UITC ABSTRACTS 2016

Wednesday morning

1. ELASTICITY 1

1.1 **Building a virtual open-source simulation platform for breast ultrasound elastography**, Yu Wang, Bo Peng, David Rosen and Jingfeng Jiang, *Michigan Technological U. jjiang1@mtu.edu*

Introduction: The primary objective of this study was to build a virtual simulation platform for breast ultrasound elastography (UE) leveraging existing open source software. The proposed virtual breast UE simulation system can be used to validate image pixels with known underlying soft tissue properties (i.e. "ground truth") in complex, heterogeneous media, enhancing confidence on image or measurement interpretations. The proposed system can also be used to accelerate development of new elastographic methods via virtual (imaging) prototyping.

Methods: The proposed virtual breast UE system was mainly built on four existing open source packages including Field II (ultrasound simulator), VTK (geometrical visualization and processing), FEBio (finite element [FE] analysis) and Tetgen (mesh generator). In our previous publication, we demonstrated the use of this virtual simulation platform for strain elastography (SE). Now capabilities have been extended to acoustic force-based UE simulations including point shear wave elastography (pSWE), supersonic shear imaging (SSI) and acoustic radiation force impulse (ARFI) imaging.

All acoustic-radiation-force-based simulations involve multiple steps. In the first step, acoustic radiation forces were used to excite soft tissue and generate tissue deformation using FEBio (an open source FE solver). Those aforementioned acoustic radiation force inputs were determined by Field II simulations. In the second step, ultrasound simulations using Field II were performed to obtain a series of pre-deformation and post-deformation ultrasound radio frequency (RF) data. Such ultrasound simulations were performed using three different numerical breast models with increasing complexity – one uniform phantom, one inclusion phantom and one virtual complex breast phantom derived from MRI data. In the third step, speckle tracking was performed on these RF data to estimate the tissue deformation and subsequently infer mechanical properties of virtual tissues being imaged (e.g., shear wave speed, time-to-peak, normalized displacement).

Results: Simulated breast lesions were clearly visible in all three breast models for SSI and ARFI. Their overall sizes and shapes were visually consistent with all virtual phantom designs. In both pSWE and SSI, the estimated shear wave speed value in the uniform phantom was within 5% as compared to the known value. Shear wave speed values estimated from all hard inclusions in soft background materials were underestimated by 20%, similar to what has been reported.[1]

Conclusions: A virtual acoustic-radiation-force-based UE simulation platform has been successfully implemented by extending our previous work on virtual quasi-static elastography simulation platform. The initial results are encouraging and warrant more developments.

Palmeri et al. in *Proc IEEE International Ultrasound Symp* (2010).

1.2 **Placenta tissue characterization using single tracking location shear-wave elasticity imaging**, Juvenal Ormachea, Stephen A. McAleavey, Ronald W. Wood, Christopher J. Stodgell, Philip J. Katzman, Eva K. Pressman, Richard K. Miller and Kevin J. Parker, *U. Rochester, jormache@ur.rochester.edu*

Background and motivation: The placenta is the critical interface between the mother and the developing fetus and is essential for survival and growth. Improved diagnostic assessment of the placenta could enable earlier recognition of adverse conditions such as intrauterine growth restriction (IUGR), a major clinical public health problem which is defined as a failure of the fetus to achieve its optimal growth.[1] Elastography is a technique that attempts to characterize the elastic properties of tissue in order to provide additional and more useful information for clinical diagnosis. However, the biomechanical properties (shear wave speed (SWS)) of the normal placenta have not been studied extensively. In that sense, elastography may be able to provide information of the range of normal SWS values, possible dependence on physiological variables such as fetal blood pressure and flow, and the effects of specific pathologies on the placental tissue.

Methods: Eleven human placentae from healthy, uncomplicated, term pregnancies were obtained immediately following caesarean section delivery, placed in a plastic container, and transported to the perfusion laboratory within 20 minutes. Then, a well-developed protocol for perfusing whole placentae, post-delivery, to maintain tissue integrity and function for hours was performed. In this model, the placenta is living, whole, and maintained within normal physiological parameters such as flow, arterial pressure, and oxygen, throughout examination by ultrasound, and shear wave elastography. Additionally, a titration procedure was applied to evaluate the placenta response to vasoactive agents. Placentae were placed on an acoustically-absorbing pad, immersed in a buffered saline bath at 37°C, and scanned during perfusion. Single tracking location shear wave elasticity imaging (STL-SWEI),[2] an acoustic radiation force based-technique, was applied to measure the SWS in the placental tissue. The SWS measurements from the fetal side of the perfused tissue were obtained from a typical 1x1cm^2 ROI within the placenta.

Results: The SWS data have a mean of 1.92 m/s with a standard error of ± 0.05 m/s and generally are in the range of 1.5-2.5 m/s for normal placental tissue (baseline). An analysis of the measured data using the Tukey-Kramer test showed that the baseline groups were significantly different (p <0.05) from the measurements following vasoconstrictor and vasodilator injections in the placental tissue.

Conclusion: Preliminary results indicate that normal placental tissue on the fetal side have SWS in a defined range around 2 m/s, comparable to the tissue elasticity found in animal livers. Some abnormalities are found outside this range, and thus elastographic measures of the placenta can provide useful assessments related to the state of the tissue.

(1) Conde-Agudelo A et al., *BJOG 120*, 681-94 (2013). (2) Langdon JH et al., *IEEE Trans UFFC 62*, 1225-44 (2015).

1.3 ***In-vivo* shear-wave elastography of a rhesus macaque model of the uterine cervix: changes during pregnancy**, Ivan M. Rosado-Mendez, Andrew Santoso, Quinton Guerrero, Lindsey C. Drehfal, Swetha Subramanian, Sarah Kohn, Michele Shotzko, Mark Palmeri, Helen Feltovich and Timothy Hall, *U. Wisconsin-Madison, Wisconsin National Primate Research Ctr., Duke U. and Intermountain Healthcare,rosadomendez@wisc.edu*

Objectives: We are investigating the use of Shear Wave Elasticity Imaging (SWEI) to objectively quantify changes in the stiffness of the uterine cervix during pregnancy in order to assess abnormal softening that may lead to spontaneous preterm birth. Difficulties of *in vivo* human research during pregnancy motivate the study of animal models with similar anatomy and physiology. This work presents preliminary results of the use of SWEI methods to assess cervix stiffness changes during pregnancy in a rhesus macaque nonhuman primate (NHP) model.

Methods: NHP subjects are scanned before conception and 4, 10, 16, 20, and 23 weeks after conception, and two weeks after delivery (~week 24). SWEI is applied transabdominally with a linear array transducer on a Siemens Acuson S2000 ultrasound scanner (Siemens Healthcare, Mountain View, CA, USA). Shear waves are induced with an Acoustic Radiation Force Impulse excitation and tracked within 5×5mm^2 regions of interest placed in the uterine end of the cervix. Displacements are calculated using the Loupas' routine[1] and shear wave speed (SWS) is estimated using two estimators: a RANSAC[2] linear fit to the time-to-peak displacement as a function of the distance from the excitation, and a Radon-sum method[3] that selects the largest displacement-projection trajectory on a time vs. distance plane. The "best" of 4 to 6 estimates from various ROIs are chosen considering the agreement between estimators, low noise levels, and goodness of fit. ANOVA was used to test for statistical significance.

Results: From 23 subjects currently enrolled, 7 have successfully completed the study. SWS values significantly decreased from 5.0m/s (median) before pregnancy, to 2.0m/s at week 16 (p=0.005), and to 1.4m/s one week before term (p=0.002). Two weeks after delivery, SWS values rose to 2.2m/s. SWS variability, assessed through the interquartile range at each time point, decreased from 2.3m/s to 1.0m/s after week 16. This is possibly due to collagen breakdown and microstructural homogenization of the cervix close to term.

Conclusions: SWEI show promise to track cervical softening during pregnancy in the NHP model. We are expanding our study to include 50 subjects in total and exploring effects of age, weight, parity, as well as viscosity. 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) Loupas T et al., *IEEE Trans Ultrason Ferroelect Freq Contr, 42*, 672-688 (1995). (2) Wang MH, et al., *Ultrasound Med Biol 36*, 802-813 (2010). (3) Rouze NC et al., *IEEE Trans Ultrason Ferroelect Freq Contr 57*, 2662-2670 (2010).

1.4 **Quantifying fibrous-cap thickness with acoustic radiation force impulse (ARFI) ultrasound: blinded-reader study**, Tomasz J. Czernuszewicz, Jonathon W. Homeister, Melissa C. Caughey, Benjamin Y. Huang, Ellie R. Lee, CarlosA. Zamora, Mark A. Farber, Joseph J. Fulton, Peter F. Ford, William A. Marston, Raghuveer Vallabhaneni, Timothy C. Nichols and Caterina M. Gallippi, *U. North Carolina, Chapel Hill, cmgallip@email.unc.edu*

Background: Acute cerebrovascular events, such as stroke, are commonly associated with the rupture of vulnerable carotid plaque. An important characteristic of vulnerable plaque is the thickness of the fibrous cap, a layer of protective collagen that separates a necrotic core from luminal blood. Noninvasively identifying thin fibrous caps may aid in the differentiation of vulnerable plaques from stable plaques that may not require immediate intervention. Our group has been investigating ARFI imaging as a method for interrogating fibrous cap thickness. We previously demonstrated feasibility with a finite element method (FEM) study and a single *in vivo* example with matched histology. In this work, we continue our analysis of ARFI imaging of fibrous caps *in vivo* and present results from a statistical reader study involving radiologists blinded to the histological results.

Methods: Patients (N = 25) undergoing clinically indicated carotid endarterectomy (CEA) were recruited from UNC Hospital and imaged with ARFI implemented on a Siemens Acuson Antares modified for research (6 MHz tracking pulses). After surgery, the extracted specimens were sectioned according to noted arterial geometry for spatial registration to the ultrasound imaging plane. Parametric 2D ARFI images of peak displacement were rendered and evaluated by three radiologists blinded to the histology result. Using a custom MATLAB interface, the radiologists were asked to identify fibrous caps and manually segment their outlines. Similarly, a pathologist blinded to the ARFI results segmented fibrous caps from digitized histological slides. Mean fibrous cap thickness (± standard deviation) was automatically measured from both radiologist and pathologist segmentations. To determine agreement, results were compared using regression (R^2), Spearman correlation (ρ), and Bland-Altman (BA) analysis.

Results: Of the 25 CEA samples, 16 fibrous caps were successfully measured from histology. Reader 1 identified 11 fibrous caps with moderately high agreement with histology (R^2 = 0.64, ρ = 0.81), and a small but non-significant negative bias from BA analysis (-0.05 ± 0.18 mm, p = 0.41). Reader 2 identified 7 fibrous caps with high agreement with histology (R^2 = 0.89, ρ = 0.75), and a small, statistically-significant positive bias (0.13 ± 0.087 mm, p = 0.007). Finally, reader 3 identified 11 fibrous caps; however, with weak agreement with histology (R^2 = 0.27, ρ = 0.56) and large positive bias (0.28 ± 0.38 mm, p = 0.04). The smallest fibrous cap measured accurately (i.e. less than ±0.1 mm absolute error) by any radiologist was 0.49 mm thick.

Conclusions: In general, the blinded radiologists were able to successfully identify and measure mean fibrous cap thickness that fell within the expected axial resolution limit of the system (~0.4 mm). Caps less than this were either not identified, or measured with error. Results from BA analysis suggest that ARFI may introduce a slight positive bias into fibrous cap measurement, consistent with our observations from FEM simulation studies. Overall these results suggest ARFI is relevant to measuring fibrous cap thickness *in vivo* and it is expected that higher center frequencies for ARFI tracking pulses may improve the resolution limits presented herein.

1.5 **Gradient-based search of k-space for calculation of shear-wave phase-velocity dispersion in simulations of acoustic radiation force-based elastography**, Matthew W. Urban, Bo Qiang, Shigao Chen and James F. Greenleaf, *Mayo Clinic Coll. Med.*, *urban.matthew@mayo.edu*

Objectives: Shear wave elastography has been used in many applications to provide diagnostic information related to the tissues' material properties. Most of these methods assume that the tissues are purely elastic. However, soft tissues are known to be viscoelastic. As a result, evaluating the viscoelasticity provides a fuller characterization of the tissue. One of the ways to evaluate the viscoelasticity is to analyze the phase velocity dispersion from propagating shear waves. Many groups have used a two-dimensional Fourier transform of the spatiotemporal data to give a Fourier representation or k-space, which can be used to estimate the phase velocities over a certain bandwidth. The conventional approach is to find peaks in the k-space at each frequency, f, and use the coordinates (f_p, k_p) to find the speed using $c(f_p) = f_p/k_p$. However, this method can produce a bias in simulated results using an acoustic radiation force (ARF) push beam. We propose a new search method based on taking a gradient in the k-space and looking for zero-crossings, which correspond to finding the "ridge" of the k-space distribution.

Methods: As part the RSNA QIBA shear wave speed committee's effort to standardize shear wave speed measurements for liver fibrosis staging, we performed finite element model (FEM) simulations of shear wave propagation. The forcing function used for the FEM simulations were ARF push beams generated by a curved array transducer. We simulated the push beams for different focal depths, f-numbers, and time duration of the ARF push. We applied these push beam configurations in three different viscoelastic media that cover different stages of liver fibrosis. The viscoelastic media were modeled using a generalized Maxwell model (GMM) with three components. The spatiotemporal data were extracted from the simulated data at the nominal focal depth. The gradient-based approach (GA) was compared with the frequency-based approach (FA) in k-space analysis and the median absolute difference (MAD) was calculated between the measured phase velocities and the reference phase velocity given for the GMM.

Results: For all the different parametric combinations, the mean MAD for the FA was 0.24 m/s with a range of 0.17-0.33 m/s compared to the reference values. The mean MAD for the GA was 0.07 m/s with a range of 0.03-0.14 m/s. The mean difference MAD between FA and GA was 0.17 m/s with a range of 0.13-0.23 m/s. There was a small difference in the MAD when different ARF push durations were used for both approaches. The MAD was increased results obtained with ARF pushes using a higher f-number. The MAD for both methods was generally larger for the mediums with higher velocity dispersion.

Conclusions: The new gradient-based approach provides smaller errors than the frequency-based approach for obtaining the phase velocity dispersion in simulations of realistic ARF push beams in viscoelastic media. Future work will be to use this approach in the analysis of *in vivo* human data. Supported in part by NIH grant R01DK092255 and HHS contract HHSN268201500021C.

1.6 **Plane-wave motion tracking for VisR imaging**, Christopher J. Moore, Md Murad Hossain and Caterina M. Gallippi, *North Carolina State U. and U. North Carolina, Chapel Hill*, *cmgallip@email.unc.edu*

Background: Viscoelastic Response (VisR) ultrasound is an ARF-based imaging technique used to characterize the viscoelastic properties of tissue. Characterization using VisR is achieved by fitting ARF-induced displacements to the Mass-Spring-Damper (MSD) model, which yields estimates of both elasticity and viscosity of the tissue relative to the applied ARF excitation amplitude. These tissue properties, herein described as relative elasticity (RE) and relative viscosity (RV), can be measured at multiple lateral locations by translating the region of excitation (ROE) in order to form a two-dimensional image. This process to formulate an image requires acoustic energy deposition in the tissue, and it is time consuming to perform. In this work, we investigate the feasibility of reducing acoustic energy deposition and shortening the duration of VisR imaging sequences using plane wave motion tracking and ARF-induced shear wave propagation. *We hypothesize that using plane waves to track ARF-induced motion in VisR can produce images similar in quality to conventional VisR images, while reducing sequence duration and acoustic energy deposition.*

Methods: Finite element (FE) simulation (LS-DYNA, 250 μm^3 fully integrated elements) was used to simulate two tissue-like phantom meshes consisting of a homogeneous viscoelastic background material (1 cm lateral x 1 cm elevational x 3 cm axial; MAT_KELVIN_MAXWELL VISCOELASIC), with Young's modulus of 10 kPa and compressive viscosity of 6 Pa·s, and a 10 mm cylindrical inclusion placed in the center of the cube laterally, spanning elevation, at an axial depth of 2.15 cm. The Young's modulus of the inclusion was 10 kPa in phantom 1 and 30 kPa in phantom 2, while the viscosity was 2 Pa·s in phantom 1 and 6 Pa·s in phantom 2. Both phantoms were encased by a perfectly matched layer (MAT_PML_ELASTIC) to prevent reflection at the mesh boundaries. Using these phantom meshes, simulated ARF excitations were applied as point loads, calculated from the FIELD II simulated pressure field of a linear array transducer focused at 2.15 cm, with an F/1.5 focal configuration. The point loads were excited using a VisR excitation sequence consisting of two 70-µs pulses, separated in time by 0.47 ms. The point loads were then shifted laterally in steps of 0.35 mm, in nine separate FE simulations to construct a conventional VisR sequence. To compare this conventional sequence to plane wave tracked VisR sequences, the number of lines acquired from each lateral simulation was swept from 1:1 (Conventional VisR, 0.25 mm line width) up to 16 (16:1 parallel acquisition plane wave tracking, 4.0 mm region width). Displacements from each of these simulations were then fit to the MSD model using a custom C++ implementation of Nelder-Mead non-linear minimization, in order to formulate images of RE and RV for each case within the N:1 tracking line sweep. The RE and RV images were then normalized using depth dependent gain before computing lesion contrast (mean within lesion / mean in the background at similar depth) and CNR (|mean inside – mean background| / standard deviation of background) metrics. Ranges of CNR and Contrast values are reported as Mean ± Standard Deviation.

