruction (ADMIRE), short-lag spatial coherence (SLSC) and a new coherence-based method designed specifically for the kidney-stone scenario.

We performed *in vitro* and *ex vivo* evaluations of all four methods. For the *in vitro* evaluation, we placed variously-sized kidney stones (n=7) on top of a gelatin phantom doped with graphite. The gelatin phantom served as a platform for the stone and provided a diffuse scattering background to facilitate comparisons. The phantoms were imaged 4 and 8 cm above the stone. The stones were degassed and rehydrated for at least 24 hours prior to imaging. We also performed an *ex vivo* evaluation where several stones were implanted into pig kidneys. The pig kidneys were immersed in water for imaging.

We will show the qualitative results from the study in the kidneys but here we report the results of our *in vitro* study assessing stone sizing. The distribution of stones was 11±5.1 mm. The sizing error for plane wave synthetic aperture, SLSC, ADMIRE and our custom approach were, 1.5±0.66 mm, 1.4±1.0 mm, 0.79±0.31 mm and -1.2±4.5 mm. Based on these data ADMIRE performs best for the sizing task.

2.6 **Beamforming challenges in swept synthetic-aperture imaging**, Matthew R. Morgan[1], Nick Bottenus[1], Gregg E. Trahey,[1,2] [1]*Departments of Biomedical Engineering and* [2]*Radiology, Duke University, Durham, NC, mrm63@duke.edu*

Introduction: In abdominal and fetal ultrasound imaging, targets of interest are often located at depths beyond several centimeters. However, diffraction effects and the use of low-imaging frequencies decrease lateral resolution, which can severely limit target conspicuity.

Our group has recently proposed a new imaging technique to markedly improve lateral resolution by synthesizing a large effective aperture: Swept Synthetic-Aperture (SSA) imaging. SSA imaging employs a conventional matrix-array transducer connected to a real-time position sensing system. Through a rapid, precisely-tracked sweep, we seek to create high resolution images through coherent combination of individual channel echo data.

Many challenges remain in the development of SSA imaging, notably understanding the effects of tissue motion and nonuniform sound speed, which may result in beamforming errors, and a loss in image quality.

Methods: To evaluate the degradation in image quality, we used Field II to simulate several SSA scans using a model of the Siemens 4z1c matrix-array transducer imaging at 2.5MHz. A 10 cm sweep was simulated using diverging wave transmits at a 2 kHz PRF over 0.1 s. To simulate tissue motion, the imaging target (a point target or 1cm anechoic cyst) was translated in several directions at constant velocity over total distances ranging from 0-10λ. These simulations were repeated using sound speed errors of c ±: 2%, while simultaneously undergoing target motion.

Results Point-target results were characterized in 2D in terms of lateral and axial resolution. Cystic resolution was used to evaluate the point-spread function in 3D space. Cyst images were characterized using contrast and *CNR*. Degradation in resolution and lesion conspicuity will be analyzed in the context of target motion, gross velocity error and effective aperture size. We will discuss the implications on the feasibility of *in vivo* SSA imaging, and tradeoffs between acceptable beamforming errors and output image quality.

Monday afternoon

3. THERAPY RESPONSE

3.1 **Computer-assisted technology for assessment of therapeutic cancer responses in patients with locally-advanced breast cancer**, Mehrdad J. Gangeh[1, 2], Lakshmanan Sanachi[1, 2], William T. Tran[1, 2] and Gregory J. Czarnota,[1, 2] [1]*Departments of Medical Biophysics, and Radiation Oncology, University of Toronto, Toronto, ON, Canada and* [2]*Department of Radiation Oncology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, mehrdad.gangeh@ utoronto.ca*

Background and Motivation: Therapeutic cancer response assessment in preclinical and clinical treatments is presently limited; results may not be available to the clinician for typically months. This can lead to ineffective cancer treatments continued needlessly as no faster feedback mechanisms have yet reached broad biomedical adoption. Quantitative ultrasound (QUS) methods provide a promising alternative framework that can noninvasively, inexpensively and quickly assess tumor response to cancer treatments using standard ultrasound equipment.

Methods: A large cohort of 102 locally-advanced breast-cancer patients (LABC) treated with neoadjuvant chemotherapy were imaged before and at four times during treatment administration, i.e., weeks 1, 4, 8 and preoperatively. Image acquisition was performed using a Sonix RP ultrasound machine at a central frequency of ~7 MHz. Spectral and backscatter coefficient parametric maps including mid-band fit (MBF), 0-MHz spectral intercept (SI), spectral slope (SS), effective acoustic concentration (EAC) and effective scatterer diameter (ESD) were computed by employing quantitative ultrasound spectroscopy and form-factor techniques. The ground truth labels for patients were determined based on their ultimate clinical and pathological response to treatment. Textural features were extracted using several different texture methods, including gray level co-occurrence matrices (GLCM), local binary patterns and texton-based methods. Subsequently, a kernel-based metric, called maximum mean discrepancy (MMD), was used to measure the distances between the underlying distributions of the data samples (represented using multidimensional textural features in the previous step) taken from “pre-” and “mid-treatment” scans. The MMD dissimilarity measures were used as an indication of treatment effectiveness and submitted to a classifier after compensation for an uneven distribution of data samples between the two classes of responders and non-responders. The classifier, eventually, labeled the patients as either responders or nonresponders in a leave-one-out evaluation scheme.

Results: The classification of 102 LABC patients treated with neoadjuvant chemotherapy to responders or non-responders using the texton-based texture descriptors as features and the MMD as the dissimilarity measure achieved the highest performance. The proposed method tested on the MBF parametric maps, for example, resulted in an accuracy of 89.8% and 81.8%, area under curve (AUC) of 0.81 and 0.75, sensitivity of 91.6% and 85.6%, and specificity of 88.1% and 78.4% after 1 and four weeks of treatment, respectively.

Conclusion: In this study, state-of-the-art textural features and kernel-based machine learning technique were employed to quantify the assessment of LABC response to neoadjuvant chemotherapy. The effectiveness of the developed methods was assessed on a large cohort of 102 LABC patients treated with neoadjuvant chemotherapy. The proposed system achieved a promising performance early during the course of treatment.

3.2 **Response monitoring of breast-cancer patients receiving neoadjuvant chemotherapy using quantitative ultrasound, texture and molecular features,** Lakshmanan Sannachi[1, 2], Hadi Tadayyon[1, 2], Mehrdad Gangeh[1, 2] Ali Sadeghi-Naini[1 ,2], William Tran[1], Sonal Gandhi[3], Frances Wright[4] and Gregory Czarnota[1, 2], *[1]Department of Radiation Oncology, and Physical Sciences, Sunnybrook Health Sciences Centre, [2]Department of Radiation Oncology and Medical Biophysics, University of Toronto, [3]Division of Medical Oncology, Sunnybrook Health Sciences Centre, Toronto and [4]Division of General Surgery, Sunnybrook Health Sciences Centre, Toronto, ON, canada.lakshmanan.Sannachi@sunnybrook.ca*

Introduction: Neoadjuvant chemotherapy (NAC) is a standard treatment for locally-advanced breast cancer and its effectiveness is evaluated based on clinical and pathological responses. Responses of LABC in the neoadjuvant 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), textural analysis and molecular features in patients with locally-advanced breast cancer.

Patient and Methods: The study included ninety-six (n=96) patients treated with neoadjuvant chemotherapy. Breast tumors were scanned with an ultrasound system (Ultrasonix, Analogic, Vancouver Canada) prior to chemotherapy treatment, during the first, fourth and eighth week of treatment and prior to surgery. QUS Spectral parameters, backscatter parameters and scatterer spacing were calculated from ultrasound radio frequency (RF) data within tumor regions of interest. Additionally, texture features were extracted from QUS parametric maps. Prior to therapy, all patients underwent a core needle biopsy and histological subtypes and biomarker ER, PR and Her2 status were determined. Patients were classified into three treatment response groups based on clinical and pathological analysis: complete pathological response (CR), partial response (PR) and non-responders (NR). Response classifications from QUS parameters, receptors status and pathological were compared. Discriminant analysis was performed on extracted parameters using support vector machine classifier (SVM) to classify subject into CR, PR, and NR at all scan time points.

Results and Discussion: Of the 96 patients, the number of CR, PR and NR patients were 21, 52 and 23, respectively. Mean QUS parameters classified the three response groups with accuracies of 53%, 60% and 58% at weeks 1, 4 and 8, respectively. Using only clinical tumor-molecular status predicted the three response groups with accuracies of 38%, 37% and 50% at weeks 1, 4 and 8, respectively. The best prediction of treatment response was achieved with the combination mean QUS values and molecular features with accuracies of 78%, 86% and 83% at weeks 1, 4 and 8, respectively. The recurrence free survival (RFS) of CR and PR determined based on clinical/pathology and combined QUS parameters and a molecular feature was higher than the NR group (p<0.001). However, both parameters did not reveal significant differences between CR and PR at all scan times.

3.3 **Quantitative ultrasound and texture predictors of breast-tumor response to chemotherapy prior to treatment: progress update**, Gregory Czarnota, Hadi Tadayyon, Mehrdad Gangeh, Lakshmanan Sannachi, Ali Sadeghi-Naini, William Tyler Tran, Sonal Gandhi and Maureen Trudeau, *U. Toronto and Sunnybrook HSC, gregory.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, 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 92 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: Results from the first 56 patients indicate that a combined QUS feature model demonstrated a favorable response prediction with sensitivity, specificity, and AUC of 90%, 79% and 0.81, respectively, using k-NN SVM classification.

Conclusion and future work: 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.

3.4 **Predicting radiotherapy response in head and neck patients using quantitative ultrasound: initial results**, William T. Tran[1], Harini Suraweera[2], Mehrdad Gangeh[2], Justin Lee[1], Irene Karam[1], Lakshmanan Sannachi[2], Elyse Watkins[2], Karina Quiaoit[2] and Gregory J. Czarnota[1,2] *[1]Radiation Oncology, Sunnybrook Health Sciences Centre, Toronto Canada and [2]Medical Biophysics, University of Toronto, Toronto, Canada, william.tran@sunnybrook.ca*

Background and Purpose: Head and neck cancer will account for approximately 61,760 new cases in the United States. Mortality rates are estimated as 13,190 deaths in 2016. Treatment for patients typically require several weeks of radiotherapy leading to severe radiation-induced toxicity and variable response outcomes. This study examined using quantitative ultrasound to predict clinical response in patients receiving radiotherapy to the head and neck.

Methods: This study was approved by the institution's ethics review board and 27 patients participated following written informed consent. All patients were diagnosed with carcinoma of the head of neck and underwent concurrent chemoradiation consisting of 70Gy/33 fractions. Patients were scanned using a Clarity Ultrasound System at a center frequency of ~7 MHz (Elekta Medical Corp, Montreal, Canada) at the following times relative to the start of radiotherapy: prior to treatment (baseline), week 1, week 4 and after the completion of treatment at week 7. Quantitative ultrasound (QUS) data were collected and analysis included mean QUS parameters and texture-based features (contrast, correlation, homogeneity, energy). The ground truth labels for patients were based on clinical response data from RECIST 1.1 criteria. QUS mean and texture features to were computed volumetrically and response classification was analyzed using a naïve Bayes, and *k*-nearest neighbour (*k*-NN) classifiers. A receiver-operating characteristic (ROC) analysis was performed and the optimal sensitivity and specificity was calculated using Youden's index of the average ROC curve.

Results: RECIST 1.1 classification resulted in 19 responders and 8 non-responders based on CT images of the tumours during and after treatment. Preliminary QUS results demonstrated that for naïve-bayes classification, the optimal sensitivity and specificity was 62.5%, and 100% respectively using a multiparametric model: SAS (scatterer spacing), and SI (spectral intercept)-*contrast* after 4 weeks of treatment. The AUC was 0.95 and the accuracy was 88.9%. For k-NN classification, the SAS (scatterer spacing) and SS (spectral slope)-*energy* demonstrated a sensitivity and specificity of 62.5%, and 94.7%, respectively at week 4. This corresponded with an AUC of 0.88 and an accuracy of 85.2%.

Conclusions: Preliminary results demonstrate that quantitative ultrasound parameters combined with texture-based features can predict clinical response to radiotherapy in head and neck patients. QUS analysis can potentially help modify treatments based on response-guided imaging. The clinical applications can also improve treatment outcomes based on QUS imaging biomarkers.

3.5 **Novel ultrasound imaging method for 2D temperature monitoring of thermal ablation**, Chloé Audigier, Younsu Kim and Emad M. Boctor, Jo*hns Hopkins University, Baltimore, MD, eboctor1@jhmi.edu*

Accurate temperature monitoring is a crucial task that directly affects the safety and effectiveness of thermal-ablation procedures. Compared to MRI, ultrasound-based temperature monitoring systems have many advantages, including higher temporal resolution, low cost, safety, mobility and ease of use. However, conventional ultrasound (US) images have a limited accuracy due to a weak temperature sensitivity. As a result, it is more challenging to fully meet the clinical requirements for assessing the completion of ablation therapy. A novel imaging method for temperature monitoring is proposed based on the injection of virtual US pattern in the US brightness mode (B-mode) image coupled with biophysical simulation of heat propagation. This proposed imaging method does not require any hardware extensions to the conventional US B-mode system. The main principle is to establish a bidirectional US communication between the US imaging machine and an active element inserted within the tissue. A virtual pattern can then directly be created into the US B-mode display during the ablation by controlling the timing and amplitude of the US field generated by the active element. Changes of the injected pattern are related to the change of the ablated tissue temperature through the additional knowledge of a biophysical model of heat propagation in the tissue. Those changes are monitored during ablation, generating accurate spatial and temporal temperature maps. We demonstrated *in silico* the method feasibility and showed experimentally its applicability on a clinical US scanner using *ex vivo* data. Promising results are achieved: a mean temperature error smaller than 4 °C was achieved in all the simulation experiments. The system performance is also tested under different configurations of noise in the data. The effect of error in the localization of the RFA probe is also evaluated.

