# ABSTRACTS

## 1. Elasticity/Temperature Estimation

1.1 **Ultrasonic noninvasive temperature estimation using echoshift gradient maps**, Matthew Daniels, Udomchai Techavipoo, Quan Chen, Jingfeng Jiang and Tomy Varghese, *U. Wisconsin, Madison, WI 53706*

Percutaneous ultrasound-image-guided radiofrequency ablation is an effective treatment for patients with hepatic malignancies that are excluded from surgical resection due to other complications. However, ablated regions are not clearly differentiated from normal untreated regions using conventional ultrasound imaging due to similar echogenic tissue properties. In this talk, we present the statistics that govern the relationship between temperature elevation and the corresponding temperature map obtained from the gradient of the echoshifts obtained using consecutive ultrasound radiofrequency signals. A relationship derived using experimental data on the sound speed and tissue expansion variations measured on canine liver tissue samples at different elevated temperatures is utilized to generate ultrasound radiofrequency simulated data. The simulated data set is then utilized to statistically estimate the accuracy and precision of the temperature distributions obtained. Our results show that temperature increases between 37 C and 67 C can be estimated with standard deviations of 3 C. Experimental tests of our temperature estimation technique using independent fiber-optic temperature measurement on tissue-mimicking phantoms demonstrate standard deviations of around 5 C.

Finite element analysis (FEA) models to determine the temperature distribution due to a radiofrequency ablation electrode embedded in liver tissue were also developed. FEA analysis enabled generation of temperature and tissue expansion maps of the tissue for a 12 min ablation procedure. Our results illustrate that temperature maps generated from ultrasound echo signals correspond to the temperature maps created with FEA. The location of the radiofrequency ablation electrode tines can be easily visualized using the temperature maps along with the zone of elevated temperatures due to the ablation.

The work is supported by funding from the Graduate School Research Committee at the University of Wisconsin-Madison

1.2 **Change in ultrasonic backscattered energy for temperature imaging: simulation studies with multiple scatterers and measurements from *in vivo* images**, R. Martin Arthur,[1] Jason W. Trobaugh,[1] William L. Straube,[2] Jesse Parry,[2] Yuzheng Guo[1] and Eduardo G. Moros,[3] [1]*Electrical & Systems Engineering,* [2]*Radiation Oncology, Washington University in St. Louis, St. Louis, MO, 63130 and* [3]*Radiation Oncology, University of Arkansas, rma@ese.wustl.edu*

Ultrasound is an attractive modality for noninvasive temperature imaging to enhance the ability to target tumor heating at therapeutic levels. Previously, we measured monotonic changes in ultrasonic backscattered energy (CBE) *in vitro* in 2D and in 3D that matched changes we predicted for certain subwavelength scatterers. Here we consider: (1) measurement of CBE in 2D *in vivo*, (2) simulation of CBE from multiple scatterers and (3) estimation of temperature from CBE in simulated images.

We measured CBE in living normal murine tissue and in implanted tumors (HT29 colon cancer line) on nude-mouse preparations. Measurements were made in degassed water heated homogeneously. Four mice, one with an implanted tumor, were anesthetized with Ketamine Xylazine and heated. Temperature was measured with a thermistor at the hind limb contralateral to the one imaged. Imaging was done with a Terason 2000 (Teratech Corp., Burlington, MA), laptop-based, phased-array system. The imaging system used a

7-MHz linear probe (model 10L5) focused at 2 cm, the center of the mouse leg. Images were taken in 0.5ºC steps from 37.0ºC to 45.0ºC. For image regions within each preparation, nonrigid motion compensation was applied using cross-correlation of rf signals at adjacent temperatures. Envelopes of motion-compensated image regions were found with the Hilbert transform then smoothed with a 3 3 running average filter. Backscattered energy at each pixel was referred to the value at 37ºC to find CBE. CBE was nearly monotonic with temperature. BE differed by 5-6 dB at 45ºC from its value at 37ºC.