Results: For phantom 1, when the inclusion viscosity was 2 Pa·s, the contrast ratio for RV was < 1 for both conventional and plane wave tracking images, suggesting lower relative viscosity in the lesion compared to the background. For plane wave tracking, the CNR for 2:1 through 8:1 cases (8.22 ± 2.46) was similar to the CNR of conventional 1:1 VisR (7.9). At and above 9:1, the CNR of the RV images (1.84 ± 0.77) was lower than the CNR of conventional 1:1 VisR. In phantom 2, when the inclusion elasticity was greater than that of the background, the contrast ratio from the RE parameter image was > 1, consistent with increased elasticity within the inclusion, for conventional 1:1 VisR and plane wave tracking up to 12:1. Above 12:1, the contrast ratio of the RE image fell below 1, falsely indicating a flip in the image contrast. The CNR of the RE images for 2:1 up to 8:1 plane wave tracking cases (3.23 ± 2.64) was again similar to the CNR of conventional 1:1 VisR (4.3), while at and above 9:1 the CNR decreased (0.55 +- 0.29).

Conclusions: These results suggest that VisR imaging performed using plane wave tracking with up to 8:1 parallel acquisition provides similar image contrast and quality to that of conventional 1:1 VisR imaging. 8:1 parallel acquisition of VisR data would require 87.5 percent less energy than that of conventional VisR sequences and shorten the duration of the sequence (~77.5 % in the case of the 10 kPa phantom used in this work). Shortening the sequence duration may reduce the impact of common noise sources, such as physiological motion, which can confound VisR estimates of viscoelasticity. Regarding reduction in the acoustic energy, VisR with plane wave tracking can potentially be performed using more complex excitation sequences, such as those with multiple axial foci, while maintaining a low acoustic dose. The potential impact of reduced resolution and SNR associated with plane wave tracking is the topic of ongoing investigation. Overall the results presented herein suggest that VisR imaging may be performed using plane wave tracking of ARF-induced displacements, and such sequences are capable of producing images with quality similar to that of conventional 1:1 VisR, while reducing the acoustic energy and duration of the VisR sequence.

1.7 **FEM analysis of the quantitative potential of Viscoelastic Response (VisR) ultrasound using matrix-array transducers**, Md Murad Hossain, Christopher J. Moore and Caterina M. Gallippi, *U. North Carolina, Chapel Hill and North Carolina State U., cmgallip@email.unc.edu*

Background: Viscoelastic Response (VisR) ultrasound is an acoustic radiation force (ARF)-based imaging method that fits induced displacements to a one-dimensional (1D) mass-spring-damper (MSD) model to estimate the ratio of viscous to elastic moduli, τ, in viscoelastic materials. A source of error in VisR τ estimation is inertia. Although the MSD model accounts for inertia due to mass in response to an idealized point force excitation, it does not account for complex and interrelated three-dimensional system inertia. In tissue (and in FE simulation), the system inertia arises from interactions of both compressive and shear dynamics in response to volumetric ARF excitations. We hypothesize that minimizing the volumetric extent of ARF excitations (i.e., by minimizing the lateral and elevational F/#s of ARF focal configurations using a matrix array transducer) will diminish the degree of error due to complex system inertia in VisR τ estimates.

Methods: ARF excitations were modeled, using Field II, as the 3D acoustic intensity fields produced using a 206 x 206 matrix array transducer centered at 4.21MHz. The lateral F/# was maintained at 0.75, while the elevational F/# was set to 5.0, representing a conventional linear array transducer, or 0.75, as achievable using a matrix array. Using these focal configurations, VisR sequences were implemented using two, 70-μs ARF excitations administered to the same region of excitation and separated by 0.6 ms in time. These VisR sequences were applied to modeled viscoelastic materials (MAT_KELVIN-MAXWELL_VISCOELASTIC material model provided with the commercially available FEM solver, LS- DYNA). In a first set of materials, Young's modulus was fixed at 10 or 100 kPa, and viscous modulus was varied from 1 to 15 Pa.s by steps of 1 Pa.s. In a second set of materials, viscous modulus was fixed at 1 or 15 Pa.s, and Young's modulus was varied from 10 to 100 kPa by steps of 10 kPa. Additionally, two phantoms with spherical inclusions of 4 mm diameter were modeled, in which both background and inclusion had Young's modulus of 10 kPa, while background and inclusion viscosity was 5 and 15 Pa.s, respectively, in the first phantom and 15 and 5 Pa.s in the second phantom. VisR τ was calculated by fitting the MSD model to the FEM displacements, and parametric τ images were rendered. Then, inclusion contrast ratio was measured as the ratio of the median τ values inside versus outside the inclusion.

Results: When the elevational F/# was decreased from 5.0 to 0.75, median percent error in VisR τ estimates decreased by 40% in materials with fixed viscosity of 1 Pa.S and by 95% in materials with fixed viscosity of 15 Pa.S. Further, in materials with fixed elasticity of 10 or 100 kPa, median percent error decreased by 65% when the elevational F/# was decreased from 5.0 to 0.75. For the FEM phantom with an inclusion more viscous than the background, the contrast ratio of the inclusion was 1.26 and 0.85 when the elevational F/# was 0.75 and 5.0, respectively. The contrast ratio was 1.23 and 1.03 when the elevational F/# was 0.75 and 5.0, respectively, for FEM phantom with inclusion less viscous than backgrounds.

Conclusion: When using a volumetric ARF body force to induce displacement, VisR τ estimates are skewed by the complex system inertia. However, these data show that as the volumetric extent of ARF excitation is reduced by reducing the elevational F#, the estimated τ became similar to the true material τ.

2. THERAPY RESPONSE

2.1 **Quantitative ultrasound and texture predictors of breast tumor response to chemotherapy prior to treatment,** Gregory Czarnota, Hadi Tadayyon, Mehrdad Gangeh, Lakshmanan Sannachi, Ali Sadeghi-Naini, William Tyler Tran 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, for the first time, we demonstrate the clinical utility of pre-treatment QUS texture features in predicting the response of breast cancer patients to NAC.

Methods: Using a 6 MHz center frequency clinical ultrasound imaging system, radiofrequency (RF) breast ultrasound data were acquired from 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: The QUS feature AAC_{cor} demonstrated a favorable response prediction with sensitivity, specificity, and AUC of 86%, 83%, and 0.77, respectively, using the Naïve Bayes classifier.

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.

2.2 **Multivariate analysis using quantitative ultrasound and diffuse optical spectroscopy to monitor neoadjuvant chemotherapy response in locally-advanced breast cancer,** William Tyler Tran, Charmaine Child, Lee Chi, Elzbieta Slodkowska, Lakshmanan Sannachi, Hadi Tadayyon, Elyse Watkins, Sharon Lemon Wong, Belinda Curpen, Ahmed El Kaffas, Azza Al-Mahrouk, Ali Sadeghi-Naini and Gregory J. Czarnota, *Sunnybrook HSC, U. Toronto and Sheffield Hallam U., william.tran@sunnybrook.ca*

Purpose: This study evaluated clinical response to neoadjuvant chemotherapy using combined quantitative ultrasound (QUS) and diffuse optical spectroscopy imaging (DOSI) markers in locally advanced breast cancer (LABC).

Materials and Methods: The institution's ethics review board approved this study. Subjects (n=22) gave written informed consent prior to participating. US/DOSI data were acquired, relative to the start of neoadjuvant chemotherapy, at weeks 0, 1, 4, 8 and preoperatively. QUS parameters such as the mid-band fit (MBF), 0-MHz intercept (SI), and the spectral slope (SS) were extracted from tumor ultrasound data using spectral analysis. In the same patients, DOSI was used to measure several parameters including total hemoglobin (HbT), water fraction (%Water), scattering amplitude (SA) and the tissue optical index (TOI). Discriminant analysis and a receiver-operating characteristic (ROC) analyzed the performance of parameters in classifying ultimate clinical and pathological response during treatment. Additionally, multivariate analysis was carried out for QUS/DOSI pairwise combinations using a logistic regression model, and the area under the curve (AUC) was estimated.

Results: Individual QUS and DOSI parameters, such as the 0-MHz Intercept (SI), oxy-hemoglobin (HbO_2), and total hemoglobin (HbT) showed a significant difference between responders and non-responders after one week relative to the start of chemotherapy ($p<0.01$). Multivariate (pairwise) combinations of these parameters demonstrated an increase in the sensitivity, specificity and AUC at this time; the combination of SI+HbO_2 showed a sensitivity and specificity of 100%, and an AUC of 1.0. After four to eight weeks from the start of chemotherapy, combinations of QUS+DOSI parameters such as the QUS spectral slope (SS) and the SA improved the sensitivity and specificity and AUC (%Sn/%Sp= 71.4%-87.5%; AUC range 0.893-0.955), compared to classification estimates of those parameters alone.

Conclusion: QUS and DOSI demonstrated potential, as coincident markers for treatment response and may potentially facilitate response-guided therapies. Multivariate QUS and DOSI parameters may increase the sensitivity and specificity of classifying patients into chemotherapy response groups in locally advanced breast cancer, as early as one week after treatment.

2.3 **Early prediction of breast tumor response to chemotherapy using texture analysis of quantitative ultrasound parametric images,** Hadi Tadayyon, Mehrdad Gangeh, Lakshmanan Sannachi, Ali Sadeghi-Naini, William Tyler Tran, Maureen Trudeau and Gregory Czarnota, *U. Toronto and Sunnybrook HSC, gregory.czarnota@sunnybrook.ca*

Background: Locally advanced breast cancer (LABC) is an aggressive subtype of breast cancer whose response to chemotherapy treatment varies from patient to patient. Thus, frequent monitoring of LABC tumors makes early detection of refractory patients and switching to a more aggressive regimen possible. In this study, a quantitative ultrasound (QUS) imaging combined with texture analysis was used to characterize treatment response of breast tumors in LABC patients receiving neoadjuvant chemotherapy (NAC).

Methods: Radiofrequency ultrasound data were collected from 100 LABC patients prior to treatment and at weeks 1, 4, and 8 of their NAC treatment using a clinical ultrasound scanner operating a ~7 MHz linear array transducer. Within gated RF regions of interest inside the tumour, QUS images of parameters including midband fit (MBF), spectral slope (SS), spectral intercept (SI), spacing among scatterers (SAS), attenuation coefficient estimate (ACE), average scatterer diameter (ASD), average acoustic concentration (AAC), as well as their corresponding gray level co-occurrence matrix (GLCM) – based texture features including contrast (CON), correlation (COR), energy (ENE), and homogeneity (HOM) were computed and the results were compared with the patient's true response determined based on established clinical guidelines of tumour size reduction.

Results: Response classification analysis using a multiparametric k nearest neighbor classifier revealed the best set of QUS features for classifying response to be ASD_{HOM} at week 1, (SAS_{COR}, SS_{HOM}, ASD_{HOM},MBF_{ENE}) at week 4, and (MBF_{CON}, SS_{ENE}, SAS_{mean}) at week 8, with accuracies of 70%, 83%, and 73%, respectively.

Conclusion: This work demonstrated the potential of quantitative ultrasound texture features and machine learning methods for predicting the response of breast tumors to chemotherapy early and guiding the treatment planning of refractory patients.

2.4 **Monitoring clinical and pathological response of breast cancer to neoadjuvant chemotherapy using quantitative ultrasound method in conjunction with textural analysis,** Lakshmanan Sannachi, Hadi Tadayyon, Mehrdad Gangeh, Ali Sadeghi-Naini, William Tran, Sonal Gandh, Frances Wright and Gregory Czarnota, *Sunnybrook HSC and U. Toronto, gregory.czarnota@sunnybrook.ca*

Background: The aim of this study is to classify clinical/pathological response to neoadjuvant chemotherapy using quantitative ultrasound (QUS) and texture analysis techniques in patients with locally advanced breast cancer.

*Method***:** Thirty-six patients were enrolled into the study. Breast tumors were scanned with a 5 MHz clinical ultrasound system 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 the tumor region of interest. Additionally, texture features were extracted from all QUS parametric maps. Patients were classified into three treatment response groups based on pathological analysis: complete pathological response (CR), partial response (PR) and non-responders (NR). These classifications were determined by examining tumor diminishment and levels of cellularity of the mastectomy specimens after treatment. Response classifications from QUS parameters and pathological were compared. The classification analyses were performed on extracted parameters to differentiate CR, PR, and NR at all scan time points.

*Results***:** Combined mean QUS values and texture features of QUS parametric maps yielded the most accurate response classification, with accuracies of 72%, 81%, and 82% at weeks 1, 4, and 8, respectively. For responders, R (CR and PR) vs. NR classification, both mean values and texture features contributed almost equally at week 1, however, analysis based on the means of the QUS parameters provided higher accuracies at weeks 4 and 8. Furthermore, QUS parameters, in conjunction with texture features significantly improved responder and non-responder classification. For CR vs. PR classification, texture features estimated from structural parametric maps such as ASD, SS and SAS were the strong contributors at all scan time points. Classification accuracy based on these texture features were 76%, 69% and 94 % at week 1, 4, and 8 respectively.

Conclusions: This study demonstrated potential of texture characteristics of QUS parametric maps in tumor response classification early after the start of neoadjuvant chemotherapy. While QUS parameters were sufficient for responder and non-responder classification, second-order texture properties of those QUS parametric maps were required to further differentiate responder group into complete and partial responders.

2.5 **Real-time cancer treatment response monitoring using a GPU Accelerated Spectral Processing (GASP) system**, Naum Papanicolau, Ervis Sofroni, Alireza Sadeghian and Gregory Czarnota, *Ryerson U., Evrika Res. Tech., U. Toronto and Sunnybrook HSC, npapanic@scs.ryerson.ca*

Background: Quantitative ultrasound methods have been demonstrated to reliably detect changes in tissue morphology as a result of cancer treatment administration in a variety of experimental and clinical models. The ability to detect changes primarily related to tumor cell death has led to research in a variety of cancer treatment monitoring applications. Current methods of computing QUS parameters have limited cancer treatment monitoring applications to a post-processing computational paradigm, retarding the pace of research. In this study, we investigate the viability of a graphical processing unit (GPU) Accelerated Spectral Processing (GASP) real-time QUS device to detect changes in tumor microstructure as a result of cancer treatment administration during ultrasound data acquisition.

Methods: Experimentation was conducted using a SCID mouse model. Xenograft human prostate PC-3 tumors were grown on mouse hind legs to a size of 7-9 mm. Prior to image acquisition, mice were anesthetized with 100 mg/kg ketamine, 5 mg/kg of xyzaline and 1 mg/kg of acepromazine with the tumor and surrounding area epilated (Nair™ Church & Dwight Co.). Tumors were treated with activated microbubble therapy. Microbubble activation was achieved via an ultrasound excitation pulse centered at 500 kHz with a pulse repetition frequency of 3 kHz and peak negative pressure of 570 kPa for a total administration time of 750ms over a 5-minute period in order to avoid any potential hyperthermic effects on the tissue. ROI analysis of tumors was conducted using a GASP real-time QUS device coupled to a SonixTouch (Analogics Inc.) ultrasound device using a L14-5/4 transducer operating at ~7 MHz. Analysis was conducted prior to the onset of treatment, and at 24 hour following treatment administration. Rectangular regions of interest (ROI) were selected in the centre of each scan plane accounting for approximately 2/3 of the tumor cross sectional area and normalized to data previously collected from a glass bead embedded calibration phantom collected with the same acquisition settings. Spectra were computed for independent axial segments using a gate length of 10 wavelengths with axial and lateral overlaps of 95% and a Hanning window applied to each segment. Quantitative ultrasound parameters calculated included the midband fit (MBF), spectral slope (SS), spectral intercept (SI) which were compared to results from post-processing analysis computed in MATLAB.

Results: Changes in QUS parameters were found to be consistent with previous post-processing studies. Average changes in parameter values of ΔMBF – 6.005 dBr, ΔSS – 1.355 dBr/MHz and ΔSI -13.815 dBr were measured. Results demonstrated a high degree of agreement with post-processing CPU based analysis with an average difference of < 0.01% between data points in calculated parameter arrays. Histopathology results were confirmatory of tissue changes.

2.6 **Clinical cancer therapy assessment using multiview learning on quantitative ultrasound parametric maps**, Mehrdad J. Gangeh, Brandon Fung, Hadi Tadayyon, William T. Tran and Gregory J. Czarnota, *U. Toronto and Sunnybrook HSC, gregory.czarnota@sunnybrook.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 non-invasively, inexpensively, and quickly assess tumor response to cancer treatments using standard ultrasound equipment.

Methods: Fifty-six patients with locally advanced breast cancer (LABC) who received neoadjuvant chemotherapy were imaged before and at 4 times during treatment, i.e., weeks 1, 4, 8 and pre-operatively. Data were acquired using a Sonix RP ultrasound machine at a central frequency of ~7 MHz. Mid-band fit, 0-MHz intercept, and spectral slope parametric maps were computed by employing quantitative ultrasound spectroscopy techniques. The patients were grouped into responders and non-responders based on their ultimate clinical and pathological response to treatment. Since several parametric maps are available for each scan, one main question is how to combine the complementary information in these multiview representations to generate the most concise and discriminative features set. We propose to use supervised dictionary learning, an emerging machine learning algorithm in recent years, to compute one dictionary and subsequently sparse representations for each view (parametric map). Subsequently, the sparse coefficients, which are discriminative representations of the parametric maps in the space of learned dictionaries, were combined to generate the ultimate feature set. The feature sets computed for the “pre-treatment” scans as the baseline were compared with those computed on “mid-treatment” scans using a dissimilarity measure as an indication of treatment effectiveness. Eventually, the patients were classified as either responders or non-responders using a classifier based on the dissimilarities computed in the previous stage.