3.6 **HIFU ablation monitoring using active ultrasound elements: feasibility study**, Younsu Kim, Chloe Audigier, Austin Dillow and Emad M. Boctor, *Johns Hopkins University, Baltimore, MD, eboctor1@jhmi.edu*

Ablation therapy is a procedure that uses a heating source to destroy tumors. HIFU (high intensity focused ultrasound) is a minimally-invasive treatment to eradicate prostate cancer and other cancerous tissues. HIFU is a technique that focuses high-intensity ultrasound on a target region to destroy malignant tissues. The main goal of ablation therapy is to preserve as much healthy tissue as possible while removing malignant tissue. Therefore, the ablation process has a need for temperature monitoring to control the thermal dose. MRI (Magnetic resonance imaging) is often integrated with HIFU systems for temperature monitoring. MRI provides reliable temperature information in real-time during the HIFU therapy; however, MR-HIFU also has disadvantages such as the lack of portability and high-cost. Thus, people have investigated thermal-monitoring methods using ultrasound due to its noninvasiveness, cost-effectiveness and portable nature. The speed of ultrasound changes along with temperature changes. By detecting the sound-velocity change, we can detect the temperature increase caused by the heating therapy. We propose a new method using active ultrasound elements to generate temperature maps during a HIFU treatment. The active ultrasound elements can transmit and receive ultrasound signals. By taking an advantage of the fact that HIFU also transmits ultrasound signal, we collect times-of-flight through the target tissue using the active ultrasound elements. We add minimal components for the thermal-monitoring system. We show the feasibility of our method with a simulation and phantom study.

4. IMAGE GUIDANCE/ROBOTICS

4.1 **Photoacoustic-based visual servoing of needle tips to improve surgery on obese patients**, Joshua Shubert and Muyinatu Bell, *Johns Hopkins University, Baltimore, MD, jshuber2@jhu.edu*

Purpose: Traditional ultrasound imaging experiences scattering and high signal attenuation in obese patients. This limits its usefulness as an intraoperative imaging modality. Photoacoustic imaging has the benefit of signals being generated at the ROI so there is no scattering on the way to the ROI as with traditional ultrasound.

Methods: Laser pulses were fed through a fiber into a hollow needle pressed against a tissue phantom. The photoacoustic signal was generated by a Pulsed Laser Diode at 29 ns pulse length with 226 W peak power. The photoacoustic data was captured with a linear-array ultrasound probe connected to a clinical ultrasound scanner. The probe was held by a custom holder rigidly attached to a 7 DOF Sawyer robotic arm (Rethink Robotics). Photoacoustic images were segmented using local intensity-based thresholding. As a precaution, consecutive frames of segmentation results were compared for consistency before sending a command to the robotic arm. Needle-tip pixel coordinates were sent as UDP packets over an ethernet connection to the robot controller, where they are transformed into the robot base reference frame. An inverse kinematics solution for placing the ultrasound probe centered over the needle tip is then computed and then sent to the robot joint controllers for execution.

Results: From 26 starting positions the visual servoing system was able to center the ultrasound probe over the needle tip with 1.04 mm error in end-effector space with a standard deviation of 0.808mm.

Conclusions: Our robotic photoacoustic-based visual servoing system was able to align the ultrasound probe over the needle with a high degree of accuracy. The system can segment the location of the needle tip at a rate of 20 Hz. This system could potentially improve the placement of needles for biopsy in obese patients.

4.2 ***In-vivo* catheter tracking using photoacoustics**, Alexis Cheng, Younsu Kim, Clifford Weiss, Russell H. Taylor and Emad M. Boctor, *Johns Hopkins University, Baltimore, MD, eboctor1@jhmi.edu*

Catheters are commonly used in surgical procedures such as cardiac catheterization and kidney embolization. In these procedures, it is often difficult for surgeons to determine where the catheter is currently located without the use of some intraoperative imaging or tracking technology. The current standard of care is to use x-ray fluoroscopy continuously to obtain an up-to-date catheter location. This has its obvious disadvantages as real-time x-ray fluoroscopy delivers a high level of radiation dose for a non-therapeutic purpose.

Previously, we proposed a method that uses photoacoustic markers to tracker a piezoelectric sensor integrated onto the tip of the catheter to supplement the use of x-rays. We demonstrated the efficacy of this method through phantom experiments. In this work, we explore the feasibility of this method in an *in vivo* scenario.

4.3 **Incorporation of ultrasound imaging into assistive devices for inferring motor intent and proportional control,** Siddhartha Sikdar, Elizabeth Tarbox, Ananya Dhawan, Nima Akhlaghi, Clayton Alex Baker, Parag Chitnis and Paul Gammell, *George Mason University, Fairfax VA 22030, ssikdar@ gmu.edu*

The past decade has seen a steady increase in the technological sophistication of assistive devices, such as prostheses and exoskeletons for persons with mobility impairments. Many commercially-available devices have actuators for multiple degrees of freedom. These advances have been driven by a need for increased functional independence in performing activities of daily living. Control of these devices requires real time sensing of the volitional motor intent of the mobility-impaired user, as well as the ability for the user to proportionally control the device response during performance of tasks related to activities of daily living. Traditionally, surface electromyography (EMG) has been used to sense the user's volitional motor intent. However, EMG is known to suffer from a number of limitations, including poor signal-to-noise ratio and limited specificity for sensing the electrical activity of deep-seated muscles. Our research group has been investigating the use of wearable ultrasound imaging sensors as an alternative to overcome the limitations of EMG. Real time ultrasound imaging can be used to monitor dynamic mechanical activation of spatially-resolved deep-seated muscles. The spatio-temporal pattern of activity observed on the ultrasound image sequences can be used to infer the user's motor intent and the continuous mechanical deformation of the muscle during contraction can be used for proportional control. In this paper, we will describe our recent advances in developing wearable imaging systems and control paradigms for multi-articulated prosthetic hands. Studies in able-bodied subjects demonstrate the ability to accurately classify motor intent, exceeding that of state-of-the-art myoelectric control methods, as well as the ability to seamlessly switch between various tasks with proportional control. Studies in an amputee subject demonstrate the feasibility of infer motor intent from muscles in the residual stump. Ongoing studies incorporating ultrasound sensing into other assistive devices such as exoskeletons will also be discussed. Research supported by National Science Foundation grants 13298nd 1646204, and Department of Defense grant W81XWH-16-1-0722.

4.4 **Cooperatively-controlled, three-dimensional robotic synthetic tracked-aperture ultrasound imaging**, Haichong K. Zhang, Ting Yun Fang, Rodolfo Finocch and Emad M. Boctor, *Johns Hopkins University, Baltimore, MD, eboctor1@jhmi.edu*

Three-dimensional (3D) ultrasound provides intuitive anatomical information by showing whole structure compared to a single slice B-mode image. Conventional 3D ultrasound imaging is mostly scanned either by using a two-dimensional matrix array or by motorizing a one-dimensional array in the elevation direction. However, the former system is not widely assessable due to its cost, and the latter one has limited resolution and field-of-view in the elevation axis. Here, we propose a 3D ultrasound imaging system based on the synthetic-tracked aperture approach, in which a robotic arm is used to provide accurate tracking and motion. While the ultrasound probe is moved through human-robot cooperative control, each probe position is tracked and can be used to reconstruct a wider field-of-view as there are no physical barriers that restrict the elevational scanning. At the same time, synthetic-aperture beamforming gives a better resolution in the elevation axis. To synthesize the elevational information, the single focal point is regarded as the virtual element and forward and backward delay-and-sum are applied to the radio-frequency (RF) data collected through the volume. The concept is experimentally validated using a general ultrasound phantom and the elevational resolution improvement was measured. We also discuss the future integration of the constrained control strategies, including virtual-fixture control.

Tuesday morning

5. TISSUE PARAMETERS 2

5.1 **Local sound-speed estimator by means of model-based approach,** Marko Jakovljevic[1], Rehman Ali[2], Scott Hsieh[3] and Jeremy J. Dahl,[1] *[1]Departments of [1]Radiology and [2]Electrical Engineering, Stanford University, Stanford, CA, jeremy.dahl@stanford.edu*

There is a long history of speed-of-sound estimation techniques using pulse-echo ultrasound; however, clinically-translatable methods that are capable of accurately and noninvasively quantifying the speed of sound at a particular location in tissue are still lacking. Most existing techniques can only estimate an average speed of sound and suffer from large bias and variance when inhomogeneous media are present in the propagation path. Current local speed-of-sound estimation techniques are better suited for quantifying the speed of sound *in vivo* but are difficult to implement on commercial ultrasound scanners and/or lack accuracy to detect small changes in sound speed necessary for disease identification.

We have developed a model and method for quantifying the local speed of sound of tissue from conventional pulse-echo ultrasound, which can be easily implemented on current clinical ultrasound scanners. The model is based on linear equations that relate direct measurements of the average speed of sound between the transducer and the reflection point to the local speed of sound values along the wave-propagation path. The system of equations is solved numerically (via the gradient descent-method) to determine the local sound-speed estimates. In a homogenous speed-of-sound medium with diffuse scatterers, the method achieved a bias and precision similar to existing average speed-of-sound estimators. We further applied the local-estimator method to simulations of phantoms having two layers with different speeds of sound. The phantoms consisted of a 15-mm thick top layer having a speed of sound 1480 m/s and bottom layers of 1520, 1540 and 1570 m/s. The proposed method yielded local sound speed estimates in the bottom layer with biases of -8.2, -17.1, and -21.7 m/s for sound-speed values of 1520, 1540 and 1570 m/s, respectively. For the same phantoms, the average sound-speed estimator achieved biases of -32.6, -46.4 and -67.4 m/s, respectively. The standard deviation of the local estimator was slightly higher than that of the average estimator, with values of 1.6, 3.7 and 2.3 m/s, compared to values of 0.4, 0.8 and 0.6 m/s, respectively, indicating that both methods were very precise. We discuss the advantages and challenges of our method and its opportunities for disease identification.

5.2 **Extended nearly-local Kramers-Kronig approximation for ultrasonic tissue characterization in soft and hard tissue**, James G. Miller, Constance F. James and Jonathan I. Katz, *Department of Physics, Washington University, Saint Louis MO 63130, james.g. miller@wustl.edu*

The objective of this investigation was to compare the results of a recently extended nearly local (in frequency) approximation to the Kramers-Kronig relations with the exact analytical result in the context of parameter-based ultrasonic tissue characterization. Our group introduced the nearly local approximation to the generalized dispersion relation at the 1978 Ultrasonic Imaging and Tissue Characterization meeting, followed initially by a brief publication(1) and subsequently by a more detailed development.(2) The nearly local approximation replaces the (maximally nonlocal) KK integral equations with a simple first derivative relationship. For a wide range of soft tissues exhibiting an approximately linear increase of the attenuation coefficient with frequency, dispersions that increased logarithmically with frequency, as predicted by the original nearly local

KK approximations were found to be in excellent agreement with experiment. However, subsequent work by T.L. Szabo identified a significant error in the nearly local approximation for values *n* of the frequency to *n*th power sufficiently far removed from 1 (the value typical of ultrasonic tissue characterization data).[3, 4] Subsequent studies from our laboratory incorporated the insights that Szabo's work provided[5-7] determined the limitations of finite bandwidth measurements[8] and established the links between integral and differential forms of both time and frequency domain analyses.[9] The current talk examines the range of validity for ultrasonic tissue characterization of an extended form of the nearly local approximation with the aim of understanding the relevant physics in cases for which it breaks down. Acknowledgements: Contributions by many previous members of our laboratory will be acknowledged in the presentation.

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5.3 **Characterization of cortical bone using multiple scattering of ultrasound**, Yasamin Karbalaeisadegh[1], Omid Yousefian[1], Kay Raum[2], Gianluca Iori**Error! Bookmark not defined.** and Marie Muller,**Error! Bookmark not defined.** *[1]North Carolina State University and 2Charité – Universitätsmedizin Berlin, muller2@ncsu.edu*

This simulation study quantifies microstructural parameters in cortical bone using multiple-scattering of ultrasound that could be helpful in diagnosis and monitoring of diseases like osteoporosis. A finite difference time domain approach is used to simulate the propagation of 8 MHz ultrasound pulses in cortical bone. A multi-element linear array is simulated and each of the elements transmit pulses one by one. For each transmit, the backscattered intensity is collected on the array and the incoherent contribution is extracted from the signals. Once the coherent and incoherent backscattered intensities are separated, the growth of the diffusive halo over time was used to calculate the diffusion constant and transport mean free path of the cortical microstructures. All simulations were performed on human tibia samples obtained by scanning acoustic microscopy (SAM). Results are compared for different pore volume fractions. With an increase in pore volume fraction, the distance between scattering events was found to decrease. A corresponding decrease in the values of the transport mean free path was observed as expected. These results suggest the potential of the transport mean free path measured in cortical bone as a parameter for the assessment of cortical porosity.