Theoretical results for a single scatterer showed that backscattered energy increased or decreased monotonically, depending on the lipid or aqueous nature of the scatterer. To extend our theory to a more realistic tissue composition, we have developed methods for simulating ultrasonic images of thousands of randomly-distributed scatterers. In the simulations, the imaging system was described by its point-spread function. The tissue medium was represented by discrete aqueous and lipid scatterers. Images were simulated to represent temperatures from 37ºC to 50ºC by changing the scatterer amplitudes according to curves predicted previously for single scatterers. CBE was computed for each image pixel, referenced to the initial image. To characterize CBE for a region, the means of the positive- and negative-changing pixels and the standard deviation of all pixels were computed. CBE showed the same monotonic increase and decrease as in experimental results and covered ranges similar to both prediction and experiment. Subsequent simulations included additive noise and showed striking agreement with experimental CBE measurements, replicating both an initial jump and noise throughout the range. These results support the use of CBE for noninvasive temperature estimation, showing that our model for the temperature dependence of CBE can be successfully applied to measurements from multiple scatterers. These simulation methods also provide a means for exploring limits on temperature accuracy and spatial resolution with varying imaging systems and tissue types.

As an example of methods that could be used for calibration and estimation, we have extended our image simulation methods to the initial development of calibration curves and use of those curves for estimating temperature from CBE. Calibration curves were generated by fitting the average CBE from multiple simulations with a polynomial. This polynomial represents the average standard deviation of the CBE for images of a simulated population of lipid and aqueous scatterers with added noise. Estimates of temperature were then generated from that same population using the calibration curve. Results showed an error of approximately ± 1ºC for these images of 1 $cm^2$ or approximately 0.3 $cm^3$ (based on a 3 mm elevation ultrasonic beam width). This error for a small volume with typical measurement noise levels suggests 0.5ºC or better accuracy may be attainable in 1 $cm^3$ volumes with noise reduction techniques.

This work was supported by R21-CA90531, R01-CA107558 and the Wilkinson Trust at Washington University, St. Louis.

1.3 **Ultrasonic *in-vivo* characterization of atherosclerotic carotid plaque**, Hairong Shi,[1] Carol C. Mitchell,[2] Tomy Varghese,[1] Mark A. Kliewer,[4] M. Shahriar Salamat[3] and Robert J. Dempsey,[5] *[1]Department of Medical Physics, [2]Ultrasound Technologist School and Departments of [3]Pathology, [4]Radiology and [5]Neurological Surgery, U. Wisconsin, Madison, WI 53706*

Various factors that promote atherosclerotic plaque formation have been described extensively in the literature. However, there is scant information regarding factors that predispose a given atherosclerosis plaque to become symptomatic or vulnerable. We propose to use *in-vivo* ultrasonic tissue characterization and elastographic imaging for the characterization of plaque composition and elasticity in vascular tissue. This may significantly help in the selection of appropriate interventional techniques to prevent plaque rupture. We report

on results obtained on a pilot study to image the *in-vivo* strain distribution and scatterer size and attenuation in the carotid artery on ten patients scheduled to undergo carotid endarterectomy. *In-vivo* scanning of the carotid plaque is performed using a Siemens Antares ultrasound system with an ultrasound research interface.

*In-vivo* tissue characterization analysis demonstrates that scatterer sizes estimated for calcified regions are larger than that for softer regions. In a similar manner, the attenuation coefficients for calcified regions are significantly higher than those for softer regions. Strain imaging results on the ten patients evaluated demonstrate the ability of *in-vivo* elastographic imaging to obtain local displacement and strain distributions in the carotid plaque. Our results indicate that different regions of plaque tissue incur a varying amount of tissue displacements, indicating the presence of different underlying stiffnesses in plaque tissue.

The work was supported in part from a grant to the University of Wisconsin Medical School under the Howard Hughes Medical Institute Research Resources Program for Medical Schools.