Results: The classification of 56 LABC patients treated with neoadjuvant chemotherapy to responders or non-responders using the proposed multiview supervised dictionary learning method resulted in an accuracy of 88.8 and 89.6, area under curve (AUC) of 0.88 and 0.84, sensitivity of 93.8% and 88.5%, and specificity of 83.8% and 90.8% after 1 and 4 weeks of treatment, respectively.

Conclusion: In this study, an advanced machine learning technique based on multiview learning was proposed to combine complementary information in multi-parametric maps computed using QUS methods. The effectiveness of the developed method was assessed on 56 LABC patients treated with neoadjuvant chemotherapy. The proposed system achieves a promising accuracy and sensitivity early after the start of treatment.

Outcome/Impact: The results of this study would permit clinicians to receive feedback and switch to alternate treatments far earlier, in a step towards the goals of *personalized medicine*.

2.7 **Improving targeting accuracy in abdominal proton therapy with real-time robotic ultrasound,** Kai Ding, Lin Su, Haibo Lin, Tuathan Oshea, Lulian Lordachita, Junghoon Lee, Sook Kien Ng, Yin Zhang, Ken Kang-Hsin Wang, John W. Wong, Emma Harris, Joseph M. Herman, H. Tutkun Sen, Peter Kazanzides, Muyinatu A. Lediju Bell and Chen Yang, *Johns Hopkins U., U. Pennsylvania, Inst. Cancer Res., UK and Zhe-jiang Cancer Hosp., China, kding1@jhmi.edu*

Purpose: Intrafraction target motion remains a major technical challenge for proton therapy to achieve its full potential. Emerging proton pencil beam scanning can significantly improve target conformity but it is susceptible to target motion. We have developed robotic arm and real-time ultrasound imaging based motion monitoring for abdominal proton therapy.

Methods: A 3D ultrasound probe with mechanical sweeping was modified with customized adapter to connect the probe to the robotic arm. Spider shaped infrared reflector was attached to the probe to improve the tracking accuracy. Clinically used infrared camera was mounted and calibrated to track probe position using infrared reflector on probe. For active arm system, it is composed of a 6 degree-of-freedom UR3 robot (Universal Robots, Odense, Denmark) and a force sensor mounted between the robot end-effector and the probe. A cooperative control software was also developed to facilitate the probe placement. The active arm systems were simulated for clinical feasibility to meet requirements for simulation and treatment procedures with an abdominal ultrasound phantom which was secured on a programmable respiratory motion platform to simulate free breathing motion. Speckle tracking algorithm was developed to track motion from the ultrasound images.

Results: During the repeated robotic arm probe placement test, the probe position showed high reproducibility (0.08 ± 0.03 mm). For target motion monitoring, ultrasound speckle tracking showed high accuracy for three different scanning protocols (0.21 ± 0.29 mm for 0.3 Hz, 0.20 ± 0.27 mm for 1 Hz and 0.29 ± 0.28 mm for 11Hz).

Conclusion: Our robotic ultrasound system was able to produce highly reproducible probe position. Ultrasound speckle tracking showed our system is able to provide 3D motion monitoring at as high as 11 Hz with high accuracy. Our system provides a solution that can potentially improve the abdominal proton therapy by monitor real-time target 3D motion.

Wednesday afternoon

3. IMAGING 1

3.1 **Resolution enhancement of B-mode ultrasound imaging with stabilized inverse filters**, Shujie Chen and Kevin Parker, *U. Rochester*, *kevin.parker@rochester.edu*

Many pulse-echo imaging systems' lateral resolution is improved by focusing, where the beam width is determined by the choice of source and apodization function, the frequency, and the physics of focusing. Based on the convolution model and Z-transform analysis, inverse filtering can be performed to the RF data to further enhance the resolution. However, this is limited by the need for conditioning due to the instabilities of the inverse filters. In this work, an analysis is presented that defines key constraints on the shape and sampling of lateral beam patterns. Within these constraints are useful symmetric beam patterns which, when properly sampled, can have a stable inverse filter. Specifically, for the approximately Gaussian-apodized broadband focal beam patterns, stable inverse filters are pre-designed with parameterization and applied to the beamformed RF scan lines.

The proposed method is applied to the B-mode ultrasound images either simulated in Field II or imaged by a Verasonics scanner with an ATL L7-4 transducer operating at 5 MHz. Simulation using Field II shows higher resolution for scatterers, anechoic cysts, hyperechoic lesions, and blood vessels at 50 mm depth. Specifically, scatterers 1.1 mm apart are resolved, and a 3 mm blood vessel is opened from barely visible to about 2.1 mm. Furthermore, the imaging of an ATS 535 QA phantom with focus at 50 mm shows that the -20 dB width of a line target is decreased to 1.19 mm from 2.26 mm, and a small 4 mm cyst is opened from 1.4 mm to 3.0 mm. *In vivo* imaging of the human carotid artery demonstrates the opening of the arterial lumen and a better-defined arterial wall.

In summary, an inverse filtering approach has been designed in the context of the convolution model and the Z-transform. A framework for analysis and processing is developed for the enhanced lateral resolution that can be realized. This framework can also be applied to improve axial resolution, where the concept of stabilized inverse filters guides the selection of the pulse shape,

3.2 **Comparison of image quality metrics for B-mode and SLSC as a function of lag**, Katelyn Flint, Vaibhav Kakkad, David Bradway, Sarah Ellestad and Gregg Trahey, *Duke U.*, *katelyn.flint@duke.edu*

During the first trimester of pregnancy, fetal ultrasound is a standard procedure that is used to assess fetal development and maternal health. Ideally, a first trimester fetal ultrasound allows for the visualization of key fetal structures and assessment of the number of fetuses, location of the placenta, and maternal pelvic structures. However, many prenatal ultrasound scans result in sub-optimal images. A novel beamforming method, short-lag spatial coherence (SLSC), was developed, which has potential to improve fetal ultrasound image quality. Conventional B-mode images delay and sum radio frequency (RF) backscattered echoes to produce images of the echo amplitude. Alternatively, the focused signals can be processed to compute the similarity of the time-delayed received signals across the transducer array as a function of their spatial separation, or lag, to create SLSC images.

We present preliminary image quality comparisons between matched SLSC and B-mode images. The images are part of an ongoing study of coherence-based fetal ultrasonic imaging, which to date has included 24 patients. All patients were scanned at the Fetal Diagnostic Center in accordance with the Duke University Medical Center Institutional Review Board. Measurements were made to ensure that the ultrasound sequences were below the safety limits of the FDA for I_{SPPA} and heating. The image quality metrics compared include signal-to-noise ratio, contrast, and contrast-to-noise ratio and, for SLSC images, are assessed as a function of lag. Lag is a parameter of the SLSC image and is typically chosen empirically. However, in this study, we optimized lag for each image quality group based on CNR. We collected images of the following fetal structures: cerebral ventricles, stomach, cord insertion, nuchal translucency, and bladder. For the image quality comparison in this study, we focused on the fetal ventricles. Statistically significant improvements have previously been shown across all imaging metrics for SLSC compared to B-mode with a static lag of 20% used for all patients. This study expands upon those results to include more patients, to show how the image quality metrics vary as a function of lag, and to assess how different patients would benefit from SLSC images created with different amounts of lag. Supported by NIH grant R01-EB017711 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.

3.3 **Compound coherent plane-wave imaging of the eye**, Ronald H. Silverman, Raksha Urs and Jeffrey A. Ketterling, *Columbia U. and Riverside Research, rs3072@cumc.columbia.edu*

Background: Diagnostic ultrasound imaging of the eye is currently conducted virtually exclusively with mechanically scanned, single-element focused transducers. Linear-array technology is largely absent due to the difficulty and expense in fabrication of high-frequency (>10 MHz) linear arrays and stringent FDA acoustic intensity guidelines for the eye. As a consequence of using mechanically scanned probes, ophthalmic imaging rates are comparatively slow (<10 Hz) and Doppler modes are unavailable. Compound coherent plane wave techniques in combination with recently developed high frequency linear arrays offer the potential for a vast improvement in frame rate and low acoustic intensity within FDA guidelines.

Methods: A programmable Verasonics Vantage-128 imaging system was used with human subjects after the acoustic intensity output by a 128-element 18 MHz linear array operated conventionally and in plane-wave mode was measured with a calibrated hydrophone. Resolution and signal-to-noise (SNR) were characterized by scanning a 20-μm diameter polypropylene thread. The posterior pole of a human subject was imaged with three modes: compound coherent plane-wave B-mode, real-time plane-wave color-flow Doppler, and high-resolution depiction of slow-flow in post-processed multi-angle plane-wave data collected continuously at 10,000 frames/sec.

Results: With the array operated conventionally, Doppler modes exceeded FDA 510k safety guidelines for ophthalmology, but plane-wave modalities were compliant. Plane-wave data allowed generation of high-quality compound B-mode images. SNR improved with the number of angles compounded, but lateral resolution was affected only by angle range. Real-time color-flow Doppler readily visualized orbital blood flow. Post-processing of continuously acquired, 2-second data blocks allowed high-resolution depiction of orbital and choroidal flow over the cardiac cycle.

Conclusions: Plane-wave techniques present opportunities for the evaluation of ocular anatomy, blood flow and visualization of other transient phenomena that are not possible with current clinical instrumentation. Supported in part by NIH grant EY025215 and an unrestricted grant to the Department of Ophthalmology of Columbia University from Research to Prevent Blindness.

3.4 **Quantitative imaging of electrical conductivity by VHF- induced thermoacoustics**, S.K. Patch, D. Hull, W.A. See and G.W. Hanson, *U. Wisconsin-Milwaukee, patchs@uwm.edu*

Background: Very high frequency (VHF) induced thermoacoustics has the potential to provide quantitative images of electrical conductivity in Siemens/meter, much as shear wave elastography provides tissue stiffness in kPa. Quantitatively imaging a large organ requires exciting thermoacoustic pulses throughout the volume and broadband detection of those pulses because tomographic image reconstruction preserves frequency content. Applying the half-wavelength limit to a 200-micron inclusion inside a 7.5 cm diameter organ requires measurement sensitivity to frequencies ranging from 4 MHz down to 10 kHz, respectively.

VHF irradiation provides superior depth penetration over near infrared used in photoacoustics. Additionally, VHF signal production is proportional to electrical conductivity, and prostate cancer is known to suppress electrical conductivity of prostatic fluid.

Methods: A dual-transducer system utilizing a P4-1 array connected to a Verasonics V1 system augmented by a lower frequency focused single element transducer was developed. Simultaneous acquisition of VHF-induced thermoacoustic pulses by both transducers enabled comparison of transducer performance. Data from the clinical array generated a stack of 96-images with separation of 0.3 mm, whereas the single element transducer imaged only in a single plane. In-plane resolution and quantitative accuracy were measured at the isocenter.

Results: The array provided volumetric imaging capability with superior resolution whereas the single element transducer provided superior quantitative accuracy. Combining axial images from both transducers preserved resolution of the P4-1 array and improved image contrast. Neither transducer was sensitive to frequencies below 50 kHz, resulting in a DC offset and low-frequency shading over fields of view exceeding 15 mm. Fresh human prostates were imaged *ex vivo* and volumetric reconstructions reveal structures rarely seen in diagnostic images.

Conclusions: Quantitative whole-organ thermoacoustic tomography will be feasible by sparsely interspersing transducer elements sensitive to the low end of the ultrasonic range.

3.5 **Perfusion imaging with non-contrast ultrasound using adaptive clutter demodulation**, Jaime E. Tierney and Brett C. Byram, *Vanderbilt U., jaime.e.tierney@vanderbilt.edu*

A Doppler ultrasound clutter filter that enables estimation of low velocity blood flow could considerably improve ultrasound as a tool for clinical diagnosis and monitoring, including the evaluation of vascular diseases and tumor perfusion. Conventional Doppler ultrasound is currently used for visualizing and estimating blood flow. However, conventional Doppler is limited by frame rate and tissue clutter caused by involuntary movement of the patient or sonographer. This involuntary motion results in spectral broadening of the clutter, which means that conventional filters employed to effectively eliminate tissue clutter also eliminate signal from slow moving blood. Due to this spectral broadening, it has been assumed for years that ultrasound is only sensitive to blood velocities greater than 5mm/s for imaging frequencies less than 8MHz. Unfortunately, this limits visualization of blood flow to vessels larger than venules and arterioles.

To overcome this long-standing limitation in the field, we propose a clutter filtering technique that may increase the sensitivity of Doppler measurements to at least as low as 0.41mm/s. The proposed filter uses an adaptive demodulation scheme that decreases the bandwidth of the clutter. To test the performance of the adaptive demodulation method at removing sonographer hand motion, six volunteer subjects acquired data from a basic quality assurance phantom. Additionally, to test initial *in vivo* feasibility, an arterial occlusion reactive hyperemia study was performed to assess the efficiency of the proposed filter at preserving signals from blood velocities 2mm/s or greater. The hand motion study resulted in initial average bandwidths of 577Hz (28.5mm/s), which were decreased to 7.28Hz (0.36mm/s) at -60 dB at 3cm using our approach. The *in vivo* power Doppler study resulted in 15.2dB and 0.15dB dynamic ranges of the blood flow with the proposed filter and conventional 50Hz high pass filter, respectively.

4. TISSUE PARAMETERS 1

4.1 **Evaluating the robustness of an ultrasound-based control strategy for upper extremity prosthesis and preliminary amputee trials**, Nima Akhlaghi, Alex Baker, Ananya Dhawan, Huzefa S. Rangwala, Jana Kosecka and Siddhartha Sikdar, *George Mason U., ssikdar@gmu.edu*

Current commercially available prostheses based on myoelectric control have limited functionality, leading to many amputees abandoning their use. Myoelectric control using surface electrodes has a number of limitations and lacks specificity for deep muscles, presenting a continued need for more robust strategies. We propose a new strategy for sensing muscle activity based on real-time ultrasound imaging. Results from our previous work demonstrate that complex motions could be classified with 92% accuracy in real-time. However, arm and hand repositioning tends to alter the geometry of forearm musculature, possibly affecting performance. To evaluate the robustness of this strategy in the presence of varied forearm positions, preliminary ultrasound imaging data of the forearm muscles of one subject was collected during 2 different scenarios using a Sonix RP with a 5-14 MHz linear probe. The subject was asked to perform four hand motions at 8 different arm positions and 3 levels of wrist pronation. Images were analyzed to generate activity patterns for each motion and then classified. Results demonstrate that forearm positions do not significantly compromise reliability, and that performance could be improved by including additional reference activity patterns corresponding to motions performed in problematic positions. Furthermore, we have preliminary data showing that transradial amputees could control a virtual hand in real-time.

4.2 **Comparison of ultrasound-based muscle-tracking algorithms**, Paul Otto, Frances Sheehan, Jennifer Jackson and Siddhartha Sikdar, *George Mason U. and NIH, ssikdar@gmu.edu*

Background and Objective: Ultrasound imaging (US) has become an important tool for tracking tissue motion in a number of applications, including dynamic functional assessment of muscles and tendons. Quantification of tissue motion using ultrasound has traditionally used speckle tracking. However, speckle tracking is limited by speckle decorrelation, especially with fast motion. Therefore, the objective of this work is to improve the accuracy of tissue velocity estimation by intelligently aggregating the results of multiple velocity estimation algorithms. These techniques can be used for estimating tissue motion using B-mode imagery from commercially-available equipment. In this paper, we demonstrate the improvement of the proposed algorithm over speckle tracking for an application involving estimation of muscle kinematics.

Methods: We investigated the accuracy of determining the rectus femoris muscle velocities using US imaging against cine phase contrast (CPC) magnetic resonance (MR) imaging. We recruited 10 healthy volunteers for this study. Each subject was first placed in a supine position in the MRI scanner with their knee slightly bent and supported by a cushion. The subject performed cyclic knee flexion and extension to the rhythm of a metronome, while CPC anatomic images and velocity data were collected. Then the subject remained on the scanning plinth as it was moved out of the MR scanner to an exam room. The rectus femoris was then imaged using an Ultrasonix SonixTouch US system and a 5-14 MHz linear array transducer while the subject repeated the same cyclic motion.

Two US image analysis methods are used to quantify muscle kinematics. Speckle tracking using a block-based normalized cross correlation was applied along an average grid spacing of 2.5 mm covering the image frame. This spacing balanced compute time with an assumed maximum per frame motion of 2 mm. The velocity estimates are calculated at each point on the grid. Our proposed method, an aggregation of feature displacement algorithms, measures velocity by a combination of adaptive and static techniques. The adaptive techniques use a combination of Harris corner detection along with edge enhanced energy maps to find locations for the feature displacement estimate. The static techniques rely on estimating velocity along a predetermined grid using optical flow or normalized crosscorrelation techniques. Once a high quality feature locations are identified, the feature point displacements are tracked over multiple B-mode frames until the feature points' quality criteria falls below a set threshold, typically due to speckle decorrelation.

4.3 **Analysis of plaque tissue motion in carotid artery using B-mode images**, Amir A. Khan, Joe Hecker, Brajesh K. La and Siddhartha Sikdar, *George Mason U. and U. Maryland, Baltimore, ssikdar@ gmu.edu*

Investigation of carotid atherosclerosis using ultrasound imaging has been clinically proven to be a critical tool for studying the precursors to stroke. However, the analysis of the acquired ultrasound images is still an open research problem. Recent studies have demonstrated the potential of analyzing plaque motion using B-mode cine loops. However, *in-vivo* results are fairly limited in literature and those too are derived from carefully controlled lab based samples with good image quality and acquisition rate. In this work, we present a framework based on dense optical flow for characterizing plaques on a large *in-vivo* data set acquired at clinical setup with variable acquisition parameters (acquisition frequency, image quality and observers). We propose some metrics for post-analysis of the motion vectors in the plaque region and at the vessel walls. The eventual goal is to establish the viability of these motion based techniques for characterizing plaque severity. In this regard, we also explore the influence of plaque tissue composition on the overall metrics as well as the variability of these metrics across different patients and plaque types.