5.4 **Studying the effect of pore volume fraction and pore size in cortical bone on ultrasonic parameters**, Omid Yousefian, Yasamin Karbalaeisadegh and Marie Muller, *Department of Mechanical and Aerospace Engineering, North Carolina State University, Raleigh NC, 27606, mmuller2@ncsu.edu*

Technically, osteoporosis occurs when the pore size and volume fraction value in bone change. Still, the effect of pore size and volume fraction change on ultrasonic parameters of cortical bone is unclear. Hence if a theoretical model can estimate the USP in cortical bone, it means that the model can be further used to estimate geometrical parameters of cortical bone. Studying the USP change due to change in pore size and volume fraction can reveal the mechanism for addressing the micro-architectural of cortical bone. Moreover, it can lead to diagnose of osteoporosis in cortical bone.

In this study, we address the effect of changing pore size and pore volume fraction on ultrasound attenuation and phase velocity in cortical bone. A finite-difference, time-domain numerical approach is used to simulate the elastic-wave propagation to see the effect of changing two architectural parameters on ultrasonic parameters. This approach is applied to CT images of bovine and human cortical bone for different values of pore volume fraction and pore size. The results revealed that for a given pore size, attenuation changes linearly with pore concentration. On the other hand, for a given pore concentration, attenuation will have a maximum value at a certain pore size.

The results show how this method can be applied to track the micro-architectural changes of cortical bone through ultrasound through transmission, in order to detect the osteoporosis.

5.5 ***In-vivo* characterization of lung parenchyma using ultrasound multiple scattering**,
Kaustav Mohanty[1], John Blackwell[2], Thomas Egan[2] and Marie Muller[1] *[1]Department of Mechanical and Aerospace Engineering, NC State University, Raleigh, NC 27695 and [2]Division of Cardiothoracic Surgery, Department. of Surgery, UNC Chapel Hill, Chapel Hill, NC 27599, kmohant@ncsu.edu*

The lung parenchyma is a highly complex and diffusive medium for which ultrasound techniques have remained qualitative. The approach presented here is based on ultrasound multiple scattering and exploits the complexity of ultrasound propagation in the lung structure. Diffusion constant (*D*), mean free path (*L**) along with the backscattered frequency shift (*BFS*, MHz/cm) have been proposed as co-dependent prediction parameters to characterize the lung parenchyma and some associated pathologies, such as pulmonary edema and fibrosis. We use these parameters to quantitatively characterize the micro-architecture of the lung parenchyma in order to predict the extent of pulmonary edema and fibrosis and discriminate it from a healthy lung. The experimental setup consisted of a linear transducer array with a 7.8 MHz central frequency placed in contact with the lung surface. The diffusion constant *D* and transport mean free path *L** of the lung parenchyma were estimated by acquiring the impulse-response matrix (IRM), separating the incoherent and coherent intensities in the near field and measuring the growth of the incoherent diffusive halo over time. The BFS was evaluated using plane-wave imaging and calculating the frequencies corresponding to the peak amplitudes of the backscattered waves along the depth. In the control rat lung, *L** was found to be 330 μm (±79 μm, *N*=6), whereas in the edematous and fibrotic lungs, it was found to be 876 μm ±179 μm, *N*=5) and 1103 μm (+/-356 μm, *N*=5). Since there is a clear overlap between the *L** values obtained from edematous and fibrotic lungs, we calculate the *BFS* to be able to discriminate the fibrotic lung from the edematous lung. The *BFS* values obtained from control, edematous and fibrotic lungs were found to be 0.74 MHz/cm (±0.08, *N*=2), 0.23 MHz/cm (±0.05, *N*=2) and 0.58 MHz/cm (±0.14, *N*=2). To conclude, measuring the mean free path enabled us to discriminate healthy from fibrotic and healthy from edematous lungs. Measuring the *BFS* enabled us to discriminate between fibrotic and edematous lungs. The *BFS* combined with *L** demonstrate the potential of ultrasound for the quantitative characterization of the lung parenchyma.

5.6 ***In-vivo* feasibility of noninvasive and real-time acoustic assessment of inflammation,**
Julian Garcia-Duitama[*], Boris Chayer[*], Damien Garcia[*†§], Yves Goussard[‡], Guy Cloutier[*§] *[*] Laboratory of Biorheology and Medical Ultrasonics, University of Montreal Hospital Research Center (CRCHUM), [†] Research Unit of Biomechanics and Imaging in Cardiology, CRCHUM, [§] Department of Radiology, Radio-Oncology and Nuclear Medicine and Institute of Biomedical Engineering, University of Montreal, [‡]Department of Electrical Engineering and Institute of Biomedical Engineering, École Polytechnique of Montreal, Montreal, Quebec, Canada, guy.cloutier@umontreal.ca*

Background and Objective: Ultrasound has been proposed as a promising technology for detection of acute inflammation. The technique is based on quantifying the erythrocyte aggregation level using RF spectral analysis (i.e., backscattering coefficient), as the aggregate size is increased during the acute phase reaction. The main advantage of such a technique is that it could be applied *in vivo*, with real-time feedback. However, *in vivo* measurement is still challenging because it is affected by a few confounding factors. In particular, shearing forces caused by the blood flow can mislead the measurement. We hypothesized that reducing the blood flow by applying a controlled pressure on the vein would allow to measure the erythrocyte aggregation in repeatable conditions. We aimed to validate the reproducibility and sensitivity of *in vivo* measurements of erythrocyte aggregation using ultrasound spectral analysis.

Materials and methods: RF data were acquired from the median antebrachial vein of eleven human volunteers. No particular exclusion criteria were applied. Two of the subjects disclosed to have metabolic or cardiovascular diseases, which are known to increase the erythrocyte aggregation. A single element transducer at 27.5 MHz at a frame rate of 26 fps was employed. To reduce the blood flow, a pneumatic cuff was applied downstream of the probe. The pressure on the cuff was increased manually until the median shear rate of 3±1 s^{-1} was attained. Blood flow and shear rate were monitored by particle-image velocimetry in real time. Ultrasound blood data were summarized by their spectral slope and mid band amplitude. *In vivo* ultrasound measures were compared to laser laboratory erythro-agregameter measurements on venipuncture blood samples. Reproducibility was evaluated by repeating ten times the measurements in a single subject and calculating the coefficient of variation.

Results: Control of the *in vivo* shear rate was well performed by the pneumatic cuff keeping median shear rates at 2.2±0.5 s^{-1} during the ten repetitions. The spectral slope was the most repeatable parameter with a coefficient of variation of 11%. Laboratory results showed an important biological diversity of aggregation in the cohort, ranging from very low to moderately high aggregation. Excellent agreement was found between the ultrasound spectral slope and *ex vivo* laboratory results (R^2=82.7%, p-value <0.0001).

5.7 **Ultrasound characterization of interface oscillation as a proxy for ventriculo-peritoneal shunt function**, April Aralar, Matthew Bird, Robert Graham, Beomseo Koo, Mahesh Shenai, Parag Chitnis and Siddhartha Sikdar, *George Mason University*, *ssikdar@gmu.edu*

Introduction: Ventriculoperitoneal shunts (VPS) are the current gold standard for treatment of hydrocephalus. However, these shunts have a high failure rate: 12.9% fail within the first month after implantation and 28.8% fail within the first year.(1) Currently, there are no noninvasive, objective techniques capable of accurate diagnosis of shunt failure. Therefore, surgical exploration is required to properly diagnose shunt failure. The goal of this study is to investigate a novel, easily-adaptable method of objective, noninvasive detection of shunt failure.

Method: In this proof-of-concept report, ultrasound is utilized to noninvasively monitor the shunt valve, and characterize its mechanical response to different flow conditions which represent various shunt functional states. We hypothesized that the silastic valve interface found in the shunt reservoir would respond to pulsatile pressure changes in CSF, and that this motion could be detected using ultrasound imaging. *In vitro* and *in situ* testing was carried out by running deionized water through a VPS system using a pulsatile flow generator to replicate the flow rates expected *in vivo*. Different flow conditions were then tested: no flow, normal flow, proximal blockage, and distal blockage. Blockage conditions were simulated by attaching A-clamps to either the proximal or distal catheter to prevent fluid flow. Ultrasound data taken from the pressure relief valve were analyzed to determine differences in displacement of valve components over time between flow states.

Results: Each flow condition was found to exhibit a distinct displacement profile. *In vitro* monitoring showed a cessation of displacement oscillation when a proximal blockage was created, while creation of a distal blockage caused an increase in the amplitude of the oscillations from the normal flow condition.

Conclusions: Our results suggest that ultrasound imaging of the pressure relief valve can be used to easily differentiate between flow conditions that mimic physiologic shunt function and failure. Ultrasound monitoring may be a promising approach to assist in the clinical decisions of physicians in determining if shunt revision surgery is required. Continued *in situ* and *in vivo* testing is required to confirm our preliminary results in a physiological setting.

(1) Al-Tamimi, YZ et al. in *Neurosurgery* (2014).

5.8 **High-speed vector-flow imaging of *in-utero* mouse embryo at 18 MHz**, Jeffrey A. Ketterling, Orlando Aristizábal, Daniel H. Turnbull, Colin K.L. Phoon, Billy Y.S. Yiu and Alfred C. H. Yu, *Riverside Research, NYU School of Medicine, University of Hong Kong and University of Waterloo, jketterling@riversideresearch.org*

High-speed plane-wave imaging methods allow for image capture at frame rates equal to the round-trip acoustic propagation. Plane-wave imaging is well suited to cardiovascular (CV) imaging where fine-temporal resolution can reveal important information about cardiac mechanics and blood-flow patterns. Plane-wave imaging has been demonstrated in humans for CV studies but its use in mouse models has received minimal attention even though the mouse is the most common experimental organism to study gene function and human disease, including CV disease (CVD). While high-frequency ultrasound Doppler modes are used to study mouse models, traditional linear-array imaging modes are limited in terms of spatial and temporal resolution which limits the amount of functional information that can be mined from mouse models of CVD. Here, an 18-MHz linear-array probe was used to acquire plane-wave data at a frame rate of 10 kHz from an *in utero*, E16.5 mouse embryo. The probe had 128 elements, a 1.5-mm elevation aperture and an 8-mm elevation focus. The mother was placed supine on a heated mouse imaging platform and then a series of 2D+time data sequences were captured. The data were beamformed using standard delay-and-sum methods and then vector-flow estimates were obtained at each pixel location using a least-squares, multi-angle Doppler analysis approach. The 18-MHz data clearly revealed blood flow patterns in the heart, liver and umbilical cord showing that plane-wave methods can be applied to mouse models to study CVD.

5.9 **3D ultrasound imaging of pelvic floor-muscle injury,** Qi Wei, Qi Xing, Connor Stapp, Parag Chitnis, Siddhartha Sikdar, Ghazaleh Rostami and Seyed A. Shobeiri, *George Mason U., Inova Women's Hospital and Virginia Commonwealth University, qwei2@gmu.edu*

In this study, we investigated the feasibility of using 3D endovaginal and Doppler ultrasound imaging to quantitatively assess the levator ani muscle injury associated with labor and delivery. 3D ultrasound data was collected from women subject to various degrees of muscle injury. Our first hypothesis is that texture analysis in ultrasound images can be used to assess muscle injury. In order to accurately locate the muscle region of interest, volumetric datasets from the same patient pre-and-post biopsy were optimally co-registered using a novel 3D registration algorithm. The image-intensity histogram of the levator ani muscle was parameterized by fitting it to a Gamma distribution. Our results supported our hypothesis in that the quantitative parameters estimated from the muscle region were able to show changes in macrostructure of the levator ani muscle resulting from the injury. Our second hypothesis is that postpartum blood flow is significantly greater than that of nonpregnancy. Blood-flow volume in the levator ani muscle was calculated from 3D Doppler ultrasound data. Our preliminary analysis showed that blood volume decreased from 4.21±1.36 (postpartum) to 0.78±0.59 (six-month postpartum revisit). In summary, 3D ultrasound imaging of the pelvic floor has great potential in providing quantitative assessment of the pelvic floor structures and injury.

6. PHOTOACOUSTICS

6.1 **Theoretical application of short-lag spatial coherence to photoacoustic imaging**, Michelle Graham and Muyinatu Lediju Bell, *Johns Hopkins University*, *mgraha33@jhu. edu*

Short-Lag Spatial Coherence (SLSC) is a novel beamforming technique that was developed for ultrasound imaging and applied to photoacoustic imaging with notable improvements in contrast, *CNR*, and *SNR*, when compared to traditional delay-and-sum images. Although the beamformer was applied to experimental photoacoustic images, the theory behind its performance was never developed for this application. A thorough comprehension of the underlying theory is critical to determine the breadth of applications as well as limitations of spatial coherence as it applies to photoacoustic imaging. This work investigates the theoretical derivation of spatial coherence and SLSC beamforming as it applies to photoacoustic imaging. A spatial coherence equation was derived based on the fundamental van-Cittert-Zernike theorem (with a modified initial linear system for photoacoustic imaging) and explored numerically to generate spatial-coherence curves.

Spatial covariance curves and short-lag spatial coherence lateral slices were generated for a virtual blood-vessel-mimicking phantom. The photoacoustic covariance curves exhibit strong similarity to experimentally obtained data – both representing sinc functions with a strong DC peak.[(2)] Lateral slices demonstrate successful and accurate imaging of blood vessel location.

Lateral resolution and *CNR* were calculated as a function of lag and predicted ultrasound frequency. For resolution, a decaying exponential relationship was observed up to a specific lag, which was dependent on ultrasound frequency. For frequencies of range 3 MHz to 6 MHz, that lag was 45. In this frequency range, when lag > 45, average resolution remained constant at 0.75 mm. *CNR* remained constant across all lags (with a greater standard deviation at lags <15). *CNR* increased with ultrasound frequency from 20 dB (3 MHz) to 39 dB (6 MHz). These results provide a theoretical basis for choosing an optimal lag for photoacoustic-imaging situations based on probe frequency ranges.