1.4 **Elastography as an adjunct to sonography for the diagnosis of breast cancer: blinded preliminary analysis of cases from a two center clinical trial**, Brian S. Garra,[1] Christina M. Chant,[1] Louise M. Mobbs[1] and Jonathan Ophir,[2] *[1]Department of Radiology, University of Vermont College of Medicine & Fletcher Allen Health Care, Burlington, Vermont, 05401 and [2]Department of Diagnostic and Therapeutic Imaging, University of Texas Medical School, Houston, TX 77030*

As part of a two center clinical trial testing the usefulness of elastography as an adjunct to mammography and sonography for the diagnosis of breast cancer, over 150 biopsy proven patients have been so far studied at the University of Vermont. A blinded review of the first 59 cases was performed by a single experienced observer. A level of suspicion score was assigned using a 100 point scale based upon three features subjectively evaluated by the observer. The features were: lesion hardness relative to the surrounding tissue, lesion border characteristics and the difference in apparent size of the elastographic lesion relative to the sonographic lesion. Also, the transverse maximum diameters of both the elastographic and sonographic lesions were measured and compared. ROC analysis was used to evaluate the performance of the features.

The area under the ROC curve (Az) for all lesions was 0.79, which is indicative of only fair performance. Using a level of suspicion score of 60/100, the sensitivity was 67% and the specificity was 92%. This performance level seemed to be related to including cases in which the sonographic lesion was not identified on the elastograms. Including such cases resulted in three of the four misclassified cancers. Both lobular carcinomas were among the missed cases suggesting that these tumors may not be significantly harder than the surrounding tissue.

Removing all the cases in which a lesion was not seen on the elastogram resulted in a markedly improved ROC curve (47 patients) with Az = 0.93 (sensitivity = 87.5%, specificity = 89.7% for a threshold score of 60).

Our findings suggest that elastography is a powerful tool for distinguishing benign from malignant breast lesions if cases in which the lesion is not seen elastographically are not further classified. With improved image quality, we are hopeful that the percentage of lesions not seen elastographically will decline.

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1.5 **Towards a molecular understanding of bioelasticity**, Michael F. Insana, Mallika Sridhar, Rebecca Yapp, Carol Shaffer and Jie Liu, *U. Illinois at Urbana-Champaign, mfi@uiuc.edu*

In elasticity imaging, tissues are stimulated with mechanical forces while the spatio-temporal strain response is observed ultrasonically. The viscoelastic properties of soft tissues and biopolymers such as hydrogels depend on the strength of the molecular bonding forces connecting the collagen matrix and fluids. The basis for diagnostic imaging is that disease processes alter molecular-scale bonding in a way that varies the measurable stiffness and viscosity of the tissues. To select from the many viscoelastic parameters that influence strain image appearance, we conducted a study of time-varying strain (compressive creep geometry) in tissue-like gelatin gels. Deriving the constitutive equations for our imaging experiments and adopting standard models, we then measured the Fourier spectrum and the retardance time spectrum of the viscoelastic response under a range on common imaging conditions. The results showed there is a broad distribution of viscoelastic processes contributing to the time-varying strain, which is consistent with known thermodynamic properties of amorphous polymers. We found that by fitting creep data to a two-component discrete Voigt model we were essentially selecting the two principal eigenvalues of the signal subspace. It seems that the high-dimensional viscoelastic response of biopolymers can be well represented by just a few carefully selected features that can be imaged. Our analysis provides investigators a method for designing elasticity imaging methods specifically for various diagnostic tasks that responds to features descriptive of the physical chemistry of disease processes.

This study was funded in part by NIH CA082497 and the UIUC Beckman Institute for Advanced Science and Technology.

1.6 **Time/frequency domain calibration curves for quantification of tissue elasticity with scanning acoustic microscopy,** J. Lawrence Katz,[1,2] Orestes Marangos,[1] Yong Wang,[2] Paulette Spencer[2] and Anil Misra,[1] *[1]School of Computing and Engineering, University of Missouri-Kansas City, Kansas City MO 64110 and [2]Department of Oral Biology, University of Missouri-Kansas City*