4.4 **Effect of gate location on ultrasonic backscatter difference measurements of bone**, Brent K. Hoffmeister, Joseph A. McPherson, Peyton L. Marshall, Ann M. Viano and Phoebe C. Sharp, *Rhodes Coll., hoffmeister@rhodes.edu.*

Background & Objective: Ultrasonic backscatter difference techniques are being developed to detect changes in cancellous bone caused by osteoporosis. Backscatter difference measurements analyze the power difference between two gated portions of a backscatter signal. The goal of this study is to investigate how gate location affects backscatter difference measurements of bone.

Methods: Backscatter measurements were performed on thirty cube-shaped specimens of human cancellous bone using a broadband 3.5 MHz transducer. Backscatter signals were partitioned into five consecutive 1 microsecond gated portions, starting 2 microseconds after the front surface echo. The gated portions were numbered 1 through 5 from earliest to latest, respectively. The normalized mean backscatter difference, nMBD, was measured for ten different gate pairs by computing the power difference in decibels between the two gated portions of the signal and dividing by their time separation. Linear regression analysis was used to measure the correlation of nMBD with the bone mineral density of the specimens.

Results: The weakest correlation between nMBD and bone density was observed for the gate pair consisting of the latest two gates, gates 4 and 5, (R_{45} = 0.20). Strongest correlations were observed for gate pairs consisting of the earliest gate, gate 1, and any later gate (R_{12} = 0.85, R_{13} = 0.90, R_{14} = 0.90, R_{15} = 0.87). The correlation coefficients R_{12}, R_{13}, R_{14} and R_{15} were not significantly different from each other.

Conclusions: nMBD is optimized as a bone assessment parameter when one gate of the pair is located on an early portion of the backscatter signal after the front surface echo. The location of the other gate is less important. Supported by NIH grant R15AR066900.

4.5 **Acoustic-impedance analysis for fatty-acid species identification in liver using high-frequency ultrasound**, Kazuyo Ito, Kenji Yoshida, Hitoshi Maruyama, Jonathan Mamou and Tadashi Yamaguchi, *Chiba U. and Riverside Research, k_ito@chiba-u.jp*

Objectives: Accurate discrimination of non-alcoholic steatohepatitis (NASH) from simple fatty liver is a critical issue in current clinical practice because NASH may progress to cirrhosis or even liver cancer. Some reports have shown differences in the content of free fatty acid (FFA) between controls and patients with NASH. Thus, an ultrasound-based diagnostic tool for NASH could be developed based on the acoustical properties of FFAs. This study investigated the use of scanning acoustic microscopy (SAM) to measure the acoustic impedance of FFAs in order to better understand how FFA content affects the acoustic properties of liver cells at the microscopic level.

Methods: Three types of samples were measured: four pathological types of harvested mouse livers; cultured cells and five kinds of FFAs (i.e., palmitate, oleate, palmitoleate, linoleate and alpha-linolenic); and. A SAM system (modified AMS-50SI, Honda Electronics Co., Ltd, Japan) using an 80-MHz center-frequency transducer with PVDF-TrFE membrane was employed. The spatial resolution of the resultant image was 20 μm. The acoustic impedance was computed from the echo amplitude and the pressure-reflection coefficient. The 2-D map of acoustic impedance was obtained by scanning the transducer in 16-μm steps. Three independent measurements of each sample were performed, and the average and standard deviation of the acoustic impedance were calculated.

Results: The calculated average ± standard deviation of the acoustic impedances of normal, simple fatty liver, NASH, and cirrhotic mouse livers were 1.73 ± 0.05, 1.66 ± 0.07, 1.64 ± 0.06 and 1.69 ± 0.05 ($\times 10^6$ kg/m^2/s), respectively. These results showed that the average acoustic impedance of NASH liver is lower than that of the other livers investigated. Results obtained in FFA solutions and cultured cells with FFA solutions demonstrated significant differences of acoustic-impedance ($p < 0.01$) for all paired tests, except for palmitate and linoleate. From these results, significant differences were observed between the palmitate acid (which is the main component of simple fatty liver) and oleic acid (which is the main component NASH) in three different kinds of samples. Therefore, these initial results suggest that NASH identification and characterization using *in-vivo* quantitative ultrasound methods may be possible.

4.6 **Characterization of vascular networks using multiple scattering of ultrasound**, Aditya Joshi, Gianmarco Pinton and Marie Muller, *North Carolina State University, Raleigh and U. North Carolina, Chapel Hill,aajoshi4@ncsu.edu*

Background: Angiogenesis is the physiological process through which new blood vessels form from pre-existing vessels. There is a significant difference between the architectural properties (orientation, density etc.) of healthy vascular networks and the angiogenic networks associated with malignant tumors. Traditional ultrasonic imaging methods do not have sufficient spatial resolution to characterize the micro-architecture of angiogenic vessels. We present a quantitative and noninvasive diagnostic technique, based on multiple scattering (MS) of ultrasound that characterizes the architectural properties of angiogenic vascular networks. Ultrasonic waves are scattered multiple times collecting, over time, information on the vessel microstructure. These signals are used to retrieve quantitative parameters, such as the scattering mean free path, which provides the mean distance between vessels.

Ultrasound contrast agents in the form of lipid microbubbles injected in the blood flow are excellent ultrasound scatterers, which enhance the MS contribution to backscattered signals. In this paper, we demonstrate that MS can be used to retrieve the distance between vessels filled with microbubbles by measuring the scattering mean free path.

Methods: Finite difference time domain (FDTD) simulations were used to model ultrasound propagation through water containing 3 vessels filled with lipid shelled microbubbles at 1% concentration.. A 64 elements linear array with a 10 MHz central frequency was simulated. The impulse response matrix of the medium was acquired using the following sequence: one by one, every single element of the array was used to transmit a 10 MHz short pulse with a 300 kPa amplitude. For every transmit, the backscattered signals were collected on all elements of the array. FDTD simulations were conducted using the Fullwave simulation tool that models a heterogeneous nonlinear attenuating wave equation developed by Pinton et al.[3] The specific response of the microbubbles to the incident pulse was simulated using a model by Paul et al.[1] which was developed based on a bubble oscillation by Sarkar et al.[2].To account for multiple scattering interactions between the microbubbles, a new iterative approach combining the bubble model and the Fullwave propagation model was developed. The scattering mean free path was determined from the impulse response matrix by measuring the ratio of multiple scattering to single scattering with a method described in Derode et al.[4]

Results: Simulations were conducted by varying the distance between the vessels from 50 micron to 300 microns in steps of 50 microns. For distances between vessels greater than 100 microns, the scattering mean free path was measured and was found to be within 15% from the actual distance simulated between the vessels.

Actual distance between vessels (microns)	Distance measured using the scattering mean free path (microns)
50	78.13
100	114.32
150	168.74
200	206.57
250	261.83
300	314.78

Conclusions: These results suggest the potential of combining microbubbles and ultrasound multiple scattering to retrieve micro-architectural properties such as the distance between vessels. A potential application of this approach will be the characterization of angiogenic networks for cancer diagnosis.

(1) Sarkar, W.T. et al., *J Acoust Soc Am 118*, 539–550 (2005). (2) Paul, S. et al *J Acoust Soc Am 127*, 3846–3857 (2010). Gianmarco et al., *IEEE Trans Ultrason Ferroelec Frequency Contr 56* (2009). (4) Arnaud Derode et al. *Appl Physics Lett 87*, 114101 (2005).

4.7 **Correlation between ultrasound clutter and tissue structure assessed by histology**, Jasmine Shu and Brett Byram, *Vanderbilt U., jasmine.l.shu@vanderbilt.edu*

Background & Objectives: Diagnostic ultrasound often suffers from image degradation, especially when imaging through the abdominal layer. One notable source of image degradation is reverberation clutter, which occurs when ultrasound signal reflects repeatedly between tissue layers. Also referred to as multiple scattering, these acoustic reflections cause a time delay in the return signal, which results in an apparent haze that is particularly detrimental to visualizing anechoic regions. Previously, studies have shown a dependency on connective tissue and abdominal compression, but most results have been limited to simulations. This study uses *ex vivo* goat tissue to determine the effect of abdominal wall tissue structures on the magnitude of reverberation clutter.

Methods: Clutter was introduced by imaging through goat abdominal wall samples into a water tank (n=6). With a curvilinear probe (Cephasonics, San Jose, CA) in contact with the tissue, channel data were acquired in parallel. The data was beamformed and analyzed in MATLAB. Post data collection, 2 tissue cross-sections per sample were cut out and fixed in 10% formalin for at least 24 hours. The samples were then stained with Masson's trichrome and the slide images segmented into sections of muscle, adipose, and connective tissue. Tissue layers were counted and the values were averaged between the 2 cross-sections. Multiple regression was used to identify possible correlations between measured clutter magnitude at various laterally averaged depths below the tissue and sample thickness, number of tissue layers, and relative amounts of muscle, fat and connective tissue types.

Results: On examining the B-mode images, mirror image reverberation artifacts occurred in all the samples to varying degrees. Abdominal wall samples averaged 1.05cm (0.913cm to 1.25cm) thick. At a depth of 0.75cm below the tissue, within the location of the mirror image artifacts, a multiple regression of clutter magnitude as a function of relative connective tissue content and number of tissue layers revealed an indirect relationship (R2=0.981). Equivalent calculations with muscle tissue and adipose tissue yield R2 values of 0.312 and 0.100, respectively. Multiple regression showed sample thickness and number of tissue layers did not have a strong correlation to clutter power just below the tissue sample (R2=0.271 at 0.75cm), but they do weakly correlate past the reverberation artifacts (R2=0.765 at 2cm, R2=0.785 at 3cm). Single linear correlations did not show strong correlations, possibly due to the small sample size.

Conclusions: Multiple regression results demonstrate clutter power is correlated to connective tissue and the number of tissue layers to a greater degree than muscle or adipose tissue. In contrast, thickness and number of tissue layers do not strongly correlate to the power of mirror image artifacts, but may be related to diffuse clutter farther beyond the abdominal wall tissue.

Thursday morning

5. PHOTOACOUSTICS

5.1 **Photoacoustic imaging of muscle oxygenation during exercise,** Clayton A. Baker, Nashaat Rasheed, Parag V. Chitnis and Siddhartha Sikdar, *George Mason U., cbaker6@gmu.edu*

Monitoring muscle hemodynamics and oxygenation is important for researching muscle function and fatigue. The current state-of-the-art for noninvasive oximetry is near-infrared spectroscopy (NIRS), which makes use of differences in the absorption spectra of oxy- and deoxy-hemoglobin to provide relative oxygen saturation (sO2) with good sensitivity. However, NIRS has limited spatial resolution and depth sensitivity. In many applications, such as imaging injury and inflammation, it is important to provide anatomically registered oxygenation maps. Photoacoustic (PA) imaging has been proven capable of determining sO2 via the same spectroscopic mechanism as NIRS, and allows for direct spatial correspondence with conventional ultrasound (US) images collected in synchrony.

In this study, we demonstrated the utility of a dual-modality system imaging system capable of generating co-registered US and PA images for real-time, functional imaging of muscle oxygenation. All study procedures were approved by our Institutional Review Board. The system consisted of a wavelength-tunable pulsed laser (Opotek) integrated with a research ultrasound system (Verasonics). US images provided anatomical context and the PA images acquired at 690 nm and 830 nm were processed to estimate sO2 during a sustained isometric contraction and return to rest. PA-based sO2 was compared to measurements acquired from a commercially available NIRS oximeter under the same conditions. Preliminary results showed good qualitative agreement between sO2 dynamics observed via PA-based approach and NIRS, with contraction coinciding with an exponential decay in sO2, and relaxation with a return to original levels. This *in vivo* study demonstrated the feasibility of PA imaging for measuring temporally and spatially resolved muscle oxygenation during functional tasks.

5.2 **Assessment of photoacoustic-based sO2 estimation in an excised prostate,** Trevor Mitcham, Houra Taghavi, Dvid Fuentes, John Ward, Brian Hobbs and Richard Bouchard, *U. Texas MD Anderson Cancer Ctr. and U. Texas at Houston, rrbouchard@mdanderson.org*

Background and Objective: Hypoxia, a region of low oxygen concentration in tissue, is known to commonly occur in tumors. The presence of hypoxic regions can lead to reduced efficacy of radiotherapy and chemotherapy treatments; however, treatment planning can compensate for this effect if the location and extent of the hypoxic regions are known. Spectroscopic photoacoustic (sPA) estimation of oxygen saturation (sO_2) in the blood supply can be used to assess the location of hypoxic tissue. An sO_2 estimate can be made using sPA imaging due to the unique absorption properties of oxy- and deoxyhemoglobin in the low-NIR wavelength range. The estimate can be improved through the use of multiple wavelengths as well as reducing the optical path length through the use of an interstitial irradiation fiber in the tissue of interest. In this study, we investigate the precision and accuracy of PA estimation of sO_2 values of oxygenated and deoxygenated *ex vivo* blood introduced into an *ex vivo* bovine prostate when imaged with an interstitial irradiation source and a conventional transrectal ultrasound (TRUS) transducer.

Methods: Heparinized *ex vivo* bovine blood was prepared at various sO_2 levels via a titration method consisting of bubbling pure oxygen or nitrogen into a flask filled with blood to oxygenate or deoxygenate the hemoglobin. Upon reaching saturation in each flask, the blood was mixed to a specified sO_2 and verified using a CO-oximeter. First, accuracy and precision of PA sO_2 estimates were determined on the Vevo 2100 LAZR system with a 21-MHz transducer (VisualSonics) in a phantom model with known scattering and absorption. Once precision and accuracy were determined in a phantom environment, blood of a known sO_2 was injected into tubing embedded into an *ex vivo* bovine prostate, and sPA imaging was conducted to estimate the oxygenation concentration using a Vantage 128 US imaging system (Verasonics) and a C9-5 TRUS transducer. Additionally, the accuracy and precision of PA estimates using a basic 2-wavelength compared to a more robust multiple-wavelength (up to 6) acquisition were compared at each step.

Results: Phantom sO_2 estimation determined that 2-wavelength PA estimation consistently overestimated sO_2 values by 10% between 20% and 80% oxygenation, while the use of 6 wavelengths provided significantly improved precision and accuracy. PA estimation of sO_2 was possible in the *ex vivo* prostate at a depth of 3 cm from the TRUS surface.

Conclusion: In order to generate accurate PA sO_2 estimations *in vivo*, estimation techniques and light delivery must be carefully considered. In any setting, high precision is possible, leading to the possibility of matched comparisons in longitudinal studies. Spectroscopic PA imaging with an interstitial irradiation source should allow for optimal accuracy and precision of sO_2 estimates at depth *in vivo*.

5.3 **Study of photoacoustic measurement of bone health based on clinically-relevant models**, Xueding Wang, Ting Feng, Meng Cao, Kenneth M. Kozloff, Jie Yuan and Cheri X. Deng, *Tongji U., U. Michigan and Nanjing U., xdwang@umich.edu*

Photoacoustic (PA) imaging and sensing techniques evaluate bone based on highly sensitive optical contrast which holds distinctive advantages over conventional quantitative ultrasound methods. In previous work, the capability of PA techniques for bone evaluation has been evaluated on small-animal models. Before potentially translating the techniques to clinical management of osteoporosis, the feasibility of PA imaging and sensing in dealing with clinically relevant bone models still needs to be investigated. In this work, we first studied the optical and ultrasonic penetration in bone which determines the PA imaging depth. Then PA imaging and quantitative evaluation of bone physical properties, including bone mineral density and bone micro-architecture, has been explored. We have also evaluated the feasibility of multi-spectral PA (MSPA) measurement for assessing the chemical changes in bone specimens. Experimental results from cow bones demonstrate that PA penetration is sufficient to probe trabecular bone through cortical layer and soft tissues. PA images can reflect the changes in bone microstructure, including the decreased cortical thickness and enhanced porous feature as results of treatment using ethylene diamine tetraacetic acid (EDTA). By performing quantitative PA spectral analysis (PASA), bone specimens before and after EDTA can be successfully differentiated. MSPA also shows capability to sense the chemical changes in bones after EDTA treatment. Besides the studies on cow bones, we have also started a clinical study on human bones *in vivo*. Initial results suggest that the PA signal from trabecular part in human radius bone can be detected through cortical layer and overlaying soft tissues non-invasively with a good signal to noise ratio. PA signal from the trabecular part contains sufficient high frequency component that is essential for successful PASA. Moreover, the MSPA measurement from human radius bone shows similar optical absorption spectrum as that from fresh cow bones, suggesting that PA technique can study not only physical properties but also chemical properties in human bones *in vivo*.

[1] American Cancer Society Facts and Figures (2016). (2) Sadigh et al., *European Radiology*, 1006-1014 (2012). (3) Mehrmohammadi M et al., *Current Molecular Imaging 2*, 89 (2013). (4) Boyd NF et al., *JNCI 102*, 1224-1237 (2010). (5) Duric et al., *2008 International Conf BioMed Engineer Informatics*, pp. 713-717 (2008).