(1) Mallart et al. *J Acoust Soc Amer* (1991). (2) Bell MA et al., *Ultrasonics Symp (IUS)* (2014)

6.2 **Evaluation of a convolutional neural network for identifying reflection artifacts in photoacoustic imaging**, Derek M. Allman, Austin Reiter, and Muyinatu A. Lediju Bell, *Department of Electrical and Computer Engineering, Johns Hopkins University, dallman1@ jhu.edu*

Photoacoustic imaging has promising potential to detect anatomical structures or metal implants inside the human body but its clinical utility is hampered by several noise artifacts, such as strong acoustic reflections from hyperechoic structures. These reflected signals can corrupt the final image, presenting the clinician with an inaccurate image of important features of interest. Currently, beamforming methods do not sufficiently model these reflection artifacts due to the complexity of the imaged environment. Given many variables that determine acoustic signal locations, this work evaluates the potential of a region-based convolutional neural network (RCNN) to both detect and classify signals as true signals or artifacts in pre-beamformed photoacoustic images.

We trained an RCNN using photoacoustic images which were simulated in the Matlab toolbox k-Wave. This database contained 17,340 images in total, 13,871 of which were used for training and 3,469 for testing. Each image contains two acoustic wavefronts, one originating from a true source and the other arising from an acoustic reflection. We chose to train and test using the Fast-RCNN algorithm VGG16 network architecture. We classified network detections as correct if the resulting score was greater than 0.01, which corresponded to a total of 1938 and 404 images when detecting true sources and artifacts, respectively. Among these correct detections, 97.2% of source detections fell within 0.5 mm of the simulated source location and 100% of artifact detections fell within 1 mm of the simulated artifact location. When considering depth error rather than total error, 93.6% of artifact detections were within 0.25 mm of the simulated artifact. Results demonstrate promise for using machine learning to identify and remove reflection artifacts.

6.3 **Real-time photoacoustic imaging of microvasculature beneath the skin,** Yoshifumi Saijo, Ryo Nagaoka, Israr Ul Haq, Syahril Siregar, Shin Yoshizawa and ShinIchiro Umemura, *Graduate School of Biomedical Engineering, Tohoku University, Sendai, Japan, saijo@tohoku.ac.jp*

Generation of a photoacoustic (PA) signal is highly dependent on the directions of light and sound to the surface of the target. Multi-angle illumination or multi-angle reception of PA signals is efficient for compensation. Besides the angle problem, the PA pressure is a few kPa and the signal should be averaged. In the present study, a real-time PA imaging system with a parabolic-array transducer for multi-angle reception is developed to visualize microvasculature beneath the skin.

The parabolic array transducer had a diameter of 42.4 mm, opening angle of 90°, 256 channels, 1-3-composite elements and center frequency of 10 MHz. A hole of 10.4 mm diameter was made in the center of the transducer for irradiation of the laser. The PA signal was received by a programmable ultrasound data acquisition system (Vantage, Verasonics, Redmond, WA, USA) with a sampling rate of 60 MHz. A tunable laser with OPO with wavelength available between 400 and 2100 nm, power of 10 mJ and repetition rate of 20 Hz was equipped for generation of the PA signals. A three-dimensional (3D) image was reconstructed by Delay-And-Sum (DAS) beamforming of the PA signals received by all the channels. The XY, YZ and XZ planes were displayed in real-time with a frame rate of 10 Hz. A holographic 3D image was displayed after several minutes.

The resolution of the system was found to be 80 μm by visualizing a mesh phantom immersed in water. In a mouse study, a vein was visualized at the wavelength of 490~600 nm and a lymphatic vessel infused with indocyanine green (ICG) was visualized at 670~770 nm. Finally, the microvasculature of a human palm was successfully visualized at the wavelength of 490~580 nm with a frame rate of 10 fps.

6.4 **Photoacoustic quantification of brain-tissue oxygenation for focal stroke piglet model *in vivo***, Jeeun Kang[1], Haichong K. Zhang[1], Ernest Graham[2], Raymond C. Kohler[2] and Emad M. Boctor[2], [1]*Johns Hopkins University and* [2]*Johns Hopkins University Medical Institute, kangj@jhmi.edu*

Perinatal arterial ischemic stroke can result in long-term deficits. In this study, we present photoacoustic (PA) quantification for brain-tissue oxygenation on an *in vivo* focal stroke model based on a newborn piglet. We injected incremental doses of 15-μm microspheres unilaterally to produce graded ischemia in an entire hemisphere and track the changes in HbO_2, deoxyHb, and tHb as a function of the percent change of laser Doppler flowmetry (LDF) bilaterally placed. Near-infrared PA spectrum at 21 wavelengths (700 to 900 nm in 10 nm increments) was acquired from the sagittal sinus by employing an optical parametric oscillator fed by Nd:YAG pulsed laser (Phocus, Opotek Inc., USA) and ultrasound system (SonixDAQ, Ultrasonix Corp, Canada). To calculate deoxy Hb, HbO2 and tHb, we derive a least-square-error fit between the PA spectrum and reference absorbance of Hb at varying O2 saturation. The *in vivo* experimental protocol is as follows; after obtaining baseline measurements of arterial blood gases, arterial blood pressure, *LDF* and PA spectrum, we injected 3 million spheres over a 5-min period through a catheter placed in an ascending pharyngeal artery. Additional doses of 3 million spheres were made, and measurements were repeated until *LDF* in the affected hemisphere is < 20% of baseline. The results indicate that the PA imaging can quantify the graded reductions in tHb and tissue HbO2 saturation, while the contralateral tHb and HbO2 saturation showed only minor changes, which are well correlated with *LDF* measurement.

6.5 **Listening to membrane potential change through photoacoustic voltage-sensitive dye**, Haichong K. Zhang, Jeeun Kang, Ping Yan, Diane S. Abou, Hanh N. D. Le, Daniel L. J. Thorek, Jin U. Kang, Albert Gjedde, Arman Rahmim, Dean F. Wong, Leslie M. Loew and Emad M. Boctor, *Johns Hopkins University, Baltimore, MD, eboctor1@jhmi.edu*

The quantification of neurotransmitter (NT) activity with high temporal resolution is essential to build a comprehensive map of brain function. Voltage-sensitive dyes (VSD) sense electrical events occurring on the cell membrane through fluorescence changes. However, conventional fluorescence-based imaging approaches have limited penetration depth, which is a big obstacle for deep-brain imaging. Photoacoustic (PA) imaging gives noninvasive absorbance dependent acoustic-signal mapping, and can visualize several centimeters in depth. Here, we proposed a photoacoustic-based VSD whose PA intensity changes corresponding to membrane potential. The principle of the dye is to manipulate fluorescence quantum yield to enhance PA intensity through fluorescence quenching while the total absorbance remains stable. In the polarized state, this VSD enhances PA intensity while decreasing fluorescence output in a lipid vesicle membrane model. With a 1-9 μM VSD concentration, we measured a PA signal increase and observed a corresponding signal reduction in fluorescence emission. In addition, we established a theoretical model that predicts the expected PA intensity increase of the dye, as a function of fluorescence and absorption properties. These results not only demonstrate the voltage sensing capability of the dye but also indicate the necessity of considering both fluorescence and absorption spectral sensitivities to optimize the characteristics of novel photoacoustic probes. Together, our results demonstrate photoacoustic sensing as a potential new modality for recording and imaging of electrophysiological events.

Tuesday afternoon

7. IMAGING 2

7.1 **Simulated and *ex vivo* large-aperture imaging through the human abdomen**, Nick Bottenus[1], Will Long[1], Matthew Morgan[1], Gianmarco Pinton[2] and Gregg Trahey,[1, 3] *[1]Department of Biomedical Engineering, Duke University, Durham, NC, [2]Department of Biomedical Engineering, University of North Carolina at Chapel Hill and North Carolina State University, Chapel Hill, NC and [3]Department of Radiology, Duke University, Durham, NC, nick.bottenus@duke.edu*

Objectives: Ultrasound image quality is fundamentally constrained by the limited size of the transmitting and receiving apertures. The extent of the spatial frequency content and therefore the lateral resolution are dependent on aperture size. A large array also has the opportunity to sample more of the spatially-variant clutter imposed by the body wall. This work demonstrates the improvement in image quality attainable with arrays larger than the current commercial devices for deep abdominal imaging.

Methods: Large apertures were synthesized experimentally using the swept synthetic-aperture technique with the Siemens 4Z1c volumetric transducer and SC2000 scanner. This setup was used to study point and lesion targets with a variety of transmit focal configurations with and without excised cadaveric abdominal wall tissue in the imaging path. Additionally, a 10 cm x 2 cm concave array was simulated using the Full-wave nonlinear simulation software to model imaging through an abdominal wall section. Image quality analysis was performed on both data sets to study the impact of clutter and imaging configuration.

Results: Resolution was observed to improve roughly linearly with F-number, even in the presence of the abdominal layer. The corresponding reduction in speckle texture size improved the detectability of small anechoic targets. Contrast was observed to improve by up to 8.06 dB and *CNR* by 17.4% compared to images formed with a 1.92 cm array. Strong agreement was observed in the relationship between aperture size and image quality for the simulated and *ex vivo* data sets.

Conclusions: Large-aperture imaging arrays, extending beyond those of the current standard shows promise for clinically-relevant imaging tasks. Improved resolution drives an increase in image quality, even in the presence of aberration and reverberation clutter.

7.2 **Beamforming improvement for non-contrast perfusion imaging with adaptive tissue-clutter demodulation**, Jaime E. Tierney and Brett C. Byram, *Department of Biomedical Engineering, Vanderbilt University, Nashville, TN, jaime.e.tierney@vanderbilt.edu*

Blood-perfusion imaging is clinically important for monitoring and evaluating treatment of vascular diseases and cancers. Such applications often require repeat scanning, making expensive and invasive imaging modalities and contrast agents impractical. In comparison, non-contrast ultrasound is affordable and completely noninvasive. However, tissue clutter caused by patient physiological and sonographer hand motion make slow blood flow or perfusion imaging with ultrasound difficult. In addition to the tissue being 10-100 dB brighter than blood, this motion causes spectral broadening of the tissue signal, causing it to overlap with the signal from lower-velocity blood flow.(1, 2) Therefore, with conventional imaging and tissue clutter filtering, ultrasound is limited to blood velocities greater than 5-10 mm/s for clinical-imaging frequencies.(2)

To address this limitation, we previously introduced an adaptive frequency and amplitude demodulation scheme to reduce the bandwidth of the tissue clutter signal.(3) We developed and validated the technique on phantoms and *in vivo* human leg muscles using unfocused plane-wave power-Doppler imaging to overcome frame rate, ensemble length and directional limitations associated with conventional scanning. We showed that velocities below 0.52 mm/s could potentially be detected with the proposed technique and that the previously-determined lower limit on velocity estimation with ultrasound is conservative.(2) In a sonographer hand-motion phantom experiment, we also tested the algorithm using synthetically-focused angled plane wave imaging and showed that the bandwidth could be suppressed more and potentially allow for even lower velocities to be detected with this alternative beamforming.

To further explore the benefits of alternative beamforming with adaptive clutter demodulation, we performed a simulation study with controlled tissue clutter, blood and thermal noise. We simulated a single 0.5 mm diameter vessel with 2 mm/s parabolic flow of blood scatterers within a 1.5 by 3 cm area of tissue scatterers. To simulate realistic tissue clutter, displacements estimated from sonographer hand-motion phantom data were used to displace the tissue and blood scatterers. Blood-to-background *SNR* was computed on power Doppler data before and after adaptive clutter demodulation using three different beamforming methods: single plane wave (SPW), plane wave synthetic focusing (PWSF) and coherent flow power Doppler (CFPD). Without adaptive demodulation, the SPW, PWSF, and CFPD cases had *SNR*s of 0.06dB, 1.48dB and 0.57dB. Adaptive tissue clutter demodulation resulted in *SNR*s of 2.57dB, 5.37dB and 2.22dB for the SPW, PWSF and CFPD cases, respectively.

(1) Jensen JA. *Estimation of Blood Velocities Using Ultrasound: A Signal Processing Approach.* Cambridge (1996). (2) Heimdal A et al. *IEEE Trans Ultrason Ferroelectr Freq Contr 44*, 873-881 (1997). (3) TierneyJE et al, in *Proc IEEE Ultrason Symp* (2016).

7.3 **Ultrafast imaging of ocular blood-flow**, Ronald H. Silverman[1, 2], Raksha Urs[1], Jeffrey A. Ketterling[2], Alfred C.H. Yu[3] and Billy Y.S. Yiu[3, 4], *[1]Department of Ophthalmology, Columbia University Medical Center, New York, NY, [2]Riverside Research, New York, NY, [3]University of*

Waterloo, Waterloo, ON and [4]University of Hong Kong, Hong Kong. rs3072@cumc.columbia.edu

Background: Clinical ophthalmic ultrasound is almost exclusively performed with mechanically scanned single-element transducers. Such systems provide B-scans but no blood-flow information. We developed linear-array based ultrafast plane-wave systems for ophthalmic imaging and blood-flow measurement and applied this system to human subjects.