Scanning acoustic microscopy (SAM) is one of the few nondestructive techniques that provide micromechanical properties of samples, including biological tissues, at very high resolution.(1) One technique used by many SAM researchers is to quantify the micromechanical properties of materials by measurement of the reflection coefficient, $r = (Z_2-Z_1)/(Z_2+Z_1)$, where $Z_2$ and $Z_1$ are the acoustic impedances ($Z =$ **.v)** of the material being studied and the acoustic coupling fluid respectively.(2-6) However, in these studies, measurement of the reflection coefficient requires calibration of the received signal amplitude as related to the reflection coefficients of known materials. This is based on the common assumption that the received signal amplitude is proportional to the reflection coefficient. Thus, in these previous SAM studies, linear fits typically have been used based upon either a narrow range(3,4) or a wide range(5,6) of material reflectance. For biological materials, the reflection coefficients vary over a wide range and are often frequency (scale) dependent. Furthermore, nonlinearities induced by the detection system electronics may introduce instrument drift in the measurements(2) that may influence the measured signal, greatly compromising the accuracy of the micromechanical properties obtained using linear fits. Thus, linear fits could result in erroneous results when: (1) the linear fit does not agree with the theoretical relationship; (2) the reflectance of the target material lies outside the range of the calibration materials; and (3) the target material has heterogeneous reflectances varying over a wide range. In addition, materials with very low $r$ values ($r \sim <0.2$) do not provide a strong signal so that system amplification settings have to be used in order to obtain a measurable signal. Therefore, for any quantification purposes, the calibration has to be performed for the specific material as well as for the specific SAM system. In this study, two methods of calibration for SAM micrographs are utilized: (1) a time domain analysis and (2) a frequency

domain analysis. These analyses were applied to develop calibration curves for the WINSAM 100 SAM system (Kramer Scientific Instruments GmbH, Herborn, Germany) using a 30 MHz central frequency transducer (KSI PT30-002). Eleven reference materials with acoustic impedance ranging from TPX® ~ 1.8 MRayl to Tungsten (W) ~ 100 MRayl were used. Signals from the SAM then were analyzed using both the time and frequency domain calculations in order to obtain gain functions for various system amplification settings. These settings then were used to predict the relationships between reflection coefficients and signal amplitude or signal average power. The power of such analyses is that it now is possible to separate effects of materials from system electronic effects. This results in better estimates of errors in measured material properties. Validation of the developed calibration curves was done by comparison with independently-measured reflection coefficients for the two lowest impedance materials, LDPE and TPX®.

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## 2. Tissue Parameters 1

2.1 **Physiologic wave propagation and characterization in the murine heart and aorta,** E.E. Konofagou, J. Luo, K. Fujikura and M. Pernot, *Department of Biomedical Engineering, Columbia University, New York, NY*

The cardiac function could be summarized by two phases: active contraction and passive relaxation. In reality, over the course of an entire cardiac cycle, the myocardial motion is affected by several mechanical and electrical events such as vascular flow, valve opening and closing and electrical conduction of the myocytes. Most of these events are short-lived (on the order of 1ms duration) compared to the much larger phases of systole and diastole. Therefore, these events cannot be imaged by conventional imaging systems due to their limited temporal resolution. In this study, we propose a method for imaging and characterizing the waves that are generated in the murine myocardium as a result of the aforementioned transient motions. High resolution (30 MHz) imaging using a Vevo 770 (Visualsonics, Inc.) was used at high frame rates (up to 8,000 fps) by synchronizing the two-dimensional rf signal acquisition on the electrocardiogram (ecg) signals. In-vivo imaging of mechanically- and electrically-induced waves will be demonstrated in anesthetized mice. The waves propagated in a direction orthogonal to that of the estimated myocardial motion. The motion was estimated using cross-correlation techniques on successive rf images. The propagation of several transient mechanical waves was imaged in different regions of the myocardium.

The wave velocities were found to be between 0.44 m/s and 5 m/s depending on the location and type of origin of the wave. These waves may be generated by either a purely mechanical effect or through the electromechanical coupling in the myocardium depending on the phase of the cardiac cycle, in which they occur. Finally, the murine abdominal aorta was imaged using the same imaging technique and the propagation of a mechanical pulse wave was imaged during pulsatile flow over one cardiac cycle. The pulse wave velocity was measured equal to 3.1 m/s and the Young's modulus of the vessel wall of 79 kPa was derived based on the Moens-Korteweg equation. This method could potentially be used for mapping the stiffness of the myocardium and aortic or arterial walls and may constitute a new imaging technique for the early diagnosis of cardiovascular diseases based on its mechanical and/or electromechanical properties.