5.4 **Characterizing intestinal strictures with acoustic resolution photoacoustic microscopy**, Guan Xu, Hao Lei, Sheng-chun Liu, Laura A. Johnson, David Moons, Peter D.R. Higgins, Jun Ni and Xueding Wang, *U. Michigan*, *guanx@umich.edu*

Crohn's disease (CD) is an autoimmune disease of the intestinal tract affecting 700,000 people in the United States. The pathology of CD is characterized by obstructing intestinal strictures due to inflammation, fibrosis, or a combination of both. Inflammatory strictures are medically treated. Fibrotic strictures have to be removed surgically. The accurate assessment of the strictures is thereby critical for the management of CD. The standard procedure for characterizing an intestinal stricture is endoscopic biopsy in which small sample pieces are extracted for histopathology. Conclusive diagnoses are reached by observing the histochemical content and stratified microarchitecture within the samples. Most concurrent imaging modalities can only assess either of the histological features. This study proposes an endoscopic, acoustic resolution photoacoustic (PA) microscopy system for characterizing intestinal strictures. The PA microscopy system can assess the histological features of the strictures at ultrasonic resolution and optical sensitivity. The noninvasive diagnostic approach allows unlimited sampling locations. A tunable laser with output range of 680-1700 nm was used to cover the strong optical absorption of hemoglobin and collagen, correlated to inflammatory and fibrotic strictures, respectively. A ring illumination pattern was generated at the sample surfaces with optical intensity of 1 mJ per square centimeter. An US transducer with bandwidth of 20 MHz, central frequency of 50 MHz and focal length of 3 mm was used to acquire the PA signals. Imaging experiments on animal and human intestinal tissues have validated that the proposed approach can assess the histochemical content and microarchitecture of intestinal strictures.

6. TISSUE PARAMETERS 2

6.1 **Quantitative ultrasound of the uterine cervix in late stage pregnancy**, Quinton W. Guerrero, Lindsey C. Drehfal, Ivan Rosado-Mendez, Helen Feltovich and Timothy J. Hall, U. *Wisconsin and Intermountain Healthcare*, *qguerrero@wisc.edu*

Objectives: Acoustic attenuation in the human cervix has been shown to change throughout gestation and when softening is exogenously induced (using misoprostol). Quantitative ultrasound parameters measured in the cervix have been shown to be heterogeneous and anisotropic in an *ex vivo* study. The magnitude of backscatter anisotropy at the end stages of pregnancy has not been reported and could be a source of bias in attenuation estimates. The goal of the study was to quantify backscatter parameter anisotropy in the 3rd trimester when the cervical microstructure has undergone the (nearly) full extent of remodeling.

Methods: Women at 37-41 weeks gestation undergoing cervical softening for induction of labor were recruited (n=20). Examinations, performed before and 4 hours after administration of misoprostol, consisted of a transvaginal ultrasound measurement on the anterior portion of the cervix in the middle to mid-proximal region. Cervices were scanned 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 frames were collected at 21 different angles, from -40 degrees to +40 degrees in steps of 4 degrees. Subjects were divided into two groups, "not-in-labor" and "marked-progression" (of labor), based on clinical evaluation at the second examination. Reference phantom data was collected for the same angles and quantitative ultrasound parameters were calculated using the Reference Phantom Method. Attenuation estimate bias was minimized with respect to spectral estimation regions and parameter estimation regions using the multitaper method.

Results: A paired analysis of attenuation estimates in each individual measured 4 hours after misoprostol administration showed no significant change compared to pre-administration measurement in either group. Mean attenuation before the administration of misoprostol was significantly higher ($p<0.01$) in the marked-progression group versus the not-in-labor group (2.38±0.33 vs 1.37±0.10 dB/cm-MHz (mean±SE), respectively). Attenuation dependence on interrogation angle and backscatter anisotropy, observed in non-pregnant *ex* vivo specimen, was not observed in the 3rd trimester. Results of this study suggest, in this late stage of pregnancy, the cervical collagen structure has broken down which is consistent with observations in animal models. 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.

6.2 **Quantitative ultrasound and spectroscopy for the characterization of suspected breast cancers,** Farnoosh Hadizad, Harini Suraweera, Aparna Jain, William Tran, Ali Sadeghi-Naini and Gregory Czarnota, *U. Toronto and Sunnybrook HSC*, *gregory.czarnota@sunnybrook.ca*

Background and Motivation: Breast cancer is one of the most common cancer types accounting for 29% of all cancer cases. Early detection and treatment has a crucial impact on improving the survival of affected patients. Ultrasound (US) is non-ionizing, portable, inexpensive, and real-time imaging modality for screening and quantifying breast cancer. Due to these attractive attributes, the last decade has witnessed many studies on using quantitative ultrasound (QUS) methods in tissue characterization. However, these studies have mainly been limited to 2-D QUS methods using hand-held US (HHUS) scanners. With the availability of automated breast ultrasound (ABUS) technology, this study is the first to develop 3-D QUS methods for the ABUS tissue characterization in breast tumors.

Methods: Data was acquired from 25 patients over the last 8 months. The patients were grouped to two groups of 15 benign and 10 malignant cases. All malignant cases were confirmed with a gold standard biopsy test. Ultrasound B-mode and raw radiofrequency (RF) data were acquired using a SonixEmbrace™ (Ultrasonix Med. Corp., Richmond, BC, Canada) ABUS system equipped with a concave L14-5/115 transducer with the centre frequency of 5.8 MHz and an adjustable imaging bed. Using an ABUS system, unlike the manual 2-D HHUS device, the whole patient's breast was scanned in an automated manner. The patient lay on the bed in prone position with the breast resting in the imaging dome. The custom concave US transducer embedded into the imaging dome rotated around the entire breast by an automated step motor capturing 154 2-D frames with a known angular radial distance. The acquired frames were subsequently examined and a region of interest (ROI) was selected in each frame where tumour was identified. Standard 2-D QUS methods were used to compute spectral (mid-band fit, spectral intercept, and spectral slope), and backscatter coefficient (BSC-average acoustic concentration and average scatterer diameter) parametric maps on the selected ROIs. In order to identify the parametric maps which are discriminative on the two patient groups, a statistical test of significance was performed using unpaired, two-sample *t*-test.

Results: Among the 3 spectral and 2 BSC parametric maps, mid-band fit resulted in significant differences between the two groups of benign and malignant (p = 0.015). In addition, spectral intercept and average acoustic concentration alarmed very close to significant differences between the two groups. The effectiveness of these parameters to discriminate between benign and malignant cases will be further investigated in future using a larger cohort of patients.

Conclusion: In this study, 3-D QUS methods were used, for the first time, for tissue characterization in patients with breast cancer. The approach achieved a promising discrimination between the two groups of benign and malignant on 25 patients. This would potentially enable a rapid and inexpensive monitoring tool to identify women with breast cancer as an alternative or complementary imaging system to mammography.

6.3 **3-D quantitative ultrasound in breast cancer tissue characterization**, Mehrdad J. Gangeh, Abdul Raheem, Hadi Tadayyn, Aparna Jain, Farnoosh Hadizad and Gregory J. Czarnota, *U. Toronto and Sunnybrook HSC*, *gregory. czarnota@sunnybrook. ca*

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6.4 **GPU-Accelerated Spectral Processing (GASP) system for real-time ultrasound spectroscopy**, Naum Papanicolau, Ervis Sofroni and Alireza Sadeghian, *Ryerson U. and Evrika Research Tech., npapanic@scs.ryerson.ca*

Background: Current methods of computing quantitative ultrasound (QUS) parameters limit spectroscopic characterization methodologies to a post-processing computational paradigm. A graphical processing unit (GPU) Accelerated Spectral Processing (GASP) approach has been developed capable of computing QUS spectral parameters from ultrasound radiofrequency data with speeds orders of magnitude faster than current state of the art approaches. The GASP system architecture harnesses the design of single instruction multiple data (SIMD) GPU processor architectures found on modern computer video cards to approach ultrasound spectroscopic computations in a massively parallelized fashion, drastically increasing computational throughput. The objective of this study was to employ a GASP system to develop the first real-time ultrasound spectroscopy device capable of computing QUS parameters in conjunction with ultrasound data acquisition.

Methods: The GASP device was communicatively coupled to receive radiofrequency data from a SonixTouch (Analogics Inc.) ultrasound device using a L14-5/6 transducer operating at ~7 MHz. The system was designed to compute QUS parameters and display resulting parametric map visualizations for entire frames or user defined regions of interest (ROI) selected during data acquisition. Linear regression analysis was performed on computed power spectra, normalized to data previously acquired from a glass bead embedded calibration phantom collected with the same ultrasound device at corresponding acquisition settings. Spectra were computed for independent axial segments using a gate length of 10 wavelengths with axial and lateral overlaps of 95% and a Hanning window applied to each segment. Quantitative ultrasound parameters calculated included the midband fit (MBF), spectral slope (SS), spectral intercept (SI) and attenuation coefficient estimate (ACE). Post-processing of radiofrequency data acquired during testing was performed in MATLAB and used to validate results obtained from the GASP system testing.

Results: GASP system throughput indicates processing speed capabilities suitable for multi-frame per second data processing requirements of clinical real-time QUS applications. Frame processing speeds reaching 13 frames per second were demonstrated in a variety of data acquisition and computational settings. Frame rate was dependent upon data acquisition dimensions, as well as computational parameters such as axial and lateral analytical region and overlap settings. Significantly higher rates were computed during ROI analysis computations. High degrees of agreement were found in all cases between GASP and CPU based analysis results with an average difference of $< 0.01\%$ between data points in calculated parameter arrays.

Conclusions: A real-time GASP ultrasound spectroscopy device was designed and built to compute QUS parameters in conjunction with ultrasound data acquisition. In all test cases, GASP system processing throughput demonstrated orders of magnitude increases in QUS parameters processing speeds when compared against serial CPU based computational approaches. This work will for the first time permit QUS spectroscopic analysis to be performed in conjunction with ultrasound data acquisition, allowing for the evolution of tissue characterization applications from post-processing to real-time analytical paradigms.

6.5 **Quantitative-ultrasound-based assessment of prostate cancer using a novel 29-MHz high-frequency micro-ultrasound system**, Daniel Rohrbach, Brian Wodlinger, Jerrold Wen, Jonathan Mamou and Ernest Feleppa, *Riverside Research and Exact Imaging, drohrbach@riversideresearch.org*

Background: Prostate cancer is the second most common male cancer in the United States. Definitive diagnosis is performed using core-needle biopsies obtained transrectally or transperineally guided by transrectal ultrasound (TRUS) imaging. Currently, no technology is available that reliably detects cancerous regions in the prostate for guiding biopsies, which contributes to false-negative diagnoses and unnecessary biopsies. Previous studies by our group demonstrated that quantitative ultrasound (QUS) has a strong potential for detecting cancerous prostate tissue. The conventional TRUS systems used in biopsy procedures operate in the 6 to 9-MHz frequency range. Recent technological advances have led to development of a novel micro-ultrasound system operating at far higher frequencies (29 MHz) that enable ultrafine resolution of the prostate anatomy. We performed a preliminary study to investigate potential of incorporating our QUS approaches in the ultrasound micro-scanner for identifying cancerous regions in the prostate.

Methods: In this preliminary study, RF data from 16 patients (192 biopsy cores) were acquired using a 29-MHz, transrectal, micro-ultrasound system and transducer (ExactVu™ micro-ultrasound, Exact Imaging, Markham, Canada). These retrospective data consist of a subset of data acquired in an ongoing, multisite, 2,000-patient, randomized, clinical trial (clinicaltrials.gov NCT02079025); the subset consists of 8 patients with biopsy-determined Gleason Sums (GS) of 7 and above (positive class), and 8 patients with only negative biopsy results (negative class). Directly before each biopsy, 2D RF data in the longitudinal biopsy plane were acquired using a linear array. For each RF data set, power spectra were computed along the biopsy needle trace located inside the prostate using a sliding region of interest (ROI) of approximately 1 mm^2 in size. Spectra from the set of ROIs, were averaged and normalized by a reference spectrum. The reference spectrum was computed from RF data acquired from a calibration phantom consisting of 18-µm polystyrene beads. A linear model was fit to the normalized spectra, and QUS estimates of midband (M), intercept (I) and slope (S) were calculated. The QUS estimates were used to train linear discriminant classifiers (LDC). No other variables, e.g., PSA value, were used for classification. Classifier performance was assessed using area under the curve (AUC) values obtained from receiver operating characteristic (ROC) analyses with leave-one-out cross validation.

Results: When I, M, and S values were used alone for classification, then AUC values respectively were 0.66, 0.61 and 0.55. When a combination of 2 parameters was used for classification, then an AUC value of 0.74 was obtained.

Conclusion: In a previous study, a protocol for prostate-cancer risk identification using micro-ultrasound (PRI-MUS™) was introduced for the ExactVu™ system to provide a subjective, user-dependent, B-mode-based scoring system for assessing prostate-cancer likelihood. This study demonstrated a peak AUC value of 0.74 for higher GS values (GS > 7) when read by an expert. Our results with AUC values of 0.74 are very encouraging for developing a new, entirely objective, prostate-cancer risk-assessing tool. Currently, we are testing approaches involving additional QUS estimates (e.g. based on envelope statistics), and non-linear classifiers, such as support-vector machines, to improve the classification performance.

6.6 **Optimal frequency-shift attenuation estimation and *in-vivo* imaging applications**, Kayvan Samimi and Tomy Varghese, *U. Wisconsin-Madison, samimi@wisc.edu*

Background and Objectives: The ultrasonic attenuation coefficient is an important parameter of interest for Quantitative Ultrasound (QUS) and Tissue Characterization. Various methods for estimating this parameter are described in the literature that either measure spectral difference (i.e., decay) or spectral shift of the backscattered echo signal. Under ideal conditions, i.e., in the absence of abrupt changes in tissue backscattering, Spectral Difference methods can produce estimates with high accuracy and precision. On the other hand, diffraction-corrected Spectral Shift methods are better suited for application in clinical settings using clinical scanners. However, current Spectral Shift methods produce estimates with high variance and low spatial resolution. As a result, high-quality clinical attenuation imaging remains elusive. A main contributor to the high estimation variance of Spectral Shift methods is their use of inefficient frequency-shift estimators. In this study, an efficient correlation-based shift estimator is presented that achieves the Cramér-Rao lower bound (CRLB). Using this estimator in conjunction with a well-characterized reference phantom, we demonstrate greatly improved accuracy and precision for spectral-shift attenuation estimation. Subsequently, feasibility of clinical attenuation imaging is tested by processing post-procedure radiofrequency (RF) data frames from patients who underwent microwave ablation of liver tumors.

Methods: A probabilistic model of the backscattered RF echo was used to derive the CRLB on estimation variance of frequency shifts, and a correlation-based estimator was introduced that achieves this lower bound. RF data was acquired from uniformly attenuating simulated and physical tissue-mimicking (TM) phantoms. RF data was analyzed using our new method and a previous method (i.e., the Spectral Shift Hybrid method) in order to statistically compare their performance. For the clinical study, post-ablation RF data was collected from 10 liver cancer patients immediately after microwave ablation of their tumors and processed using our new method. The resulting attenuation maps were color-coded and superimposed on corresponding B-mode images of the ablation site.

Results and Conclusion: Both simulated and experimental phantom studies demonstrate a minimum of a 3-fold reduction in the standard deviation of attenuation coefficient estimates using our new method when compared to the Hybrid method. Additionally, presence of negative attenuation estimates which has been a common occurrence in attenuation imaging endeavors is nearly eliminated using the new method. Clinical post-ablation attenuation images correctly delineate the expected ablation zone as it presents with an increased attenuation coefficient compared to the background tissue. The improved stability, reduced estimation variance, and near elimination of the negative slope of attenuation estimates makes it possible to pursue mapping of attenuation coefficient as a new ultrasonic imaging modality. Supported in part by National Institutes of Health grants R01 CA112192 and T32 CA09206-36A1.

6.7 **Quantitative ultrasound measures of lymphedema,** Robert Dinniwell, William Tyler Tran and Gregory Czarnota, *U. Toronto and Sunnybrook HSC, gregory.czarnota@sunnybrook.ca*

Background: Secondary lymphedema is a well-recognized side effect of both surgery and radiotherapy. This arises from trauma to the axillary lymphatic system through surgery or radiation therapy. Quantitative ultrasound (QUS) parameters may provide a noninvasive method to identify, characterize and monitor patient with or at risk of lymphedema.

Methods: Ultrasound images were acquired using a Sonix RP system (Ultrasonix, Vancouver, Canada) operating with an L14-5/60 transducer to collect conventional B-mode and RF data (center frequency of 7 MHz, 40 MHz 8-bit dynamic range RF digitization frequency) from 11 subjects. A control scan was acquired (n=11) and compared to ultrasound images acquired in regions with lymphedema (n=22). QUS Spectral parameters examined included: Mid-band fit (MBF), 0-MHz Intercept, Spectral Slope (SS), Attenuation Coefficient Estimates (ACE), Acoustic Scatterer Diameter (ASD), and Acoustic Concentration (AAC). Texture parameters were analyzed using gray-level co-occurrence matrices (GLCM) methods to determine the concentration and energy. For statistics, all parameters were analyzed for comparisons between normal tissue controls and the corresponding regions of lymphedema using an unpaired t-test. Samples were considered significant at an alpha level of 0.05 (α=0.05).

Results: Comparison of the QUS features MBF, 0-MHz Intercept, SS, ASD and AAC revealed statistically significant (p<0.05) between normal tissue and lymphedema.