Methods: We used a Verasonics Vantage-128 imaging system with a 128-element 18 MHz linear array and developed MatLab code to support plane-wave imaging. Flash Doppler (from one Doppler angle) was used to visualize flow in real time and post-processing of multi-angle coherently compounded data used to produce high-resolution power Doppler images. For arterial high-speed flow, data were acquired from two angles (±10º), providing 6000 compounded images per second and depiction of velocities of up to 13 cm/s without aliasing. For choroidal slow flow, data from 4 angles were acquired at a 1 kHz compounded acquisition rate. Data sets were between 1.5 and 3 seconds in duration. Spectrograms were computed at each pixel position and minimum diastolic velocity (*Vmin*), maximum systolic velocity (*Vmax*), resistive index (*RI*) and spectral broadening (*SB*) determined. We measured flow in the central retinal artery (CRA), short posterior ciliary artery (SPCA) and choroid of normal subjects. All imaging modes were compliant with FDA intensity standards based on calibrated hydrophone measurements.

Results: Average values of flow in orbital arteries and the choroid were as follows: In the CRA, *Vmin* and *Vmax* were 16.5 and 58.4 mm/s, *RI* was 0.85 and *SB* 141%. In the SPCA, *Vmin* and *Vmax* were 6.5 and 85.5 mm/s, *RI* was 0.81 and *SB* was 138%. In the choroid, *Vmin* and *Vmax* were 7.9 and 33.7 mm/s, *RI* was 0.63 and *SB* was 318%.

Conclusions: Ultrafast plane wave imaging provides a means for imaging of ocular blood flow at high resolution within FDA ophthalmic regulatory limits. Spectral broadening observed in the choroid is consistent with the low directionality of flow in the choroidal capillary bed compared to the CRA and SPCA. The capacity of the plane-wave modality to characterize flow at every image location simultaneously offers a unique parameter that could be used to examine phase relationships between arterial input and choroidal filling. Supported in part by NIH grant EY025215 and an unrestricted grant to the Department of Ophthalmology of Columbia University from Research to Prevent Blindness.

7.4 **Nonlinear ultrasound propagation in homogeneous and heterogeneous media: factors affecting effective *MI***, Bofeng Zhang[1], Gianmarco F. Pinton[2,3], Yufeng Deng[1] and Kathryn R. Nightingale[1], *[1]Duke University, [2]University of North Carolina at Chapel Hill and [3]North Carolina State University, bofeng.zhang@duke.edu*

Background: The Mechanical Index (*MI*) is used by the US FDA in regulatory decisions regarding the acoustic output of diagnostic ultrasound. Its formula is based on predictions of acoustic cavitation under specific conditions. It is calculated using peak rarefactional pressure measurements made in water and linearly derated to account for tissue attenuation *in vivo*. However, acoustic propagation through water is a highly nonlinear process that differs from wave propagation in tissue due to inherent differences in attenuation and nonlinearity. This work investigates how varying attenuation, nonlinearity, focal configuration and propagation path heterogeneity affect *in situ* peak rarefactional pressures (PRP) in the presence of nonlinear ultrasound propagation.

Method: A full-wave ultrasound propagation simulation package was used to simulate nonlinear acoustic propagation.[(1)] Source-pressure measurements were obtained with hydrophone measurements for a 2-cycle Gaussian-weighted sinusoidal transmit pulse at 2.2 MHz from a 4C1 curvilinear transducer (typical clinical abdominal probe) focused at 5 cm, using a transmit voltage that corresponded to a focal *MI* measurement of 1.9. Parametric studies were performed over the following ranges that are typical for tissue: attenuation: 0.3-1.1 dB/cm/MHz; nonlinearity parameter (*B/A*): 7-10; and focal configuration was varied from F/1-

F/6 by changing the source aperture while modulating transmit voltage to maintain a focal *MI* = 1.9.

The impact of a range of heterogeneous body walls was also evaluated. For each simulation, the *in situ PRP* amplitude and location was evaluated and compared to the water-based *MI* measurement (1.9).

Results: As expected, increasing attenuation in homogeneous material decreased *PRP* but did not change the *PRP* location significantly (<1 mm). Changing *B/A* in homogenous material varied peak amplitudes <5%, and did not change *PRP* location significantly (<1 mm). Changing F/number was associated with considerable shifts in *PRP* location, from the focal point (F/2) to 2 cm proximal to the focal point (F/6) in homogeneous material. Propagation through heterogeneous body walls was associated with decreases in *PRP* compared to the homogeneous case with a constant α=0.5dB/cm/MHz and to that predicted by the water-based *MI* calculation. The body walls also introduced spatial variability in *PRP* location, depending upon the focal configuration. For more tightly-focused beams (F/# <=3), the PRP was located near the geometric focus as with the homogenous materials. However, for smaller apertures (F/# >=3), the location of the PRP was quite variable, often occurring within the body wall as opposed to near the geometric focus. Supported by NIH Grant R01EB022106.

(1) Pinton et al. *IEEE UFFC 56,* 474–488 (2009).

7.5 **Quantitative 3D assessment of flow in printed hydrogel vascular phantom,** Samantha J. Paulsen, James Long, Bagrat Grigoryan, Wolfgang Stefan, Jordan S. Miller and Richard R. Bouchard, *University of Texas MD Anderson Cancer Center and Rice University, rrbouchard@md anderson.org*

Background and Objective: While tissue-mimicking phantoms have historically proven to be useful in the validation of ultrasonic equipment and image processing techniques, they remain limited in terms of geometric complexity. Most notably, they are unable to reproduce biologically realistic flow due to limitations in vascular network complexity and scale. To address this need, a novel technique has recently been employed to fabricate 3D-printed photocurable polyethylene glycol (PEG) hydrogel constructs that can be readily imaged with ultrasound and allow for the construction of complex, small-scale (e.g., 100s of µm in diameter) vascular networks. In this study, we use high-frequency Doppler ultrasound to obtain a high-resolution, volumetric dataset of the 3D velocity vector field through hydrogel phantoms with varied vascular network geometries.

Methods: The geometry of each hydrogel phantom was first encoded in a stereolithographic computer-aided-design program and then printed in layers using an iterative process of photocuring and hydrogel excursion. A water-based blood substitute containing 25% glycerol and 3- µm polystyrene beads was infused into the channel at a constant velocity, during which concurrent ultrasonic B-mode and color Doppler images were taken with the Vevo 2100-LAZR photoacoustic-ultrasonic imaging platform at 24-MHz and with motor-controlled translation in the elevation dimension. Six partially-correlated color Doppler acquisitions were obtained at transducer orientations of 0°, 45° and 90° and transmit steering angles of ±15°. Independent Doppler acquisitions were then retrospectively co-registered based on segmented B-mode data of the lumen. Matched COMSOL-based numerical modeling and optical flow tracking were implemented for comparison and validation, respectively.

Results: Throughout each channel a radially symmetric, parabolic flow profile was observed. Maximum velocities around 12 mm/s were found at the radial center of the channel. Small inconsistencies in the flow profile were found near regions of the channel that contained irregularities – as confirmed from B-mode – from the intended print geometry. Doppler flow velocities were found to correlate well with optical-flow measurement for planar geometries.

Conclusion: In this study, 3D velocity vector data were obtained in 3D-printed hydrogel vascular phantoms. As phantom technologies continue to progress and become more complex and physiologically relevant, 3D Doppler-based flow assessment could play a critical role in empirically characterizing complex flow to ensure phantoms function as intended and/or to ensure numerical modeling assumptions match their phantom-based experimental analogs.

8. TISSUE PARAMETERS

8.1 **Homodyned K-distribution parametric maps with application to assessment of vulnerable atherosclerotic plaques of internal carotid arteries**, François Destrempes[1], Marie-Hélène Roy-Cardinal[1], Gilles Soulez[1, 2], Guy Cloutier,[1, 3] [1]*Laboratory of Biorheology and Medical Ultrasonics, University of Montreal Hospital Research Center (CRCHUM),* [2]*Department of Radiology, University of Montreal Hospital,* [3]*Department of Radiology, Radio-Oncology, Nuclear Medicine and Institute of Biomedical Engineering, University of Montreal, Montréal, Québec, Canada, guy.cloutier@umontreal.ca*

Background and Objectives: The goal of this work was to assess vulnerability to rupture of atherosclerotic internal carotid plaques by performing tissue characterization. It was hypothesized that the echo envelope of radiofrequency signals of carotid arteries at 7.2 MHz is distributed locally according to homodyned K-distributions (HKD). Based on the three statistical parameters of this distribution, various parametric maps could be constructed, from which quantities were extracted by considering mean or median values and inter-quartile ranges. The objective was to test if such HKD features, together with elastograms, as well as echogenicity features, could distinguish between non-vulnerable carotid artery plaques and neovascularized or vulnerable ones, as assessed with magnetic resonance imaging.

Methods: The plaque in a sequence of images was segmented with a semi-automatic method. The pixels within the segmented plaque were then classified into at most three labels based on a statistical model. At each pixel within the plaque, the three local HKD parameters were estimated in a sliding window that was clipped with the set of pixels with same label. Then, these local parameters yielded 12 HKD features extracted from the corresponding parametric maps. In addition, 4 features based on the echogenicity were computed directly from the compressed B-mode images. Lastly, 10 features were extracted from the elastograms. A feature selection based on the mean decreased accuracy, which was estimated from random forests, was performed to obtain the best 3 parameters overall, as well as the best feature in each category (HKD, elastography and echogenicity). The resulting combinations of features were tested using random forests comprising 1000 decision trees, trained on plaques of 31 patients (12 non-vulnerable plaques, 19 neovascularized or vulnerable ones). To address over-fitting, the number of maximal terminal nodes of the trees was increased from 2 to 20 by steps of 2. Area under the Receiver Operating Characteristic (ROC) curve (AUC) was estimated with the 0.632+ bootstrap method. Confidence interval for the AUC was estimated with the Jackknife method.

Results: Feature selection yielded the following 3 overall best features, which turned out to be based on elastograms: 1) cumulated axial translation; 2) cumulated axial strain to cumulated axial translation ratio; and 3) cumulated lateral translation. The best feature in each of the two other categories were: 4) mean local diffuse-to-total signal power ratio (HKD feature), and 5) the coefficient of variation of the normalized echogenicity. Classification based on the best 3 elastography features yielded an AUC of 0.859 (95% CI [0.844 0.886]) with a maximal number of 18 terminal nodes. On the other hand, combining feature 3 with features 4 and 5 yielded an AUC of 0.907 (95% CI [0.885 0.925]) with a maximal number of 6 terminal nodes. A statistically significant difference was observed between the AUCs of classification based on these two combinations of features ($p = 4.7e\text{-}10$, Wilcoxon signed rank test).

Conclusions: These results suggest that combining features extracted from the same radio-frequency data but based on distinct paradigms may significantly increase the accuracy of a classification scheme, compared to the classification based on features of a same nature (here, based on biomechanical properties), even if the latter features have highest rank based on the mean decreased accuracy criterion.

8.2 **Delineation of lumen-plaque boundary in human carotid artery with ARFI Variance of Acceleration (*VoA*)**, Gabriela Torres, Tomasz J. Czernuszewicz, Jonathon W. Homeister, Mark A. Farber and 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: Cardiovascular disease is characterized by the development of atheromatous plaque in the walls of arteries that feed vital organs, i.e., heart or brain. Recent histological studies have shown that plaque features, including lipid rich necrotic core, plaque hemorrhage, neovascularization and fibrous cap thickness are relevant biomarkers for assessing plaque-rupture risk. A previous study demonstrated the sensitivity and specificity of Acoustic Radiation Force Impulse (ARFI) imaging for delineating plaque features by interrogating the tissue's peak displacement (*PD*) in response to a pushing beam.[(1)] ARFI-derived *PD* showed a positive bias in fibrous cap thickness measurement, owing in part to ambiguous delineation of the lumen-plaque boundary. In this study, the analysis of the variance of acceleration (*VoA*) of ARFI-induced displacements is used to improve delineation of the lumen-plaque boundary. Here, *VoA*-derived boundaries are compared to those derived from *PD*, with reference to matched histology.

Methods: This study analyzed ten plaques that were acquired *in vivo* in a previous clinical study involving patients undergoing carotid endarterectomy (CEA) (1). The raw RF data from the carotid plaque were acquired *in vivo* prior to CEA using a Siemens Acuson Antares imaging system and a VF7-3 linear array. For ARFI imaging, excitation pulses had a frequency of 4.21 MHz and a 300-cycle length, tracking pulses had a frequency of 6.15 MHz and a two-cycle length. CEA specimens were harvested for histological validation of ARFI outcomes. From the displacement profiles, *VoA* was calculated as the variance of the second time derivative of displacement 3-5 ms after excitation per pixel. For both *VoA* and *PD* images, values were normalized to the median value within the plaque ± two mean absolute deviations. Using the normalized images, the lumen-plaque boundary was identified and CNR and contrast metrics were calculated for regions 1 mm above and below the boundary.

Results: *PD* contrast was higher by an average of 61.54% for *VoA*-derived (0.84±0.65) versus *PD*-derived boundaries (0.52±0.39), and *VoA* contrast was on average 165.71% higher for *VoA*-derived (0.93±0.26) versus *PD*-derived boundaries (0.35±0.19). Similarly, *PD CNR* improved by an average of 29.17% for *VoA*-derived (0.62±0.39) versus *PD*-derived boundaries (0.48±0.31), and *VoA* contrast was on average 62.50% higher for *VoA*-derived (1.17±0.22) versus *PD*-derived boundaries (0.72±0.28). *VoA* also yielded an average 74% decrease in measurement variability in comparison to *PD*, indicating that *VoA* more consistently contrasts plaque from lumen in *in vivo* imaging.