2.2 **Vascular growth factor and extracellular matrix protein downregulation with siRNA in uveal melanoma xenografts: an ultrasound backscatter study**, Mark J. Rondeau,[1,2] Ronald H. Silverman,[1-3] Harriet O. Lloyd,[1] Avnish A. Deobhakta,[1] Monica S. Patel,[1] Omer Gal[1] and D. Jackson Coleman,[1,2] *[1]Department of Ophthalmology, WMC of Cornell University, New York, NY 10021, [2]Margaret M. Dyson Vision Research Institute, New York, NY 10021 and [3]Frederic L. Lizzi Center, Riverside Research Institute, New York, NY 10038, mark.rondeau@cornell.edu*

Previous work, using an experimental tumor model with significantly upregulated expression of genes encoding for a critical vascular growth factor (VEGF) and an important extracellular matrix (ECM) protein (laminin) expression, demonstrated an increase in overall ultrasound backscatter that was also correlated with increased vascular and extracellular matrix density as measured by histological means. In this study, we examine the use of a more biological relevant model to perturb tumor growth, where the constitutive expression of genes for VEGF and laminin are reduced using systemic application of short interfering RNA, and the effect of these critical growth factors on tumor backscatter is evaluated.

M619 human tumor xenografts were grown in nu/nu athymic nude mice. Selected tumors were treated with IP injection of siRNA shown to reduce tumor growth *in-vivo*.

Control tumors were untreated. Mice were scanned with a 3-D vhf ultrasound system to obtain parameter images and calibrated ensemble-averaged power spectrum measurements, as well as tumor volume. We examined the relationship between ultrasound backscatters and angiogenesis qualitatively using immunohistochemistry with antibodies to CD-31 and laminin and quantitatively using flow cytometry to determine percentage of cells expressing the given protein.

Both VEGF-siRNA and laminin-siRNA tumors show global reduction in backscatter (MBF) compared with control tumors. A correlation with reduction in vascular and ECM expression as measured by flow cytometry was also seen.

The downregulation of genes that control angiogenesis and the deposition of extracellular matrix proteins both influence tumor backscatter in xenograft models. This is consistent with clinical studies that correlate vascular density and ECM features with ultrasound backscatter. To better understand the origin of tumor backscatter and it relationship with tumor growth and treatment effects, the interactions of these and other genes active in tumors growth and metastasis should be evaluated in models with multiple downregulated genes.

2.3 **Scattering theory validation and extension**, Shreedevi Dasgupta, Jonathan Mamou and Ernest J. Feleppa, *Riverside Research Institute, New York, NY*, *feleppa@rrinyc.org*

We have initiated a study to test the hypothesis that the theoretical framework first published by Lizzi and coworkers and subsequently expanded by Insana and Lizzi and their coworkers accurately relates spectral-parameter values to mechanical and geometric proper-

ties of isotropic, weak scatterers insonified by moderately focused transducers. We plan the study to go beyond rigorous validation of the original theory using its original assumptions to include assessment of spectral behavior under scattering conditions that are outside those assumptions, i.e., scattering for nonisotropic and densely-packed scatterers, scattering with strongly-focused transducers and scattering over a broad range of frequencies. Success in this study will provide a reliable, more-general basis for quantitative determination of scatterer properties in diagnosing disease, monitoring disease progression or response to therapy and evaluating tissue properties in basic biological and physiological research.