Conclusion and future work: Quantitative ultrasound analysis can demonstrate significant differences in lymphedema and normal tissue. QUS parameters: Mid-band fit, 0-MHz Intercept and spectral slope increased in patients with lymphedema, suggesting that cellular organization related to scatterer concentration, distribution and size that can contribute to ultrasound signal changes. QUS analysis may be useful for clinical applications to aid in identifying patients at risk for lymphedema or who are presenting with varying degrees of this condition.

6.8 **Quantitative ultrasound imaging for detection of prognostically-significant histological features in rabbit liver,** Lakshmanan Sannachi, Stephanie Chiu, Hadi Tadayyon, Anoja Giles and Gregory Czarnota, *Sunnybrook HSC and U. Toronto, gregory.czarnota@sunnybrook.ca*

Background: The early fatty infiltration is usually presumed benign and revisable, if disease is treated properly. However, cirrhosis and end-stage liver disease is irreversible and a liver transplantation is an only choice of therapy. Therefore, detecting and monitoring the condition of fatty liver infiltration early in its course could provide better chances of cure or prolong the time of survival before irreversible changes occur. Steatosis and hepatocellular ballooning are the major distinguishing histological features of early classification systems of liver disease. Aim of this study is to develop hybrid models to determine those histological features using quantitative ultrasound technique.

*Method***:** Seventeen male New Zealand white rabbits were used. One group of rabbits consumed a standard chow diet and used as a control. Another group of rabbits were placed on a special fatty diet for 2 weeks and then switched to normal diet for 6 to 12 weeks. Fat% and hepatocyte size were quantified from histology images using an image segmentation method. Ultrasound propagation properties, such as attenuation and speed of sound, scatterer spacing (SAS), spectral parameters such as the mid-band fit (MBF), spectral slope (SS) and intercept (SI) and backscatter parameters such as integrated backscatter coefficient (IBC), average scatterer diameter (ASD), and average acoustic concentration (AAC) were estimated in *ex vivo* rabbit liver samples. In addition to ultrasound parameters, four texture features, including contrast, correlation, homogeneity and energy were determined as further liver characterization parameters.

*Results***:** Fat% and cell sizes estimated from control and fatty livers were 1.6±0.6%, and 10.9±4.4%, and 20.3±0.4µm and 25.2±1.1µm, respectively. Among all ultrasound parameters, both histological features exhibited strong correlation with attenuation and speed of sound followed by moderate correlated with SAS, SS, ASD and AAC. A multiple linear regression model using these parameters resulted in good predictability of fat% (R^2 = 0.9, RMSE = 1.93 %) and of cell size (R^2 = 0.79, RMSE = 1.34 µm). Among all analyzed liver specimens, 96% could be correctly classified into one of three fat groups (control: <5%, low fat: 5 – 10%, high fat: >10%). Using a single threshold, both control and fatty liver were correctly classified with 100% accuracy.

Conclusions: This study demonstrated potential of quantitative ultrasound and texture characteristics of QUS parametric maps in liver histological feature detection in early stage fat disease. The result observed in this study suggest that gradual increase in fat deposition in liver tissues affect tissue structural and elastic properties at early stage and then their textural properties at later stage.

Thursday afternoon

7. ELASTICITY 2

7.1 **Improved shear-wave group-velocity estimation method based on spatiotemporal peak and thresholding motion search,** Carolina Amador, Shigao Chen, Armando Manduca, James F. Greenleaf and Matthew W. Urban, *Mayo Clinic Coll. Med.*, *amadorcarrascal.carolina@mayo.edu*

Objectives: Quantitative ultrasound elastography is increasingly being used in the assessment of chronic liver disease. Many studies have reported ranges of liver shear wave velocities values for healthy individuals and patients with different stages of liver fibrosis. Nonetheless ongoing efforts exist to stabilize quantitative ultrasound elastography measurements. Time-to-peak (TTP) methods have been routinely used to measure the shear wave velocity. However, there is still a need for methods that can provide robust shear wave velocity (SWV) estimation in the presence of noisy motion data. In this study two modifications of the TTP algorithm are proposed to improve the precision of SWV estimates. The SWV estimation methods are evaluated in a tissue mimicking phantom to illustrate the proposed methods and in liver *in vivo*.

Methods: The conventional TTP algorithm searches for the maximum motion in time profiles at different spatial locations. In this study, two modified TTP algorithms are proposed. The first method searches for the maximum motion in both space and time (spatiotemporal peak, STP). The second method applies an amplitude filter (spatiotemporal thresholding, STTH) to reject points with motion amplitude lower than a threshold. Motion data from both methods are processed by the RANSAC method to estimate shear wave speed. We tested these algorithms with data from a homogeneous tissue mimicking phantom (shear wave liver fibrosis, Phantom 1, Model 039, CIRS, Inc., Norfolk, VA) and fourteen healthy subjects with no history of liver disease with a protocol that was approved by the Mayo Clinic Institutional Review Board. A Verasonics Vantage system equipped with a C5-2v curved array transducer was used in this study (Verasonics, Inc., Kirkland, WA). For the phantom study, two sets of data were acquired, using 90 Volts for the transmitted push signal to achieve high signal-to-noise ratio (SNR) in the measurements and using 20 Volts for the transmitted push to obtain measurements with low SNR. For shear wave generation a single focused push beam was transmitted. Five consecutive acquisitions were obtained in both phantom and human studies. The SWV was estimated using the TTP, STP and STTH methods. Threshold values in the STTH method were studied in the phantom with values from 1 to 0.5 in steps of 0.01, then the threshold value that provided the minimum interquartile range (IQR) of SWV was used for processing data from the human study. The RANSAC method was used to find the SWV from the spatiotemporal data points for each method. The RANSAC method parameters were selected from preliminary phantom studies and according to Wang, et al. [1]: □ (the standard deviation of the shear wave time delay estimation) was set to 0.27 ms in TTP method, 0.36 ms in STP method, and 0.52 ms in STTH method for the phantom; 0.62 ms in TTP method, 0.87 ms in STP and STTH methods for the human data. The number of iterations was set to 5000 and the inlier probability was 90%.

Results: The phantom median SWV measurements of the high SNR and low SNR cases combined were 1.06 m/s with TTP method and 1.01 m/s with STP. For the STTH method different threshold values were studied for each case (high SNR and low SNR); the SWV measurements varied from 1.01 to 1.06 m/s with high SNR case and from 0.98 to 1.04 m/s with low SNR case. The threshold of the STTH that resulted in the lowest interquartile range (IQR) of the phantom SWV measurements was 85% with SWV of 1.01 m/s and IQR of 0.03. The IQR of the phantom SWV measurements were 0.06 m/s for TTP method and 0.02 m/s for STP method. The human liver SWV (median, IQR) were (1.51, 0.36), (1.44, 0.25) and (1.41, 0.20) m/s for the TTP, STP and STTH with 85% threshold methods respectively.

Conclusions: In this study, two methods for SWV estimations are proposed (STP and STTH). Although the STTH method has the ability to use a threshold level, the threshold level may vary depending on the application and its optimization was not fully investigated in the current study. Both proposed methods were able to improve the precision of SWV estimates compared to the conventional TTP method. Supported in part by NIH grant R01DK092255.

(1) M. H. Wang, et al., *Ultrasound Med Biol* 36, 802-813 (2010).

7.2 **Evaluation of nonlinear modulus using compression of *ex-vivo* kidneys and shear-wave measurements**, Sara Aristizabal, Carolina Amador, James F. Greenleaf and Matthew W. Urban, *Mayo Clinic Coll. Med.*, *aristizabaltaborda.sara@mayo.edu*

Most of the dynamic elastography techniques have been concentrated on the estimation of the elastic shear modulus in order to assess the health of different soft tissues. These techniques have proven successful for the diagnosis of multiple disease processes. To better understand pathologies for which the knowledge of the shear elasticity may not be sufficient to reach a clinical diagnosis, new methods that investigate nonlinear tissue mechanical properties have been proposed. It has been previously shown that the applied pressure of the transducer can affect the stiffness measurements in organs such as the kidney. The phenomenon where the shear wave speed changes with respect to an applied stress, such as transducer compression, is called acoustoelasticity (AE). Using AE experimentally by compressing a medium and measuring the shear wave speed of 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 in *ex vivo* kidneys.

The nonlinear shear modulus was measured in two *ex vivo* porcine kidneys embedded in 10% porcine 300 Bloom gelatin (Sigma-Aldrich, St. Louis, MO). To induce a uniform uniaxial stress, a rectangular plate (11.5 cm x 4.5 cm) was attached to the transducer, which was subsequently attached to a stepper motor and placed in contact with the phantoms. The linear motor was programmed to compress in steps of 2 mm for a total compression of 16 mm which corresponds to a 25% compression given the phantom's initial thickness. The phantoms were compressed first in the progressive direction and then in the regressive direction by releasing the compression 2 mm at a time. Three cycles of compression (progressive + regressive) were performed on each phantom. Two different views, longitudinal and transverse, were evaluated in each case. Shear waves were generated and measured at each compression step by a GE LOGIQ E9 (GE Healthcare, Wauwatosa, WI) ultrasound system equipped with a linear array transducer (9L). For the AE measurements, the shear modulus was quantified at each level of compression and the locally applied strain was assessed in the imaging plane by measuring the change in thickness of the kidney cortex. Finally, the nonlinear shear modulus (*A*) was calculated by applying the AE theory.

The range of nonlinear shear modulus values for the renal cortex in the two phantoms in the longitudinal view were -21.64 to -33.42 kPa when the compression was performed progressively and -20.77 to -22.38 kPa when the compression was performed regressively. In the transverse view, the nonlinear modulus values ranged from -15.94 to -23.95 kPa when the compression was performed progressively and -17.62 to -19.27 kPa when the compression was performed regressively. There was approximately a 30% change in strain observed in the thickness variation of the cortex when the phantoms were compressed up to 16 mm.

These phantom results demonstrate that with this methodology it is possible to recover the nonlinear shear modulus by monitoring the changes in strain and shear modulus due to deformation in the kidney. It is possible to observe that the nonlinear modulus was significantly higher when the compression is performed progressively and when the experiment is performed in the longitudinal view of the kidney, which can help guide further experiments. Nevertheless, the range of values obtained for *A* in the kidney is similar to the ones previously reported in the literature for breast tissue. Supported in part by NIH grant DK092255 from the National Institute of Diabetes and Digestive and Kidney Diseases.

7.3 **SNR limitations of plane-wave harmonic imaging**, Yufeng Deng, Mark L. Palmeri, Ned C. Rouz, Gianmarco Pinton and Kathryn R. Nightingale, *Duke U. and U. North Carolina*, *yufeng.deng@duke.edu*

Introduction: Tissue harmonic imaging (THI) is widely used in diagnostic ultrasound. THI offers higher image quality compared to fundamental B-mode imaging, because the former is less susceptible to phase aberration and reverberation clutter noise.[(1)] Most THI methods use a focused transmit because the majority of the harmonic pressure is generated around the focus due to the high fundamental pressure amplitude. Recently, plane wave harmonic imaging has been proposed in the context of shear wave imaging to improve shear wave motion tracking while maintaining high frame rates.[(2)] This work investigates the level of harmonic energy generated in plane wave transmits compared to focused transmits, and evaluates the advantages and limitations of plane wave harmonic imaging.

Methods: The 3D *k*-Wave acoustic simulation package[(3)] was used to simulate both plane wave and focused transmit harmonic imaging. A 4C1 curvilinear transducer (typical abdominal probe used for liver SWEI) was simulated and the transmit pulse was a 4-cycle sinusoid at 2.2 MHz. The sampling rate was 52 MHz. The focused transmit had an F/1.5 focal configuration at 5 cm. The source pressures of focused and plane wave transmits were 1.2 MPa and 2.8 MPa, respectively, so that both simulations had a Mechanical Index (MI) of 1.9, albeit this MI occurred at the face for the plane wave rather than at the focus. Fourier transforms were performed on the pressure waves at each axial depth to assess the relative magnitude of the fundamental and harmonic pressures.

Results/Conclusions: For a focused transmit, both the fundamental and harmonic pressures had the maximum amplitudes close to the transmit focus at 5 cm. The peak harmonic pressure was -7 dB compared to the peak fundamental pressure. For a plane wave transmit, the harmonic pressure amplitude reached the maximum amplitude at 2 cm, and decayed to zero at 5 cm. The peak harmonic pressure in the plane wave transmit was -10 dB compared to that in the focused transmit, and –15 dB compared to the peak plane wave fundamental pressure. These results indicate that plane wave harmonic imaging suffers lower SNR compared to focused transmit harmonic imaging. Plane wave harmonic imaging is also penetration depth limited (< 5 cm), which is not generally a problem in shear wave imaging, where the ARFI excitation also has a limited depth penetration. In addition, plane wave harmonic imaging is expected to be susceptible to aberration, because the majority of the harmonics are generated close to the transducer face. Future work will involve simulating and assessing B-mode and harmonic image quality in the presence of near field phase aberration and clutter noise using plane wave and focused transmits. Supported in part by NIH Grants R01EB002132 and R01CA142824.

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7.4 **Three-dimensional single-track location shear-wave elasticity imaging**, Peter J. Hollender, Samantha L. Lipman and Gregg E. Trahey, *Duke U., peter.hollender@duke.edu*

Ultrasound-based motion estimation methods are subject to speckle noise, which manifests as an unknown but stationary offset to the three-dimensional position of any given tracking beam. For conventional, multiple track location shear wave elasticity imaging (MTL-SWEI), this bias affects the apparent time delay between pairs of estimated motion waveforms, and thus local shear wave speeds. To overcome speckle noise, MTL-SWEI methods spatially regularize over multiple speckles, suppressing speckle noise at the expense of spatial resolution. Single Track Location Shear Wave Elasticity Imaging (STL-SWEI) creates shear wave images from a series of steered excitations, tracked with a single beam (as opposed to a single excitation, tracked with multiple beams). The speckle bias in STL-SWEI thus offsets all recorded motion waveforms equally, and does not affect the time delay between any pair of waveforms. We present here a system for acquiring STL-SWEI images in 3D, using a translation stage to steer a focused HIFU piston, and a fixed 3D matrix array transducer to track the induced displacements at 64 independent locations. Each track voxel is used to form a C-scan slice of the STL-SWEI volume, such that each parallel tracking beam forms a full volume, which can be averaged together to reduce noise. Volumes of elasticity phantoms are presented and analyzed, showing marked improvements in resolution over MTL_SWEI methods. Potential applications and considerations for *in vivo* implementation are discussed. Funded by NIH 5R37HL096023, NIHR01EB012484, and the Duke-Coulter Translational Partnership.

7.5 **Comparison of quantitative elastographic techniques for shear-wave speed measurements,** Juvenal Ormachea, Stephen A. McAleavey, Roberto J. Lavarello, Kevin J. Parker and Benjamin Castaneda, *U. Rochester and Pontificia U. Catolica del Peru*, *jormache@ur.rochester.edu*

Background and motivation: Recently, different studies have performed comparison studies of shear wave speed estimation using different quantitative elastographic techniques in elastic and viscoelastic tissue-mimicking phantoms. [1-3] These studies found a significant difference among measurements at different phantom/focal depths. Additionally, their results suggest that there is a component of variance attributed to the different measurement systems and highlights the difficulty in finding a reference method to assess the elastic properties. Nevertheless, there is still a lack of studies comparing quantitative elastographic techniques being actively developed based on mechanically vibrating external forces (such as crawling wave sonoelastography (CWS)) and quantitative elastographic techniques based on acoustic radiation force (such as single tracking location shear wave elasticity imaging (STL-SWEI).

Methods: To understand each technique's performance, shear wave speed (SWS) was measured in three different homogeneous phantoms (10%, 13%, and 16% gelatin concentrations) and *ex vivo* beef liver tissue. Then, the contrast, contrast-to-noise ratio (CNR), and lateral resolution were measured in an inclusion and two-layer gelatin-based phantoms. The SWS values obtained with both modalities were validated with mechanical measurements (MM) which serve as reference. Finally, the Tukey-Kramer test was applied to show differences (or lack of differences) between the methods relative to each other.

Results: The SWS results for the three different homogeneous phantoms (10%, 13%, and 16% gelatin concentrations) and *ex vivo* beef liver tissue showed good agreement between CWS, STL-SWEI, and MM as a function of frequency. For all gelatin phantoms, the maximum accuracy errors were 2.52% and 2.35% using CWS and STL-SWEI, respectively. For the *ex vivo* beef liver, the maximum accuracy errors were 9.40% and 7.93% using CWS and STL-SWEI, respectively. The Tukey-Kramer test showed that each modality is able to differentiate between the elastic properties of different materials, the SWS results for each phantom were significantly different ($p<0.05$) (10% vs. 13% vs. 16%). Additionally, the test showed that the SWS measurements, obtained with each modality, are not significantly different for the same phantom type and the *ex vivo* liver tissue. For lateral resolution, contrast, and CNR, both techniques obtained comparable measurements for vibration frequencies less than 300 Hz (CWS) and distances of the pushing locations between 3 mm and 5.31 mm (STL-SWEI).

Conclusion: The results obtained in this study agree over a SWS range of 1-6 m/s. They are expected to agree in perfectly linear, homogeneous, and isotropic materials, but the overlap is not guaranteed in all materials because each of the three methods (CWS, STL-SWEI, and MM) have unique features. It was found that CWS and STL-SWEI give comparable lateral resolution, contrast and CNR. Finally, the results of this study contribute to the limited data currently available for comparing elastographic techniques, especially techniques that use different types of force to generate shear waves inside the material.