Conclusions: These results suggest that *VoA* has potential for improving delineation of the lumen-plaque boundary, which is important for accurately measuring fibrous cap thickness and predicting rupture potential. For both *PD* and *VoA* images, *CNR* and contrast metrics increased with *VoA*-derived boundaries. Overall, *VoA* metrics were higher by an average of 151% in comparison to *PD*. *VoA* accuracy for fibrous cap thickness measurement will be assessed in a future blinded-reader study. Supported in part by NIH grants R01HL092944, K02HL105659, and T32HL069768.

(1) Czernuszewicz et al, *Ultrasound Med Biol 41*, 685–697 (2015).

8.3 **Effect of mechanical index on cardiac image quality**, Katelyn Flint[1], David Bradway[1], Yufeng Deng[1] and Gregg Trahey[1, 2], *[1]Departments of [1]Biomedical Engineering and [2]Radiology, Duke University, Durham, NC, katelyn.flint@duke.edu*

Cardiac B-Mode images are routinely used to assess cardiac function. The current standard of care is harmonic imaging, which provides improved visualization of cardiac structures. However, a major drawback for harmonic imaging compared to fundamental is the decreased signal magnitude, which limits achievable penetration depths in some patients. The transmitted pressure is subject to the FDA limit on Mechanical Index (*MI*). *MI* is defined as the attenuated measurement of the peak negative pressure divided by the square root of the acoustic-working frequency. A single attenuation value with linear frequency and depth dependence is used in *MI* calculations as well as a single-frequency power dependence.

An *MI* limit was developed to safeguard against acoustic cavitation. However, the way *MI* is calculated overestimates many *in situ* pressures. The current FDA limit of 1.9 is based on historical output levels and the assumption of pre-existing gas bodies. A recent report from the American Institute of Ultrasound in Medicine (AIUM) has recommended an estimated *in situ* value of up to 4.0 in non-fetal tissues without gas bodies if the increase improves image quality.[(1)]

An initial study of *in vivo* high mechanical index hepatic imaging has shown promising results with improved harmonic signal content, penetration depth and image quality.[(2)] The effect of altering the mechanical index has not previously been studied in cardiac B-Mode imaging applications. Preliminary *in vivo* cardiac data at *MI*s of 1.0 and 1.9 (1 volunteer, 13 image pairs) have shown an average increase in contrast of 16%. These results suggest that image quality improvements achievable above current FDA *MI*-limits should be studied for cases where insufficient image quality necessitates the use of higher transmit pressures. Supported by NIH grants R37-HL096023 and R01-EB022106 and the National Science Foundation Graduate Research Fellowship under Grant No. DGF1106401. In-kind and technical support provided by the Ultrasound Division at Siemens Medical Solutions USA, Inc.

(1) Nightingale, et al. DOI:10.7863/ultra.34.7.15.13.0001. (2) Deng, et al. DOI:10.1109/ULTSYM.2015.0299

8.4 **Acoustic anisotropy in rodent cardiac tissue** M.L. Milne[1] and C.S. Chung,[2] [1]*Department of Physics, St. Mary's College of Maryland, St. Mary's City, MD and* [2]*Department of Physiology, Wayne State University, Detroit, MI, mlmilne@smcm.edu*

Background: Previous studies have demonstrated the acoustic effects of anisotropy in samples of myocardium tissue taken from large mammals and their link to fiber orientation. The goal of this study was to extend that work by investigating the anisotropic acoustic properties of rat and mouse hearts and determine fiber orientation from echocardiographic data.

Methods: Anisotropic properties and the relationship between fiber orientation and apparent ultrasonic backscatter were obtained by imaging 2-mm diameter cores taken from the left-ventricular wall of rat hearts using a 21 MHz probe and in mouse hearts using a 40 MHz probe (VisualSonics Vevo2100). The fiber orientation and backscatter relationship was confirmed by subsequent comparison of ultrasonic and histological images.

Results: The fiber direction analysis results were consistent with previous findings for fiber direction reported in the literature and with results found from histological analysis.

Conclusion: Anisotropic acoustic effects are measureable in rodent hearts and can be related to myocardial fiber orientation. Future work will include developing *in-vivo* cardiac fiber direction map for live rodents. Supported in part by a grant from the American Heart Association (14SDG20100063 to CSC).

8.5 **Quantitative analysis of angiogenic microvasculature in tumor-bearing rats using multiple scattering,** Aditya Joshi[1], Sarah Shelton[2], Virginie Papadopoulou[2], Brooks Lindsey[2], Paul Dayton[2] and Marie Muller,[1] [1]*Department of Mechanical and Aerospace Engineering, NC State University, Raleigh, NC 27695 and* [2]*UNC - NCSU Joint Department of Biomedical Engineering, UNC Chapel Hill, Chapel Hill, NC 27599, aajoshi4@ncsu.edu*

We propose a method to quantify the density, anisotropy and tortuosity of vascular networks from contrast-enhanced ultrasound multiple scattering. These parameters are estimated by evaluating the diffusion constant *D* and transport mean free path *L** from the time evolution of the incoherent intensity in a rat model of cancer. In this process, we record the backscattered echoes using an 8 MHz linear array transducer from subcutaneous fibrosarcoma tumors and control tissue. Then we separate the coherent and incoherent intensities. *D* and *L**, can be estimated by evaluating the spatial spread of the incoherent intensity over time. For this study, tumors were implanted in the right flank of 16 female rats, and the contralateral side served as control. The present results were compared with quantitative measurements using acoustic angiography technique on the same tumors. The anisotropy was quantified by the ratio of *L** measured along two perpendicular orientations. To measure the tortuosity a map of *L** was created by translating the transducer along several planes of the tumor. The mean *L** values in control (*L*=106.54 µm ± 5.08 µm) and tumor tissue (*L*=43.58 µm ± 3.97 µm, *n*=16) were significantly different (unpaired *t*-test, $p = 1.1165 \times 10^{-30}$). The mean distance between vessels was estimated from acoustic angiography images using Monte-Carlo simulations, and was in agreement with the calculated values of L*. The tortuosity estimated using L* was also in good agreement with the tortuosity measured on acoustic angiography images.

Wednesday morning

9. ELASTICITY

9.1 **Constructive shear-wave interference velocimetry**, Peter Hollender, Anna Knight, Mark Palmeri and Gregg Trahey *Duke University, Department of Biomedical Engineering, Durham, NC, peter.hollender@duke.edu*

Shear-wave elasticity estimation techniques use the travel time of induced transverse waves to characterize a material's mechanical properties. Commonly, acoustic radiation force is used to deliver momentum to the tissue at a point, generating a shear wave that propagates away from the source location. Because of geometric spreading, the amplitude of the wave decays with distance from the source. The amplitude of the detected shear-wave signal depends both on location of the track beam relative to the source, the intensity of the ultrasound beam used to induce the displacement and the elasticity of the tissue itself. To improve the shear-wave signal amplitude, a greater intensity acoustic radiation force beam may be used, although the spatial peak intensity readily runs up against FDA limits for safety. We present here a method for increasing shear wave displacement signals and estimating material elasticity via the use of a geometrically-compound-forcing function. The method, Constructive Shear-Wave Interference Velocimetry (CSWIV), uses an annular array to focus the acoustic radiation force onto a hollow cylinder, rather than a point. The resulting shear waves constructively interfere at the center of the cylinder, where we place the tracking beam to detect tissue motion. This method is presented in theory, and with simulation and preliminary experimental results demonstrating how, through the use of constructive interference, substantial improvements in displacement signal-to-noise ratio can be achieved without increasing the spatial peak-intensity metrics. CSWIV is compared with other candidate geometries, and considerations for system design and *in vivo* applications are discussed. Funded by NIH 5R37HL096023, NIHR01EB012484 and the Duke-Coulter Translational Partnership.

9.2 **Characterization of viscoelastic material using fractional-derivative measurements of group shear- wave speeds**, Courtney A. Trutna, Ned C. Rouze, Yufeng Deng, Mark L. Palmeri and Kathryn R. Nightingale, *Duke University, courtney.trutna@duke.edu*

Introduction: Shear-wave ultrasound elastography is used to noninvasively characterize mechanical properties of tissue. Most current commercial ultrasound scanners report the material stiffness using a single group shear-wave speed, based on the assumption of an elastic material model. However, tissue is viscoelastic and a robust characterization of this higher-order behavior could improve characterization of tissue and potentially improve disease diagnosis. Most current viscoelastic characterizations involve computing either one- or two-dimensional Fourier transforms of the shear-wave data, which typically has poor *SNR*, given the transient, broad-band nature of shear waves generated *in vivo* with acoustic radiation force.

Theory: This study characterized materials using group shear-wave speeds at a series of derivative orders ν calculated from the particle-displacement signal. Building on a previous study using particle-displacement and velocity signals, with $\nu=0$ and $\nu=1$ respectively, this study extends this analysis to a continuous range of derivative orders in the $0 \leq \nu \leq 2$ range. Derivative order impacts the relationship between frequency content and the group speed measurement and thus, this series of group speeds represents a gradual variation of sensitivity to the frequency content of the shear wave. To relate the tissue viscoelastic parameters to fractional-derivative data, an analytic model for shear-wave propagation was used to calculate the expected shear-wave group speeds for a given acoustic radiation force impulse configuration and set of material properties. These analytically predicted speeds were used in a nonlinear least-squares fitting algorithm to estimate the viscoelastic material model parameters corresponding to the experimental data.

Methods: Shear-wave data were obtained using a Verasonics imaging platform and a C52 transducer. Material characterization was performed on three homogeneous viscoelastic phantoms, and corresponding parameters for both Voigt (2-parameter) and Standard Linear (3-parameter) material models were obtained. Fits were performed on the average speeds at each derivative order across 16 acquisitions obtained from different spatial locations in the phantoms. Plots of reconstructed shear-wave speed versus derivative order indicated that the Standard Linear model provided better agreement with the measurements. These observations were supplemented by a reduced chi squared quality-of-fit metric, with the three phantoms resulting in values of 0.85, 0.79 and 0.69 for the Voigt model, and 0.18, 0.14 and 0.08 for the Standard Linear model, where a lower value indicates a better fit.

Conclusion: This fractional derivative analysis offers advantages over other techniques for viscoelastic material characterization due to the relative robustness of the group shear-wave speed measurements. Additionally, expanding the number of derivative orders beyond particle displacement and velocity extends the bandwidth of the analysis and facilitates evaluation of higher order material models.

9.3 **Characterization of human-liver dispersion using group shear-wave speeds,** D. Cody Morris[1], Ned C. Rouze[1], Manish Dhyani[2], Anthony E. Samir[2], Mark L. Palmeri[1] and Kathryn R. Nightingale[1], [1]*Duke University and* [2]*Massachussets General Hospital, cody.morris@duke.edu*

Introduction: Viscoelastic materials are dispersive. This dispersion manifests as a frequency-dependent shear=wave phase velocity. One robust method to assess dispersion *in vivo* is by measuring displacement (V_{disp}) and velocity (V_{vel}) group shear-wave speeds. These speeds represent different weightings of the shear-wave frequency components. In dispersive media, the different weightings result in a change in measured speed, where $V_{vel} > V_{disp}$. Assuming a Voigt material model, these group speeds can be used to determine the stiffness (μ_0) and viscosity (η) of the medium.

Methods: In this study, we applied a multiple group speed algorithm to the raw data from two *in vivo* liver data sets. The first set of data was collected at Duke University with a Siemens

Antares using a custom sequence and the second set was provided by Massachusetts General Hospital (MGH) and was collected on a Siemens S3000 using commercial sequences. Both data sets were acquired using a Siemens 4C1 transducer and included patients with hepatic fibrosis stages ranging from F0-F4. We measured displacement and velocity signals in all datasets and used a RANSAC algorithm to determine the corresponding group shear-wave speeds. Under the Voigt model assumption, we determined the relationship between group shear-wave speeds, stiffness and viscosity in patients for whom the custom Antares sequence was utilized based upon the known excitation focal geometry.

Results: The mean difference in group speeds ($\Delta V = V_{vel} - V_{disp}$) for the Antares data is 0.36 ± 0.15 m/s. ΔV for the MGH data is 0.73 ± 0.23 m/s. In both data sets, the positive ΔV represents the presence of dispersion. For the custom Antares data set, fibrosis stages 0-2 have μ_0 ranging from 1 to 6 kPa and η ranging from 0.2 to 4 Pa s. Fibrosis stages 3-4 have μ_0 ranging from 5 to 15 kPa and η ranging from 1.5 to 4 Pa s. Supported under a subcontract from the Quantitative Imaging Biomarkers Alliance (QIBA) with their contract HHSN268201300071C from NIH NIBIB and under NIH grant EB002132.