To validate the theory, we are utilizing isolated, living and fixed, cultured cells and nuclei suspended in a liquid medium in known concentrations and having known sizes. We are acquiring ultrasound rf echo signals using broadband, focused transducers with center frequencies ranging from 10 MHz to 75 MHz and with f-numbers ranging from 2 to 4 at each center frequency. Because existing theory utilizes spatial autocorrelation functions and form factors related to the spatial distributions of the acoustic impedances of scatterers, we are computing acoustic impedances for each scatterer type from ultrasound propagation velocities and mass densities measured using cells compacted into pellets by centrifugation. The rf echo-signal data enable us to generate normalized (system-independent) power spectra for various experimental scattering and insonification conditions using standard Fourier methods; the acoustic impedance and concentration data enable us to generate corresponding theoretically predicted spectra. These two types of results provide a basis for comparing spectra computed from echo signals to spectra predicted by theory.

In future studies, we will extend our analyses to include alternative methods of estimating scatterer properties, including autoregression and wavelet methods, as well as the commonly used Fourier methods. We also will compare alternative methods of normalization, i.e., those based on deterministic reflections from planar targets and those based on stochastic returns from well-defined scattering targets. These studies will provide greater insight into phenomena related to scattering of ultrasound by tissue and will establish a firm foundation for improved ultrasonic means of evaluating and imaging tissue based on the properties of its constituent scatterers.

2.4 **On the statistics of ultrasonic spectral parameters**, S. Kaisar Alam, Frederic L. Lizzi, Samuel Mikaelian, Paul Lee and Ernest J. Feleppa, *Riverside Research Institute, New York, NY, feleppa@rrinyc.org*

Many groups throughout the world are using RRI-pioneered ultrasonic rf spectrum analysis to analyze tissue features and structural information unavailable in B-mode images. Spectrum analysis has been used to differentiate tissue types (e.g., benign vs. malignant tissue) in a variety of organs, (e.g., the eye, prostate, heart, liver, etc.,) and to monitor treatment (e.g., radiation therapy of intraocular cancers). In this presentation, we discuss how averaging procedures and the sequence of mathematical operations used to compute spectra and from them to derive spectral-parameter values affect the accuracy and precision of spectral estimates. Averaging procedures and log conversion (conversion to dB) introduce a constant bias that affects spectral amplitudes and the values of intercept and midband-fit parameters; the bias depends on the sequence of operations of log conversion and averaging and on the number of independent spectra or parameter values that are averaged. We derive expressions to correct for these biases. Finally, we show that the standard deviations for slope and midband-fit estimation can be minimized by averaging spectra prior to dB conversion and before computing spectral parameters by linear regression. Experimental results derived from phantoms are in remarkable agreement with these theoretical predictions.

This research is supported in part by NIH grant EB000238. It was inspired by the late Frederic L. Lizzi.

2.5 **Data sharing schema for ultrasound modeling**, Robert Muratore and Mark Rondeau, *Riverside Research Institute, New York NY 10038 and Weill Medical College of Cornell University, New York NY 10021, muratore@rrinyc.org*

We are developing a modular model of ultrasonic tissue characterization and bioeffects that we term the Riverside Acoustic Model (RAM). RAM is currently being realized in the MATLAB programming environment (The MathWorks, Inc., Natick MA USA). Our implementation has an object-oriented flavor, with data-sharing among modules regulated by XML (eXtensible Markup Language).

XML is based on a simple idea: filing is easier when labels are consistent. Filing activities include file manipulations by computer operating systems and sharing of experimental and numerically simulated data among software analysis routines. Consistency of labeling is facilitated in XML with a limited vocabulary defined in external reference documents called schemas. The location of these documents is called a namespace.

The RAM namespace schema is meant to complement the emerging Digital Imaging and Communications in Medicine XML standard (DICOM-X) by introducing variables that are of interest to the researcher in tissue characterization and bioeffects. (XML syntax allows multiple and indeed conflicting schemas; ambiguities are resolved by reference to specific namespaces.)

A simple schema defines a set of XML tags. Tags are indicated with angle brackets, and data are enclosed between pairs of tags. Metadata are attributed within an opening tag as needed. For example, <frequency units="MHz">40.0</frequency> indicates a 40.0 MHz frequency.