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7.6 **Robust characterization of viscoelastic materials from measurements of group shear-wave speeds**, Ned C. Rouze, Yufeng Deng, Mark L. Palmeri and Kathryn R. Nightingale, *Duke U., ned.rouze@duke.edu*

Introduction: Ultrasonic tracking of shear wave propagation following Acoustic Radiation Force Impulse (ARFI) excitation is commonly used to characterize the stiffness of materials in terms of the group shear wave speed. To characterize the frequency dependent shear modulus in a viscoelastic material, previous studies[1-3] have performed a Fourier decomposition of the shear wave signal and calculated the frequency dependent phase velocity which is then used to determine the parameters in a Voigt or linear dispersion model. Compared to the measurement of group shear wave speeds, spectral analysis methods can be sensitive to measurement noise which can lead to low yields among repeated measurements and low confidence in the accuracy of model parameters determined from model dependent fitting.

Methods: In this study, we develop a method to characterize the viscoelastic properties of soft tissue from measurements of the group shear wave speeds V_{disp} determined using the particle displacement signal $u(x,t)$ and V_{vel} determined using the particle velocity signal $v(x,t) = \frac{du(x,t)}{d□}$. Viscoelastic properties of the material, such as the Voigt model stiffness μ_0 and viscosity η, can be determined from these speeds by solving the Navier equation of motion[4] to determine the relation between the model parameters μ_0 and η and the speeds V_{disp} and V_{vel}. For a viscoelastic material with dispersion, we expect $V_{vel} > V_{disp}$ due to dispersion and the increased weighting of higher frequencies when averaging over the frequency content of the particle velocity signal $v(x,t)$ compared to the particle displacement signal $u(x,t)$.

Results/Conclusions: Preliminary data collected in a viscoelastic phantom indicate that both V_{disp} and V_{vel} can be measured accurately with $V_{disp} = 2.41 \pm 0.13 \frac{\mathbf{m}}{□}$ and $V_{vel} = 3.19 \pm 0.08 \frac{\mathbf{m}}{□}$. These values give $\mu_0 = 4.3 \pm 0.4$ **k□a** and $\eta = 3.9 \pm 0.2$ **Pa·s** for the Voigt stiffness and viscosity. Similar measurements in an approximately elastic phantom give $V_{disp} = 1.96 \pm 0.02 \frac{\mathbf{m}}{□}$, $V_{vel} = 2.00 \pm 0.02 \frac{\mathbf{m}}{□}$, $\mu_0 = 3.8 \pm 0.2$ **k□a**, and $\eta = 0.5 \pm 0.4$ **Pa·s**. Variations of the excitation duration and size of the excitation force indicate that the group speeds are nearly independent of the specific excitation configuration. Thus, we conclude that measurement of the group speeds V_{disp} and V_{vel}, combined with the use of a 2-parameter viscoelastic model (i.e., Voigt model), allows robust characterization of viscoelastic properties of materials. Supported in part by NIH Grants R01EB002132 and R01CA142824.

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7.7 **Axial resolution of physiological shear-wave elastography: phantom experiments**, Ali Zorgani, Rémi Souchon and Stefan Catheline, *INSERM, ali.zorgani@inserm.fr*

*Objective***:** Early cancer diagnostic is an important issue in oncology and medical imaging. The ability of the imaging systems to detect small cancer nodules depends on their spatial resolution. Shear wave elasticity imaging techniques known as Elastography, have already shown their ability to locally retrieve the tissue elasticity and therefore suspicious nodules. The resolution of shear wave Elastography is investigated in this presentation. Shear waves are generally generated by external sources (radiation force or mechanical shakers). In Passive Elastography, no source is used. It is based on the correlation of the physiological noise-like shear wave field induced by muscles activity, heart beating, and blood pulsatility. The spatial resolution of this technique is compared to the resolution of ultrasound on B-Mode imaging.

Methods: The experiments were conducted on a homemade gelatin phantom. Inclusions with different elasticities imbedded in the phantom were obtained by changing the concentration of gelatin. A random shear wave field is generated in the sample with multiple magnetic shakers. In a first step, using standard speckle tracking algorithm, the displacement field is measured inside the sample at a high frame rate (1000 frames/second) using 5, 10 and 15 MHz, ultrasound probes connected to an ultrafast ultrasound scanner "Verasonics® Vantage". Then with algorithms based on spatiotemporal noise correlation, local shear wave speed maps are retrieved.

Results: This study shows that, with an unchanged shear wave field, the axial resolution of the elasticity maps increases with the ultrasound frequency. It demonstrates that the near field resolution of our technique is not limited by the shear wavelength which is about 1.5cm**,** but by the resolution of the imaging system, means the ultrasonic wavelength.

8. ROBOT-ASSISTED IMAGING/TRACKING

8.1 **Cooperatively-controlled robot to standardize acoustic radiation force (ARF)-based tissue elasticity measurements,** H. Tutkun Sen, Peter Kazanzides and Muyinatu A. Lediju Bell, *Johns Hopkins U., mlediju@gmail.com*

Acoustic radiation force (ARF)-based approaches to measuring tissue elasticity have established benefits in clinical applications such as tumor detection and tissue fibrosis staging. However, several reports indicate that these measurements rely on the applied probe pressure, particularly when interrogated regions are located near the surface. Examples include imaging of the breast, transplanted kidneys, and left liver lobe. Although one option to overcome these challenges is to automatically control the applied probe pressure with a robot,(1) this option can potentially limit freehand maneuverability. We therefore propose to improve this system with a cooperatively controlled approach that utilizes both zero and non-zero desired forces. Programming a desired force of zero enables the robot to move in the direction of the applied force when the user touches the end-effector (i.e. the ultrasound probe), which mimics freehand operation. A non-zero desired force enables the robot to move until this force is achieved with probe contact pressure.

Our robot was evaluated with controlled force increments applied to a tissue-mimicking phantom and *in vivo* abdominal tissue from three human volunteers. The root-mean-square error between the desired and measured forces was 0.07 N in the phantom and higher for the fatty layer of in vivo abdominal tissue. The mean shear wave speeds increased from 3.7 to 4.5 m/s in the phantom and 1.0 to 3.0 m/s in the *in vivo* fat for compressive forces ranging 2.5 to 30 N, respectively. The standard deviation of shear wave speeds obtained with the robotic approach were low in most cases (<0.2 m/s) and comparable to that obtained with a semiquantitative landmark-based method. This approach has promising potential for longitudinal studies of disease progression, comparative studies between patients, and large-scale multidimensional elasticity imaging.

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8.2 **Tomographic reconstruction of speed-of-sound using two robotically-aligned ultrasound probes** Fereshteh Aalamifar, Haichong K. Zhang, Arman Rahmim and Emad M. Boctor, *Johns Hopkins U., eboctor1@jhmi.edu*

Ultrasound (US) tomography is an imaging technique that has been shown useful in diagnosing cancer. This kind of image shows tomographically-reconstructed tissue acoustic properties such as speed of sound and attenuation. Since these parameters are different in cancerous versus noncancerous tissue, this image can be used for detection or characterization of cancer. This technology has been used for breast tissue using a specialized circular array of US transducers. However, a circular configuration cannot be used for other parts of the body.

To reconstruct tomographic images, it is necessary to have the transmitter and receiver at opposite sides of the medium with their location known with respect to each other. Hence, it is possible to use two conventional US probes, one as transmitter and another as receiver to collect tomographic data. Thus, US tomographic imaging becomes available for other anatomies than breast. We recently proposed robot assistance to enable easy and fast alignment of such two probes. In this study, we focus on imaging speed of sound, and provide an investigation of several ray-based reconstruction algorithms that can be used with two conventional US probes aligned. We, firstly, provide simulation results based on the assumption that the US wave travels in straight path; and compare bias, contrast, and noise using three different reconstruction methods. We describe the effect of incompleteness of data in the reconstructed image; and then, provide preliminary experimental results in a phantom with three materials having different speeds of sound.

8.3 **Ultrasound monitoring of radiofrequency ablation based on computational modeling**, Chloé Audigier, Younsu Kim, Ali Kamen and Emad M. Boctor, *Johns Hopkins U., eboctor1@jhmi.edu*

Radiofrequency ablation (RFA) is the most widely used minimally-invasive ablative therapy to treat liver cancer, but it is challenged by a lack of thermal monitoring. Monitoring the thermal dose delivered during RFA would be helpful to achieve a complete ablation of the tumor. However, clinicians do not have access to this information, which results in incomplete treatment and a large number of recurrences. Various monitoring methods have been proposed in the past, using either MRI or ultrasound. We introduce a novel method, which uses one active PZT element to get the time of flight (ToF) information given by ultrasound to estimate speed of sound changes, which are directly linked to the change in temperature. The active PZT element allows us to acquire one-way ToF information between the PZT element and each of the ultrasound elements. We used a computational model of RFA to validate this method. The computational model simulates RFA on a simplified geometry and is used to generate realistic longitudinal temperature maps. The estimated temperatures given by our method are then compared to these maps. This first simulation experiment allows us to verify the feasibility of the proposed method.

8.4 **Interventional photoacoustic surgical system: tool tracking**, Alexis Cheng, Younsu Kim, Russell H. Taylor and Emad M. Boctor, *Johns Hopkins U., eboctor1@jhmi.edu*

Modern surgeries often combine imaging and surgical navigation systems to provide guidance. Photoacoustic imaging is an emerging imaging modality that can provide information about the optical properties of a particular medium. However, it has been limited to being solely an imaging modality because there has been a lack of tool tracking methods incorporating photoacoustic imaging. In this work, we present the use of photoacoustics to provide tracking for tools such as ultrasound transducers and intervention tools.

The key idea that enables this tracking is the use of photoacoustic spots. These are collimated beam of light projected onto some surface. These spots can be seen by a stereo camera system and will also generate an acoustic signal. Any tool with a piezoelectric element sensor can then detect these signals and subsequently be tracked given the presence of more than 3 photoacoustic spots. We demonstrate this method for tracking the piezoelectric elements in an ultrasound transducer as well as a stand-alone piezoelectric element. A precision of 3.52 ± 1.31 mm was achieved with this method.

8.5 **System development for robotically-implemented synthetic tracked aperture ultrasound imaging,** Haichong K. Zhang, Fereshteh Aalamifar, Rodolfo Finocchi, Kalyna Apkarian and Emad M. Boctor, *Johns Hopkins U.*, *eboctor1@jhmi.edu*

Ultrasound imaging has been widely used in many medical applications due to its low cost, real-time, safe, and convenient use. The remaining challenge for medical ultrasound is its limited field-of-view and the resolution in the deep region, which highly depends on the lateral width of the ultrasound probe. Synthetic aperture is a technique utilizing a wide aperture in both transmit and receive to enhance the ultrasound image quality. The limitation of synthetic aperture is the maximum available aperture size limit determined by the physical size of ultrasound probe. We propose Synthetic Tracked Aperture Ultrasound (STRATUS) imaging to overcome the limitation by extending the aperture size by tracking the ultrasound image location. With a setup involving a robotic arm, the ultrasound probe is moved using the robotic arm, while the positions on a scanning trajectory are tracked in real-time. Data from each pose are synthesized to construct a high resolution image. In previous studies, we have demonstrated the feasibility through phantom experiments. However, additional factors such as real-time data collection or motion artifacts should be taken into account for *in vivo* targets. In this work, we built a robot-based STRATUS imaging system with continuous data collection capability considering the practical implementation. We scanned human forearms under two scenarios: one submerged the arm in the water tank under 10 cm depth to image a deep region target, and the other directly scanned the arm from the surface to analyze the effect of tissue deformation caused by contact. The image contrast improved 5.51 dB, and 9.96 dB for the underwater scan and the direct scan, respectively. The result indicates the practical feasibility of STRATUS imaging system, and the technique can be applied to the wide range of human body. Furthermore, a system development involving a virtual-fixture-based co-robotic scanning system is also presented.

Friday morning

9. IMAGING 2

9.1 **Transmit beamforming strategies for Swept Synthetic Aperture imaging**, Nick Bottenus, Will Long and Gregg Trahey, *Duke U., nick.bottenus@duke.edu*

Introduction: Ultrasound target detectability is often reduced in applications such as deep abdominal imaging due to the link between lateral resolution and target depth. Although usable transmit frequency is constrained by attenuation, the ability to increase aperture size presents another diffraction-limited method for improving resolution. We have recently presented a preliminary study of a “swept synthetic aperture” method, coherently synthesizing a large effective aperture via transducer motion in an effort to improve resolution with existing commercial array and scanner technologies. Clinical considerations require the use of a volumetric system for future work, leaving several open questions regarding sequencing beamforming. This technique presents a unique challenge in that the transducer is in constant motion, preventing repeated interrogation from any given spatial location.

Methods: In order to evaluate the space of available beamforming strategies and pulse sequences, we simulate and experimentally evaluate several properties that factor into the resulting image quality. We use Field II to simulate swept aperture acquisitions using a volumetric probe modeled after the Siemens 4z1c transducer. Using a 5 kHz PRF, the transducer is swept over 10 cm for a target at 10 cm depth with a total theoretical scan time of 0.1 seconds. These constraints model the expected acquisition rate, acoustic window size, target depth and temporal coherence length for an abdominal scan. Within these parameters, we vary the transmit focal configuration and beamforming methods to explore the effectiveness of various diverging, plane and focused waves. Transmit beam profiles are compared to experimental results on the Siemens SC2000 scanner using the volumetric 4z1c transducer.

Results: We characterize our results in terms of lateral and elevation resolution, lesion contrast and CNR, signal SNR and spatial frequency content. Moving from diverging to plane wave to focused beams, we demonstrate the improvement in signal SNR and increased harmonic generation at the expense of field of view. Using adaptively steered, focused transmit beams, we maintain 0.7 mm lateral resolution and contrast comparable to that of broader insonifications while preserving the benefits of focused beams. Trade-offs in achievable field of view with this scheme versus spatial-frequency space coverage are discussed.

9.2 **Iterative correction method for a distribute aberrator using synthetic transmit aperture,** Marko Jakovljevic, Kevin Looby, Gustavo Chau and Jeremy Dahl, *Stanford Sch. Med., marko.jakovljevic @stanford.edu*

We have developed a new phase correction method that uses synthetic transmit pulse sequencing to correct for wavefront distortions in the presence of a distributed aberrator. The method relies on the principle of acoustic reciprocity to beamform the receive subapertures and compute the arrival time differences across the neighboring transmit channels. The aberrator-induced delays on each channel are then estimated using a multi-lag least-squares technique. In this way, the phase estimates can be computed iteratively and across the full field of view without additional transmits for correcting aberration. We show feasibility of the method using FIELD II simulations and a near-field phase screen aberrator.

A complete set of individual channel signals was simulated in FIELD II for a 2 cm, 5 MHz linear transducer while imaging a point target and an anechoic lesion in a field of diffuse scatterers. In both cases, the phase screen was specified to have a 5 mm correlation length and 40 ns rms strength. The signals originating from the individual transmit elements were summed across the full receive apertures and were cross-correlated to measure the delays for up to a lag value of three. The delays were then used to obtain a least squares estimate of the arrival times for each channel on the aperture. The procedure could be repeated using the arrival time profiles estimated from a previous iteration to achieve improved focusing. For a single iteration of the proposed method, the rms error of the estimated profile was 5 ns for the point target simulation and 18 ns for the anechoic lesion case.

To assess efficacy of the new method, B-mode images of the anechoic lesion were also created using no phase-aberration-correction, using correction on the receive channels only, and using correction on both transmit and receive channels. The receive-only correction was intended to mimic traditional phase-aberration-correction techniques that rely on focused transmits. Contrast and CNR of the anechoic lesion were computed to be -6.2 dB and 0.74, respectively, for the uncorrected image, -11.7 dB and 1.33 for the receive-only corrected image, and -12.7 dB and 1.41 for the fully corrected image. The proposed method can achieve further improvement in lesion visualization by iterations without requiring additional transmission and reception as in traditional iterative phase correction methods, thus preserving frame rate for real-time phase correction. We show phase correction results using the proposed method from a full-wave simulation containing a representation of an abdominal layer to demonstrate the method on a realistic distributed aberrator. Supported by NIH grant R01-HD086252.

9.3 **Benefits and limitations of the transverse oscillation technique for phased-array imaging**, Brecht Heyde, Nick Bottenus, Jan D'hooge and Gregg Trahey, *Duke U. and U. Leuven, brecht.heyde@ med.kuleuven.be*

Background and motivation: Myocardial deformation imaging based on ultrasound (US), is widely used to investigate cardiac performance noninvasively. While these image processing techniques are now part of daily clinical routine, obtaining robust deformation estimates perpendicular to the insonification (i.e. in the transversal direction) remains difficult due to the intrinsically lower image resolution and low transverse frequency content. In the context of blood flow and tissue imaging with linear arrays, it has been shown that transverse oscillations (TO) can be introduced during the beamforming process with plane wave (PW) insonification and a bi-lobed apodization (BA) on receive, leading to improved transverse motion tracking accuracy. However, translating this technique to cardiac phased arrays for tissue imaging is currently underexplored, and particularly challenging due to the small transducer footprint, the spread of the US beams over depth, and the relatively low operating frequency - all factors limiting the TO frequency. This study is concerned with identifying the limitations of the PWTO technique for cardiac imaging, and investigating the conditions in which PWTO is advantageous over traditional focused (FOC) beamforming.