9.4 **Imaging degree of anisotropy using Acoustic Radiation Force Impulse (ARFI) imaging,** Christopher J. Moore[1], MD Murad Hossain[2] and Caterina M. Gallippi,[1, 2] [1]*Department of Electrical and Computer Engineering, North Carolina State University, Raleigh, NC and* [2]*Department of Biomedical Engineering University of North Carolina, Chapel Hill, NC, cmgallip@email.unc.edu*

Background: Acoustic Radiation Force (ARF)-based ultrasound imaging techniques are used to characterize the mechanical properties of tissue. Some tissues are anisotropic, meaning their mechanical properties exhibit directional dependence. Noninvasively assessing directionally dependent mechanical properties may be diagnostically relevant because some pathologies alter tissue structure in a manner that affects degree of anisotropy. We have previously shown that degree of mechanical anisotropy may be assessed as a point measurement using ARF-induced peak displacements in finite element simulations. However, making these measurements with a linear-array transducer requires manual rotation of the imaging probe, potentially leading to misalignment error. The purpose of this work is to investigate the feasibility of creating 2D images of anisotropy using ARF-induced displacement and a simulated matrix array. *We hypothesize that 2D images of anisotropic features can be created from ARF- induced peak displacements using a 2D matrix array transducer.*

Methods: Finite element (FE) simulations of a 1.25 mm radius, cylindrical, transversely isotropic (TI) elastic inclusion embedded in an isotropic elastic background material were performed using LS-DYNA. A simulated 2D 38 mm square matrix array transducer with 192^2 elements was used to model the ARF excitation geometry in Field II. Each phantom was excited (for 70 µs @ 4.21 MHz) by an ARF excitation with an asymmetrical point spread function (*PSF*) geometry. The long axis of the ARF *PSF* was turned electronically to align along or across the TI material's axis of symmetry. The degree of anisotropy was then computed as the ratio of the ARF-induced peak displacements generated with the *PSF* long axis aligned along versus across the inclusion's axis of symmetry. Ratios were computed from both the raw FE displacements and simulated ultrasonic motion tracking from Field II, which included jitter and system noise. Two-dimensional images of the resulting ratios were formed by electronically sweeping the aperture laterally in 0.35 mm increments across the field of view. The imaging simulations were repeated for six inclusions with transverse shear modulus of 5 kPa and longitudinal shear moduli of 5 to 30 kPa in steps of 5 kPa. Contrast ratio and contrast-to-noise ratio (*CNR*) were computed for both the raw finite element and ultrasonically-tracked anisotropy and peak-displacement images for each of the materials. Contrast and *CNR* were calculated using a circular region of interest (*ROI*) 92% of the radius of the true inclusion for the inside value and a ring that ranged from 144% to 166% of the true lesion radius for the background *ROI*. Contrast ratio values are reported as mean ± standard deviation.

Results: The ARFI-derived ratio of peak displacements for each of the six inclusions increased as a function of increasing disparity between the longitudinal and transverse shear moduli in the TI inclusion for images generated from the raw FE and the ultrasonically-tracked peak displacements. The contrast ratios ranged from 0.99 ± 0.00 to 1.10 ± 0.01 for the raw FE displacements and from 1.01± 0.01 to 1.11 ± 0.01 for the ultrasonically-tracked anisotropy image, in the least and most anisotropic lesions, respectively. The peak-displacement anisotropy ratios were directly proportional to the programmed degree of anisotropy in all six materials. The *CNR* of the raw FE anisotropy images ranged from 0.86 to 4.18 in the least and most anisotropic materials, respectively. For the ultrasonically-tracked anisotropy images in the same materials, the *CNR* increased from -0.13 to 1.21. Although the *CNR* of anisotropy images is lower in the case of ultrasonic tracking, this *CNR* was higher than that of the ARFI peak displacement images in all cases, regardless of *PSF* orientation. The *CNR* of the peak displacement images with the long axis of the asymmetric force oriented both along and across the TI axis of symmetry was 0.42 and 0.01, respectively, for the FE peak displacement images in the most anisotropic material. After ultrasonic tracking, these values remained relatively unchanged at 0.46 and 0.01, respectively.

Conclusions: The results of this study suggest that a matrix-array transducer used to deliver an asymmetric ARF excitation in two orthogonal orientations may allow for rapid assessment of anisotropy in a 2D imaging plane within tissue. The data presented herein also suggest that the ARF-derived degree of anisotropy is directly proportional to the modeled ratio of shear moduli. Contrast ratio and *CNR* measurements on the images suggest that for the materials used in this work, anisotropy images achieved higher contrast of TI elastic inclusions than individual ARFI peak displacement images. This suggests that ARFI anisotropy imaging provides relevant information about tissue composition and structure, which may be diagnostically relevant for assessing anisotropic tissue such as kidney or muscle.

9.5 **Improvement in beat-to-beat repeatability of myocardial strain estimation: preliminary *in vivo* results**, Harrison Ferlauto[1], Vaibhav Kakkad[1], Brecht Heyde[2], Joseph Kisslo[3] and Gregg E. Trahey,[1] [1]*Department of Biomedical Engineering, Duke University, Durham NC,* [2]*Cardiovascular Imaging and Dynamics, KU Leuven, Leuven, Belgium and* [3]*Cardiology, Duke University, Durham NC, harrison.ferlauto@duke.edu*

Strain echocardiography is an ultrasonic imaging technique used to assess cardiac function by tracking deformation of the myocardium. Compared to traditional measures of left ventricular (LV) ejection fraction, global myocardial strain has been shown to be an earlier and more sensitive measure of overall LV function. Similarly, regional myocardial strain has been shown to be useful for identifying ischemic or infarcted regions of the myocardium. However, accurately quantifying myocardial strain over several cardiac cycles has proven challenging due to complications with drift and heart rate variability.

We present a drift compensation scheme that improves the reliability and repeatability of myocardial strain estimates over the course of multiple cardiac cycles. Our method involves using an elastic image-registration algorithm to track myocardial displacement forwards and backwards from several end diastole reference frames and using their linearly-weighted sums to compute robust displacement fields through individual cardiac cycles. Additionally, beat-to-beat variability in myocardial position is accounted for by tracking displacements between successive end-diastole reference frames using the same elastic image registration technique. This results in an automatic repositioning of the region-of-interest for strain estimation.

The performance of the drift compensation algorithm was tested on *in vivo* transthoracic ultrasound images of the heart in the parasternal long axis (PLAX) and short axis (PSAX) views. Images were acquired over a 5s interval so as to include 5-6 complete cardiac cycles. Drift in the

ROI at beat 5 and correlation of end-diastolic radial strain distributions between beat 1 and beat 5 were the metrics used to track performance. Between the uncompensated vs. compensated cases; drift was found to be reduced from 8.58 ± 4.96 mm to 1.73 ± 1.23 mm in PLAX and 9.11 ± 3.13 mm to 1.16 ± 0.48 mm in PSAX. Correlation of end-diastolic radial strain, for the same, was found to increase from 0.46 ± 0.21 to 0.69 ± 0.18 in PLAX and 0.43 ± 0.21 to 0.79 ± 0.05 in PSAX.

These results support the hypothesis that drift compensation techniques can be implemented to improve the reliability of myocardial strain estimation over multiple cardiac cycles. Supported by NIH Grants 5R37HL096023 and R01EB012484. In-kind and technical support provided by the Ultrasound Division at Siemens Medical Solutions USA, Inc.

9.6 **Relationship between ARFI-derived stiffness ratios and material elasticity: implications on transthoracic measurement of myocardial stiffness**, Vaibhav Kakkad, Peter Hollender, Mark Palmeri and Gregg E. Trahey, *Department of Biomedical Engineering, Duke University, Durham NC, v.kakkad@duke.edu*

Characterization of the mechanical properties of myocardium has been a topic of significant research over the last few years. Several ultrasound-based methods, such as ARFI and SWEI, have been employed to measure myocardial stiffness in a variety of settings from highly invasive environments such as open-chest preparations to noninvasive procedures, such as transthoracic imaging. While SWEI allows for assessment of tissue mechanical properties in an absolute sense, in the context of cardiac imaging it has only been shown to be feasible in diastole. ARFI, on the other hand, provides a relative estimate of tissue mechanical properties and has been shown to be viable over the entire cardiac cycle. One metric of myocardial performance that has been investigated is the ARFI-derived diastolic-to-systolic stiffness ratio. While this ratio is indicative of the change in stiffness of the myocardium over the cardiac cycle, its quantitative relationship to absolute material properties has yet to be thoroughly studied.

In this work, we performed finite-element simulations to study the relationship between ARFI-derived stiffness ratios and absolute material properties. ARF-excitations were simulated in elastic, isotropic materials over a range of Young's moduli relevant to myocardial mechanics (3 kPa – 36 kPa). The dynamic response to these excitations (both on-axis and shear wave propagation) were tracked using focused as well as plane-wave tracking configurations. ARFI-derived stiffness ratios, for each case, were compared with known material elasticity ratios for a variety of relevant parameters.

Results will be presented on the agreement of these ratios as a function of time (after the push) at which the ARFI displacement is measured, lateral offset (from push location) at which displacements are interrogated, absolute elasticity of materials, motion/motion filter induced biases in displacements, spatial extent of tracking beams and quality of displacement estimates (relative jitter). These results elucidate the inherent biases in the estimation of myocardial stiffness using ARFI. Supported by NIH Grants 5R37HL096023 and R01EB012484. In-kind and technical support provided by the Ultrasound Division at Siemens Medical Solutions USA, Inc.

9.7 **Accounting for the finite observation window in the measurement of shear-wave attenuation from the two-dimensional Fourier transform analysis of shear-wave propagation**, Ned C. Rouze, Yufeng Deng, Mark L. Palmeri and Kathryn R. Nightingale, *Department of Biomedical Engineering, Duke University, Durham, NC, ned.rouze@duke.edu*

Introduction: The frequency-dependent shear modulus of a viscoelastic material can be measured by observing shear-wave propagation following an Acoustic Radiation Force Impulse (ARFI) excitation and measuring the phase velocity and attenuation from the peak position and FWHM of the two-dimensional Fourier transform (2DFT) of the spatial-temporal shear-wave signal. However, when the shear-wave signal is observed over a finite propagation range, the measured 2DFT is a convolution of the true signal and the observation window. Thus, the measured attenuation is overestimated and approaches a finite value characteristic of the window size near zero frequency instead of the expected behavior where the attenuation is directly proportional to frequency.

Methods: In this study, we describe a method to account for the observation of shear-wave propagation over a finite propagation range by performing nonlinear least-squares fitting of the spatial-frequency dependence of 2DFT signals at discrete temporal frequencies. The fitting functions are determined using an analytic model of the shear-wave signal with two adjustable parameters given by a complex wavenumber. The Fourier transform signal is calculated numerically using the known position and size of the shear-wave observation window.

Results/Conclusions: Results have been obtained in viscoelastic and approximately elastic phantoms. For both phantoms, measurement of the frequency-dependent phase velocity using the new analysis procedure gives results that agree with measurement using the original procedure without accounting for the finite observation window. Measurements in the elastic phantom indicate that the attenuation is near zero as expected. For the viscoelastic phantom, the frequency dependence of the attenuation approaches zero in the low-frequency limit, in agreement with Voigt and Standard Linear models of viscoelasticity. We conclude that measurements of attenuation using 2DFT analysis methods can be improved by accounting for the size of the shear-wave observation window.

9.8 **Parameters contributing to variability in shear-wave attenuation estimates using amplitude-based methods**, Samantha L. Lipman, Ned C. Rouze, Mark L. Palmeri and Kathryn R. Nightingale *Department of Biomedical Engineering, Duke University, Durham, NC, samantha.lipman@duke.edu*

Introduction: Human tissues would be more accurately described by considering the associated higher-order material behaviors of a viscoelastic model, such as frequency-dependent phase velocity and shear attenuation. Amplitude-based methods have been shown to reconstruct shear attenuation as a function of frequency but the measurements can have significant variability (Budelli et al). This work evaluates the effect of the size of the depth of field as well as the starting distance from the source on amplitude derived shear attenuation estimates.

Methods: Shear-wave data was created using the analytic expression for two elastic and three viscoelastic materials representing a range of liver disease states (Rouze et al.). These data assume a cylindrically-symmetric source with no *z*-dependence. LS-DYNA was also used to simulate a Gaussian-distributed Acoustic Radiation Force Impulse (ARFI) excitation centered at 60 mm in a linear elastic (E = 12 kPa) phantom and a three-parameter viscoelastic phantom (μ_1 = 4kPa, μ_2 = 11 kPa, η = 2 Pa*s). Four Gaussian excitations, with varying aspect ratios of height to width, were simulated to mimic changing the depth of field of an ARFI excitation. Field II was used to simulate the ARFI excitation from a HIFU piston that has been used in previous 3D shear-wave imaging experiments (Jensen et al.). The displacements from a single radial trajectory were extracted at the focus of the excitation for each finite element simulation. The displacement data were differentiated to create particle velocity data that was spectrally-analyzed using a temporal Fourier transform. For each frequency, the shear attenuation was estimated with a linear fit to the log-magnitude of the Fourier transformed data as a function of position.

Results: From the analytic data, the shear attenuation was estimated over the frequency range of 100--300 Hz, with an RMS error of less than 10 Np/m for all materials. The RMS error of the shear attenuation decreased from 31.1 to 6.0 Np/m in the elastic material as the height to width ratio of the Gaussian excitation increased from 8:1 to 20:1. The RMS error of the shear attenuation calculated from the HIFU piston excitation was 12.0 Np/m. The RMS error of the shear attenuation decreased from 29.4 to 7.6 Np/m in the viscoelastic material as the height to width ratio of the Gaussian excitation increased from 8:1 to 20:1. The RMS error of the shear attenuation calculated from the HIFU piston excitation was 10.9 Np/m. The starting position was determined to need to be 4 mm away from the center of the source for the elastic material, and 6 mm for the viscoelastic material.

Conclusions: Shear-wave attenuation can be estimated using amplitude-based methods using a cylindrically-symmetric source. An extended depth-of-field is necessary to minimize the effects of diffraction and create a shear wave that more closely follows the cylindrical wave assumptions of these methods. Additionally, the starting position needs to be far enough away from the source to avoid near-field effects, which would require more complex numerical models to accurately estimate material parameters. Supported by NIH grant EB002132. We thank the Ultrasound Division at Siemens Medical Solutions, USA, Inc. for their technical and in-kind support.

9.9 **Estimation of phase-velocity dispersion in viscoelastic materials using the Multiple Signal Classification (MUSIC) method,** Matthew W. Urban[1, 2], Piotr Kijanka[1, 3], Bo Qiang[4], Pengfei Song[1], Carolina Amador[2] and Shigao Chen,[1, 2] *Departments of [1]Radiology and [2]Physiology and Biomedical Engineering, Mayo Clinic College of Medicine and Science, Rochester, MN, 55905, [3]Department of Robotics and Mechatronics, AGH University of Science and Technology, Al. A. Mickiewicza 30, 30 059 Krakow, Poland and [4]The Nielsen Company, Oldsmar, FL, 34677, urban.matthew@mayo.edu*

Objectives: Soft tissues are viscoelastic in nature. Shear-wave velocity dispersion can be used to characterize the viscoelasticity of soft tissues. However, estimation of the dispersion in the face of experimental noise can be difficult and provide limited bandwidth for characterization of the mechanical properties. Current methods typically use a phase gradient or two-dimensional Fourier transform (2D-FT) to extract the dispersion curves. We propose the use of the Multiple Signal Classification (MUSIC) method as an alternative to the 2D-FT method for dispersion curve estimation.

Methods: Data from digital and physical phantoms used in the Radiological Society of North America (RSNA) Quantitative Imaging Biomarker Alliance (QIBA) effort to standardize liver fibrosis shear-wave velocity measurement were used. The digital phantoms were created using finite-element method (FEM) simulations in viscoelastic material from acoustic radiation force excitations. The physical phantoms were viscoelastic as well created by CIRS, Inc (Norfolk, VA). The 2D-FT and MUSIC methods were used to extract the dispersion curves from the digital phantom data with different levels of noise added. Root-mean-square errors (RMSEs) were estimated compared to the theoretical dispersion curves. The same methods were applied to data from the physical phantoms using excitations at different focal depths acquired with a Verasonics ultrasound research system.

Results: The MUSIC method had consistently lower values of RMSE compared to results obtained using the conventional 2D-FT approach over a range of signal-to-noise ratios (5-20 dB). In addition, the usable bandwidth was increased in the experimental phantom data by 17-180 Hz by using the MUSIC method compared to the 2D-FT method.

Conclusions: The MUSIC method provides a robust alternative to the conventional 2D-FT method for estimating phase-velocity dispersion. Supported in part by NIH grants R01DK092255 and R01DK106957 from the National Institute of Diabetes and Digestive and Kidney Diseases and RSNA QIBA Ultrasound Shear Wave Speed Committee contract HHSN268201500021C.

9.10 **Evaluation of nonlinear modulus using compression of transplanted kidneys and shear-wave measurements,** Sara Aristizabal[1], Carolina Amador[1], James F. Greenleaf[1] and Matthew W. Urban[2, 1], *Departments of [1]Physiology and Biomedical Engineering, and [2]Radiology, Mayo Clinic College of Medicine, Rochester, MN, 55905, aristizabaltaborda.sara @mayo.edu*

Transplantation and dialysis are the treatments available for patients with end-stage renal disease. Kidney transplantation provides a better quality of life and survival rate than dialysis. After undergoing such a surgical procedure, biopsies are performed to examine the function of the kidney transplant over time. Due to the invasive nature of biopsies, shear-wave-based methods are being investigated as potential noninvasive means to detect the presence of renal fibrosis in the kidney. However, to better understand pathologies, for which the knowledge of shear elasticity may not be sufficient to reach a clinical diagnosis, new methods that investigate nonlinear tissue mechanical properties have been proposed. It has previously been shown that the applied pressure of the transducer can affect the stiffness measurements in organs such as the kidney; this phenomenon is called acoustoelasticity (AE). Using AE experimentally by compressing a medium and measuring the shear-wave speed at different compression levels, we can estimate the third-order nonlinear coefficient, A. The goal of this study was to evaluate the feasibility of performing AE and evaluate the diagnostic potential of A in the transplanted kidney.

The study was conducted on renal-transplant patients at the same time of their protocol biopsies. The study was approved by the Mayo Clinic Institutional Review Board. To estimate the parameter A, the sonographer applied stress in the transplanted kidney in two manners: 1) progressively, by pressing the ultrasound transducer (C1-6) into the patient in seven steps until reaching maximum compression, and 2) regressively, by applying maximum stress into the tissue and slowly releasing the compression in seven steps. Shear waves were generated and measured at each compression step by a GE LOGIQ E9 ultrasound system (GE Healthcare, Wauwatosa, WI). For the AE measurements, the shear modulus was quantified at each compression level and the applied strain was calculated from the B-mode images by measuring the change in thickness of the kidney cortex. Finally, A was calculated by applying the AE theory. The estimated values of A were subsequently compared against the biopsy score for interstitial fibrosis (Banff *ci*) and for tubular atrophy (Banff *ct*) as well as other clinical variables such as the Serum Creatinine (*SCr*) and Resistive Index (*RI*).

We had adequate data for the estimation of A from 46 of 54 patients when the compression was performed progressively and 19 of 43 patients where the compression was performed regressively. The maximum strain ranged from 25-30%. Our results showed that the nonlinear modulus obtained in the progressive and regressive direction of compression can be used to distinguish patients with interstitial fibrosis (*ci*) (p = 0.0078) and (p = 0.01) respectively. Additionally, the nonlinear modulus values estimated using progressive compression can help distinguish patients with interstitial fibrosis and tubular atrophy ($ci + ct \geq 1$) (p = 0.05). The correlations of patients with $ci > 0$ between A and *SCr* and A and *RI* were not statistically significant. The statistical analysis was performed using a Wilcoxon rank sum test. These results demonstrate that A could potentially be used for the identification of patients with early stages of renal fibrosis; nevertheless, we still need to further understand how the nonlinear modulus A is related to the renal allograft function. Supported in part by NIH grant R01DK092255 from the National Institute of Diabetes and Digestive and Kidney Diseases.

9.11 **Shear shock waves observed in the *ex-vivo* brain**, David Espíndola and Gianmarco Pinton, *Joint Department of Biomedical Engineering, University of North Carolina-Chapel Hill and North Carolina State University, 109 Mason Farm road, Room 348 Taylor Hall, Chapel Hill, NC 27599, david.espindola@unc.edu*

Introduction: For the past 50 years, head-injury biomechanics has been guided by measurements of accelerometers attached to the skull, which provides a partial and indirect estimate of brain motion because the internal deformation of the brain is far more complex than the rigid motion of the skull. In this context, brain tissue behaves nonlinearly under conditions that are generally met by injurious impacts. Attempts to measure the *in situ* nonlinear brain mechanics with imaging methods (MRI, CT) have lacked the penetration, frame rate or motion-detection accuracy to capture the nonlinear transient events during traumatic injury. Here, we present a high frame-rate (6200 images/second) ultrasound imaging method that can accurately (<1 µm) measure the internal brain motion during the rapid transient events associated with a relatively mild impact in an *ex vivo* porcine brain.

Methods: Our method relies on two main advancements: 1) A flash-focus ultrasound sequence that reduces the side lobes by 19 dB and increases the SNR deep in the brain compared with a conventional plane wave compounding sequence: and 2) an adaptive tracking algorithm that uses a quality weighted median filter to iteratively optimize correlation estimates. To the best of our knowledge no other imaging method (MRI, CT) has been able to achieve this combination of speed, accuracy and penetration in the brain.

Results: By imaging brain motion directly and with unprecedented accuracy, we were able to observe a new biomechanical phenomenon: the formation of shear shock waves within the brain. The measured shock waves have a specific odd harmonic signature predicted by theory describing a cubically-nonlinear elastic soft solid. Measurements of the frequency-dependent attenuation and dispersion were used to fit this nonlinear theoretical model to our data. This yielded the first estimates of the cubic nonlinear parameter for brain tissue. We have found that, compared to the initially smooth low-amplitude impact, the acceleration at the shock front is amplified up to a factor of 8.5. A 30 g acceleration at the brain surface therefore develops into a 255 g shock wave deep inside the brain.

Conclusions: By directly quantifying brain tissue motion, we demonstrated that the elastic motion of the brain is fundamentally cubically nonlinear. This previously unobserved shear shock wave phenomenology dramatically amplifies the acceleration at the shock front, deep in the brain, compared with the acceleration imposed at the brain surface. Strain and strain rate are also amplified at the shock front. The highly-localized increase in acceleration at the shock front suggests that the shear shock-wave phenomenology is a primary mechanism for traumatic injuries in soft tissue.

9.12 **High frame-rate imaging and adaptive tracking of shear shock-wave formation in the brain: full wave and experimental study**, David Espíndola and Gianmarco Pinton, *Joint Department of Biomedical Engineering, University of North Carolina-Chapel Hill and North Carolina State University, 109 Mason Farm road, Room 348 Taylor Hall, Chapel Hill, NC 27599, gia@email.unc.edu*

Introduction: Nonlinear shear waves have a cubic nonlinearity thst generates a unique odd harmonic signature. This behavior was first observed in a homogeneous gelatin phantom with ultrafast plane-wave-compounding ultrasound imaging and a correlation-based tracking algorithm to determine particle motion. However, in heterogeneous tissue, like brain, clutter degrades motion tracking and destroys the low amplitude odd harmonics that are required to observe shear shock waves. We show that under these imaging conditions, conventional-plane wave compounding is not sufficient to detect sharp motion from a shear shock wave. We present a high frame-rate ultrasound imaging sequence consisting of multiple focused emissions that improves the image quality. The proposed imaging sequence is used in conjunction with a brain-optimized adaptive tracking algorithm to measure shear shock waves propagating in the brain.

Methods: The proposed imaging sequence reduces the clutter artifacts generated by the brain allowing us to track the internal and discontinuous movement caused by a shear shock wave propagating in a *ex-vivo* porcine brain. This imaging sequence is compared experimentally to conventional plane-wave compounding. Then, the adaptive-tracking algorithm was optimized to determine the specific odd harmonic signature generated by the cubic nonlinearity of shear shock waves. This optimization was determined with a numerical description of shear shock waves using a Rusanov-Fourier scheme, that supports nonlinearity and an arbitrary frequency-dependent attenuation law with third-order accuracy. Full-wave simulations were then used to generate ultrasound images of shear shock waves propagating through a medium displaced according to the Rusanov-Fourier predictions.

Results: We demonstrate that the point spread function of the proposed flash focus imaging sequence reduces the sidelobes by 19 dB compared to plane-wave compounding. Experimentally, we show that our sequence increases our ability to track the odd harmonics signature by 14 dB. Optimal values of the tracking parameters (median filter size, kernel length, interpolation factor) are presented. The performance of the adaptive-tracking algorithm is compared to the Cramer Rao Lower Bound in terms of bias, jitter and false peak errors under different imaging scenarios.

Conclusions: It is shown that the proposed flash-focus sequence estimates interframe displacements more accurately compared to plane-wave compounding due to a 19 dB reduction in the sidelobes of the point-spread function. Furthermore, the flash-focus sequence increases the *SNR* of the RF data, which increases the correlation coefficients in the brain required to accurately determine the low-amplitude odd-harmonic signature. Our optimized adaptive-tracking algorithm produces displacements that are in agreement with theoretical predictions of the odd-harmonic development. This is required to obtain more precise estimates of the acceleration and rise time of the shock. These improvements are even more significant in a high-noise imaging environment.

9.13 **Piecewise parabolic method for propagation of shear shock waves in soft solids,** Bharat B. Tripathi, David Espíndola and Gianmarco F. Pinton, *Joint Department of Biomedical Engineering, University of North Carolina-Chapel Hill and North Carolina State University, 109 Mason Farm road, Room 348 Taylor Hall, Chapel Hill, NC 27599, bharat25@email.unc.edu*

Introduction and Background: There are currently no simulation tools that model shear shock-wave propagation in the entire head. We have recently observed this new biomechanical phenomenon: that shear waves generated by an impact develop into shock waves as they propagate into the brain. Unlike compressional shock waves, shear shocks in brain are relatively unstudied. The current numerical state-of-the-art models nonlinear shear-wave propagation only for small angles and unidirectional propagation (paraxially). Here, we present a more general numerical solution that propagates nonlinear shear waves without the paraxial approximation (full-wave).

Methods: In this work, 1) we develop a nonlinear system of hyperbolic conservation laws to model the propagation of linearly polarized shear waves in two dimensions; 2) the attenuation during the propagation is modeled using relaxation mechanisms as in generalized Maxwell body; and) the problem is numerically simulated using the Piecewise Parabolic Method (PPM), first described by Colella in 1984. This system is solved using an unsplit and conservative implementation of the PPM with a local Lax-Friedrich flux. The numerical solution is also validated experimentally with our high frame-rate (6200 images/second) ultrasound imaging method that accurately measures (<1 µm) the motion of soft solids.

Results: A CT-scan slice of human skull is used to study the propagation and formation of shear shock waves inside the brain. Due to elliptical geometry of the skull slice, the focusing of shear shock waves is observed. Moreover, observation of extremely high local-acceleration at the shock fronts reinforces our hypothesis of possible injury due to shocks. This two-dimensional solver is validated using two planar step-shock problems; first, parallel to the Y-axis, and second, inclined at 45° to the Y-axis, to quantify the anisotropy error. A comparison between the numerical and experimental observations is presented.

Conclusion: The proposed PPM accurately models the nonlinear shear-wave problem in soft solids. It captures the shock formation and the specific odd harmonic signature that are predicted by analytical solutions and measured experimentally. Numerical methods that solve the nonlinear shear-wave propagation in the brain can serve as a valuable tool to understand the biomechanical origins of TBI that cannot be measured *in vivo* in humans.