Methods: Field II was used to simulate 2D US images of a tissue phantom (80-by-40mm axial-by-lateral dimensions, centrally positioned at 60mm depth, 20 speckle realizations), imaged with a phased array (3MHz, 64 elements, 2cm aperture), and subjected to a range of lateral motions in the Cartesian domain (range: 0-1000µm in 100µm steps) under different electronic SNR conditions (range: 10-30dB in 5dB steps). Images were beamformed in polar space according to the FOC and PWTO scenario (20° opening angle, 0.25°-line density). For PWTO, a heterodyning demodulation process was performed to effectively double the TO frequency, and BA parameters were modified to obtain TO's with wavelengths between 3°-12° (in 0.25° steps) and with a lateral extent between 0.5°-20° (in 0.5° steps). In both cases, the Cramer-Rao Lower Bound (CRLB) was used to theoretically predict tracking performance of an unbiased motion estimator in polar space, thereby coupling the effects of speckle decorrelation, image frequency content and SNR.

Results: The CRLB revealed an optimal tracking performance for the PWTO imaging sequence when the TO wavelength and extent were both 3° in the polar domain. For all displacement scenarios, speckle decorrelated at a faster rate with PWTO compared to FOC, e.g. at 20dB SNR and 1000µm lateral motion, respectively 0.78 and 0.98. While intuitively this negatively impacts tracking performance, this was partially made up for by the presence of the higher transverse frequency content. At a 20db SNR, PWTO therefore outperformed the FOC sequence up to a lateral displacement of 473 µm. The advantage of using PWTO over FOC decreased when SNR increased (at 30dB only up to 151µm displacements).

Conclusions: These results suggest that PWTO has the potential to increase lateral tracking accuracy in cardiac deformation imaging but only when inter-frame cardiac displacements remain relatively low (or equivalently when frame rate is sufficiently high). These findings could also be used as a guideline to determine scanner settings in a clinical setting, e.g. when imaging a 4-chamber left ventricular view at 15db SNR conditions, opening angles should remain smaller than 25° to ensure sufficient frame rate and thereby warranting the use of PWTO beamforming.

9.4 **Assessment of ADMIRE in the presence of phase aberration using resolution-target simulations**, Kazuyuki Dei and Brett Byram, *Vanderbilt U., kazuyuki.dei@vanderbilt.edu*

Image quality can limit the usefulness of ultrasound. In attempting to identify possible mechanisms of ultrasound *in vivo* image degradation, we assessed the relative contributions of multipath scattering and phase-aberration. In our previous study, we used our aperture domain model image reconstruction (ADMIRE) algorithm to separate these two effects. We observed that ADMIRE suppresses both clutter and phase-aberration, but it was unclear whether the suppression of aberration was beneficial. Therefore, we introduced an adaptive component to the original model used with ADMIRE in order to preserve wavefront aberration. We called this method adaptive ADMIRE. Based on this, we further investigated ADMIRE with aberrated wavefronts.

To investigate the effects on image quality using ADMIRE and adaptive ADMIRE, we performed resolution target simulations in the presence of phase-aberration. We simulated five point targets, located at a 3.0 cm focal depth with lateral separation intervals of 4, 3, 2 and 1mm, with no aberration before and after decluttering. We then generated aberrated data using a near-field phase screen model with various aberration levels. Using these data, we applied ADMIRE and adaptive ADMIRE with and without phase-aberration correction. As a metric of resolution, we computed the ratio of energy at two adjacent resolution targets to the energy between the two targets. Energy levels were calculated on the enveloped but uncompressed B-mode data. The measured ratios with no aberration before and after decluttering are 24.4 dB and 24.6 dB, respectively. For aberrated data, the energy ratios of no correction, ADMIRE and adaptive ADMIRE are 17.3 ± 0.7 dB, 22.4 ± 0.5 dB and 22.7 ± 0.9, respectively. When ADMIRE and adaptive ADMIRE are followed by aberration correction, the ratios are 22.3 ± 0.5 dB and 22.9 ± 0.3 dB, respectively. Results indicate that 1) phase-aberration lowers spatial resolution and results in higher side lobes (as expected) 2) recovery of unaberrated resolution from aberrated data using ADMIRE or adaptive ADMIRE shows improvement and 3) phase-aberration correction provides negligible additional improvement in resolution. The resolution simulations also reveal that the suppression of phase-aberration using ADMIRE is beneficial.

9.5 **Improved detection of targeted microbubbles with a coherence-based beamformer**, Dongwoon Hyun, Lotfi Abou-Elkacem, Juergen K. Willmann and Jeremy J. Dahl, *Duke U. and Stanford U., dongwoon.hyun@duke.edu*

Molecular contrast-enhanced ultrasound (CEUS) is an imaging technique that uses targeted microbubbles (MBs) to detect a variety of molecular markers, including those associated with cancer. For example, tumors can potentially be detected by designing MBs that bind to epitopes commonly found in tumor neovasculature. The bound MBs can then be detected using ultrasound by isolating their non-linear response to insonification. However, to avoid MB destruction and harmonic tissue signals, CEUS requires low amplitude transmissions that are orders of magnitude weaker than diagnostic pulses. This creates low signal-to-noise ratio and limited sensitivity to the targeted MBs. In this work, the short-lag spatial coherence (SLSC) beamformer is used to improve the detection of MBs. SLSC is ideal for low signal-to-noise ratio imaging because it forms images of the level of coherence in the backscatter rather than its magnitude, reducing the impact of incoherent noises.

Experiments were performed using a real-time SLSC CEUS imaging system, developed with a Verasonics research scanner front-end and a GPU-based beamformer back-end. A Verasonics L12-3v probe was used to transmit a contrast pulse sequence with three inverted pulses in order to isolate the non-linear MB response. Conventional CEUS and SLSC CEUS images were formed from the same data and displayed side-by-side. In vitro experiments were performed on a gelatin phantom with an embedded 2mm diameter tube was perfused with MBs at several concentration levels. In the phantom, SLSC CEUS (14.8 dB) improved the SNR by a factor of 2.3 over conventional CEUS (7.6 dB) at the lowest concentration of MBs (5×10^4 MB/mL). In vivo experiments were also performed in a transgenic mouse model of pancreatic cancer. Targeted MBs were injected into the tails of the mice and accumulation of the MBs in the tumor were imaged. SLSC CEUS generated images with improved SNR over conventional CEUS imaging (2.9-fold improvement). The results of this study suggest that the SLSC beamformer has improved sensitivity to MBs, and can be used to enhance CEUS image quality and to potentially reduce the required dosage of injected MBs or provide early detection of cancer. Supported by the NIH grant R01-EB013661 from the National Institute of Biomedical Imaging and Bioengineering and from a grant by the Canary Center at Stanford for Early Cancer Detection.

10. PHANTOMS AND CALIBRATION

10.1 **New phantom material for ultrasound elasticity imaging**, Congxian Jia, William C. Vogt, S. Kaisar Alam, Keith A. Wear, T. Joshua Pfefer, Ningrui Li and Brian Garra, *FDA, Rutgers U., Improlabs Pte, Washington DC VA Med. Ctr. and George Washington U., congxian.jia@fda.hhs.gov*

Objective: Ultrasound elastography can facilitate characterization of breast lesions by detecting the increased stiffness of cancers compared to benign lesions and normal tissue. Elastography phantoms have been widely used to assess the performance of ultrasound strain imaging and shear wave imaging. However, existing elastography phantoms are generally simple, with stiff and soft inclusions in a homogeneous background. In reality, the human breast is a heterogeneous organ containing bands of fat and fibrograndular tissue. Each tissue type exhibits distinct acoustic and mechanical properties. These variations cause a complex strain pattern in ultrasound strain elastography as well as complex shear wave propagation. An anthropomorphic breast phantom has been developed using aqueous gelatin with microscopic safflower oil droplets to simulate both types of breast tissue.(1) However, this phantom did not have well-characterized backscatter coefficients, exhibited specular reflections at the lesion boundary causing elastographic artifacts, and required storage in a tank of safflower oil for long term stability. We have developed a new breast phantom material based upon poly (vinyl chloride) plastisol (PVCP) and have characterized its acoustic and elastic properties.

Methods: We have developed a tunable PVCP formulation with adjustable breast relevant acoustic properties(2) by mixing a PVC resin with a binary plasticizer mixture – benzyl butyl phthalate (BBP) and di (2-ethylhexyl) adipate (DEHA) – and glass beads. The fully mixed solution was heated and maintained at 190 °C for 15 minutes and pour into mold to cool to create desired solid phantom. Changes in both PVC concentration and cooling rate were used to modify the Young's modulus of the phantom. The PVC concentration and the volume ratio of the two plasticizers were adjusted to obtain the desired mechanical properties and other acoustic properties. Formulations were developed to mimic fat and fibrograndular breast tissue with appropriate acoustic and mechanical properties. Acoustic backscatter, attenuation and sound speed were measured in a water bath using a pair of co-axially aligned broadband transducers (V320, Panametrics, Waltham, MA) with 7.5 MHz center frequencies, 1.27 cm diameters, and 3.81 cm focal lengths in transmission mode[2]. Acoustic backscatter was measured using one of the two transducers in reflection mode.(3) Young's modulus was measured on a cylindrical sample with a diameter of 15 mm and a thickness of 15 mm using a commercial elastometer (ADMET, Norwood, MA) in compression mode.

Results: Our custom PVCP phantom material exhibits appropriate tissue mimicking acoustic properties with less than 1% change over three months [2]. Young's modulus was shown to be tunable over a range of 6 kPa to 50 kPa by varying PVC concentration from 7% to 15%. Increasing the cooling rate during fabrication to reduce the settling of the glass beads used for acoustic scattering produces a smaller increase (5 kPa) in Young's modulus. Young's modulus increases by approximately 30% over the first month and then has been stable over the next month. Specular reflection which develops at the boundary of the parenchymal and fat mimicking layers can be eliminated by melting the phantom materials to produce more complete fusion during phantom fabrication. Further investigations of phantom temporal stability and the effect of cooling rate on additive settling and stiffness are underway. Funding support from the FDA Critical Path and the FDA Office of Women's Health, as well as the ORISE fellowship program through Oak Ridge Associated Universities.

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10.2 **On-axis radiation-force-based quantitative stiffness estimation in phantoms**, Kristy M. Walsh, Mark L. Palmeri and Brett C. Byram, *Vanderbilt U. and Duke U., kristy.m.walsh@vanderbilt.edu*

In shear wave elasticity imaging (SWEI), stiffness can be found by measuring shear wave velocity at locations away from the acoustic radiation force (ARF) axis.[1] Instead, this research finds stiffness by measuring the time-to-peak displacement directly along the ARF axis, which reduces hardware and sequencing complexity. We have shown previously in simulations that it is important to use an advanced displacement estimator to reduce stiffness estimate variability. Here, we test the on-axis approach in 15 phantoms.

To quantify phantom stiffness, we apply a simulated look-up table made from 3D finite element analysis, which models the phantom properties and the ultrasonic excitation and tracking. A Bayesian displacement estimator is applied to the tracked RF data to reduce displacement estimation error. We can assume that phantoms are homogeneous, isotropic, and elastic, thus the time-to-peak displacement is directly proportional to shear wave speed. Since shear wave speed is directly related to shear stiffness, we create a stiffness look-up table using time-to-peak displacement as a function of depth. The average displacement data from 20 speckle realizations of each tissue stiffness (shear moduli of 1, 3, 5, 7, 9, 11, 13, 15 kPa, attenuation of 0.7 dB/cm-MHz) were used to generate the look-up table. We used a CH4-1 probe with an excitation focal depth of 4.9 cm, tx. F/#2, tx. frequency of 3.08 MHz. For the phantom data, we applied a quadratic motion filter and the Bayesian displacement estimator. We found the time-to-peak displacement at each depth and used the simulated look-up table to get a stiffness estimate.

The stiffness was estimated at the focal depth of 4.9 cm. To evaluate the error of the on-axis method as compared to traditional shear wave methods, we computed a robust Lateral Time-To-Peak (TTP) shear wave speed and converted to a shear modulus for each phantom.[2] The 15 phantoms had a mean shear modulus of 2.00 kPa with a range of 1.38 kPa. We took the root mean square error of the best performing motion filter from both the Bayesian displacement estimator and the NCC derived estimators. For the measurement of shear modulus, the RMSE of the quadratic motion filtered Bayesian estimator was 0.49 kPa and 1.18 kPa for the NCC estimator. These phantom results show that the on-axis method using a Bayesian displacement estimator has a stiffness performance comparable to the stiffness produced by Lateral TTP methods. This work was funded in part by R01 EB002132 and 5-T32-EB014841-03.

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10.3 **Complex breast phantom for photoacoustic imaging,** Congxian Jia, William C. Vogt, Keith A. Wear, T. Joshua Pfefer and Brian Garra, *FDA, Washington DC VA Med. Ctr. and George Washington U., congxian.jia@fda.hhs.gov*

Objective: Breast cancer is the second leading cause of cancer-related deaths in American women.[1] X-ray mammography, the main screening method, requires harmful radiation but has low sensitivity in dense breasts.[2] Ultrasound can improve breast cancer detection[3] and can distinguish benign from cancerous masses, yet up to 70% of biopsies are benign.[4] Photoacoustic tomography (PAT), a noninvasive approach using non-ionizing radiation, has shown significant promise for early breast cancer diagnosis due to its high optical contrast in imaging deep vasculature.[5] PAT combines optical (typically near-infrared) illumination and acoustic detection. PAT image quality depends on tissue acoustic and optical properties, as well as their variations within the PAT imaging domain. However, no morphologically realistic phantom with acoustic and optical properties that mimic fatty and fibrograndular breast tissue has been developed for characterizing PAT image quality in this heterogeneous organ. Therefore, we have developed and rigorously characterized a complex, bimodal breast phantom for assessing device performance.

Methods: The phantom is based on a tunable poly(vinyl chloride) plastisol (PVCP) formulation with adjustable acoustic and optical properties[6], fabricated by mixing a PVC resin with liquid plasticizer and additives. We developed two distinct formulations simulating breast fat and fibroglandular tissue. Their speed of sound and acoustic attenuation were customized by adjusting the PVC concentration and the volume ratio between a binary plasticizer mixture (benzyl butyl phthalate (BBP) and di(2-ethylhexyl) adipate (DEHA)). Acoustic backscatter coefficients for each tissue type were achieved using glass beads with diameters of 38-62 µm and 63-75 µm. Optical scattering and absorption were tuned using titanium dioxide and a black plastic colorant, respectively. Speed of sound and acoustic attenuation were characterized in material samples using a broadband through-transmission technique over a frequency range of 4-9 MHz. Backscatter coefficients were measured using reflection mode in the same spectral range. Optical absorption and scattering coefficients were calculated over 400-1100 nm using the inverse adding-doubling (IAD) method and diffuse transmittance and reflectance measurements from an integrating sphere spectrophotometer.

Results: We constructed a heterogeneous phantom using the two layers with different formulations. The top layer has an average thickness of 10 mm and mimics breast fat. The bottom layer has an average thickness of 50 mm and mimics fibroglandular tissue. Undulation at the interface of the top and bottom layers was created to simulate the fat-fibroglandular boundary. Both layers have breast tissue relevant optical and acoustic properties. The top and bottom layers have speed of sound values of 1440 m/s and 1500 m/s, respectively. Using a PAT system with an acoustic probe having a central frequency of 7.5 MHz, the top layer was determined to have an acoustic attenuation of 5 dB/cm and a backscatter coefficient of 0.003 $Sr^{-1}cm^{-1}$; the bottom layer had acoustic attenuation about 10 $dBcm^{-1}$ and backscatter coefficient about 0.03 $Sr^{-1}cm^{-1}$ at this frequency. These values are similar to published values for fatty and fibroglandular breast tissue. The difference in acoustic properties between the two layers enables study of certain PAT artifacts in a clinically-relevant environment. With further refinement, our complex PVCP phantom approach will be invaluable for instrument development, QA testing and regulatory evaluation. Supported by the FDA Medical Countermeasures Initiative and the FDA Office of Women's Health, as well as the ORISE fellowship program through Oak Ridge Associated Universities.

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10.4 **Pressure-pulse distortion by needle and fiber-optic hydrophones due to diminished low-frequency response**, Keith A. Wear, Yunbo Liu and Gerald R Harris, *FDA*, *keith.wear@fda.hhs.gov*

Objective: A previous investigation of pressure pulse distortion by membrane hydrophones due to diminished low frequency response[1] has played an influential role in acoustic output measurement standards (e.g., IEC 62127-1, AIUM/NEMA UD-2). The goal of the present study is to extend the previous analysis to needle and fiber-optic hydrophones, which are less bulky and sometimes more robust for therapeutic ultrasound measurements than membrane hydrophones. While low frequency response of membrane hydrophones is dominated by capacitance of the hydrophone and associated electronics, low frequency responses of needle and fiber optic hydrophones are highly influenced by diffraction effects related to the dimensions of the needle or fiber.

Methods: Needle and fiber optic low-frequency response was modeled by spatially averaging acoustic pressure over the end of a rigid, semi-infinite, cylindrical rod.[2] The model was compared with measurements of complex sensitivities using time delay spectrometry from 1-40 MHz[3] for a fiber optic hydrophone and two needle hydrophones (sensitive element sizes: 100, 400, 600 microns). Pulse distortion was estimated by subjecting simulated nonlinear diagnostic pulses to theoretical frequency-dependent complex sensitivities.

Results: Theoretical and experimental sensitivities agreed to within 10-16% (RMS normalized magnitude ratio) and 6-10 degrees (RMS phase difference) for the three hydrophones. Relative errors in peak compressional pressure and pulse intensity integral exceeded 20% when the needle or fiber diameter was less than half the wavelength corresponding to the fundamental frequency of the nonlinear diagnostic pulse.

Conclusion: The rigid cylindrical rod model is accurate for predicting low frequency responses of the needle and fiber-optic hydrophones investigated. Pressure pulse distortion is particularly high when needle/fiber diameter is less than half the wavelength corresponding to the fundamental frequency of a nonlinear diagnostic pulse.

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