XML tags defined by the RAM namespace schema include best-practice reporting variables as promulgated by the American Institute of Ultrasound in Medicine, e.g., transducer aperture shape, acoustic power output at transducer, range from transducer to target and intervening media acoustic attenuation coefficients.

We consider several types of data marked-up by the XML tags: field data (e.g., scalar fields such as pressure and temperature and vector fields such as radiation force), parameter data (e.g., the frequency value in the example above), and metadata (e.g., the frequency unit in the example above). Each of these is encoded in ASCII. In addition, data can be referenced by calls to databases (typically binary-encoded data from experimental acquisition and legacy simulations).

This work was supported in part by Bioengineering Research Partnerships Grant 5R01 CA084588 from the National Cancer Institute and the National Heart, Lung, and Blood Institute (USA), Ernest J. Feleppa, Ph.D., Principal Investigator.

## 3. Review, Priorities and Funding of NIH Programs

3.1 **Current status of the proposal-review process in the imaging technologies at NIH**, Lee Rosen, Ph.D., *Scientific Review Administrator for Biomedical Imaging Technology (BMIT), Center for Scientific Review, NIH*

3.2 **Current program priorities and funding opportunities in the National Cancer Institute**, Keyvan Farahani, Ph.D., *Program Director, Cancer Imaging Program, National Cancer Institute, NIH*

3.3 **Current program activities at the National Institute for Biomedical Imaging and Bioengineering**, Hector Lopez, Ph.D., Program Director, *Division of Applied Science and Technology, National Institute for Biomedical Imaging and Bioengineering, NIH*

## Panel Discussion

*Moderators:* E.J. Feleppa, J.G. Miller
*Participants:* K. Farahani, H. Lopez, L. Rosen

## 4. Tissue Parameters 2

4.1 **Regional variation in the measured apparent ultrasonic backscatter of fetal pig hearts**, Allyson A. Gibson, Gautam K. Singh, Agnieszka Kulikowska, Kirk D. Wallace, Joseph J. Hoffman, Achiau Ludomirsky, James G. Miller and Mark R. Holland, *Laboratory for Ultrasonics,Washington University, St. Louis, MO, james.g.miller@wustl.edu*

*Introduction:* Intrinsic composition and myofiber orientation of the heart can profoundly affect measured ultrasonic backscatter and attenuation values. As a result, measurements of the apparent backscatter from myocardium can provide an approach for assessing regional differences in myocardial properties. Previous studies have demonstrated regional differences in measured apparent backscatter in mature hearts.

*Objective:* The goal of this study was to characterize and compare regional backscatter properties in fetal hearts through measurements of the apparent backscatter from the left-ventricular free wall and right-ventricular free wall.

*Method:* Five excised, formalin-fixed fetal pig hearts representing 55-60 days of gestation, were investigated. Thinly-sliced specimens were obtained by cutting each heart in the transverse plane (perpendicular to the long axis of the heart) at the mid papillary level. Measurements of the backscattered energy from these approximately 1.5 mm thick slices were acquired using a 50 MHz single element transducer with insonification perpendicular to the face of the myocardial specimen in a C-scan format. The entire transverse slice of the heart was interrogated and, at each site, the frequency domain apparent integrated backscatter was obtained.

*Results:* Measurements of the apparent integrated backscatter demonstrate two distinct levels of backscatter in the right ventricle and three distinct levels of backscatter in the left ventricle. These bright bands of backscatter appear to be consistent with the anisotropy of the fiber orientation as seen in the corresponding stained histology specimen. Comparison of the apparent backscatter from the brightest region of the right ventricle demonstrates a greater level of backscatter than the brightest region in the left ventricle, suggesting an intrinsic difference in the myocardium of the left and right ventricles.

*Conclusion:* The anisotropy of the fiber orientation within a ventricle and between the right and left ventricles are seen by the brightness of the bands in the apparent backscatter images. The level of backscatter from the myocardium of the right ventricle is greater than that of the left. This study suggests that the intrinsic properties of the left and right ventricle are distinct in fetal pig hearts as young as 50 days gestation, half the gestational period.

[NIH 4 R37 HL040302 & R21 HL086304]

4.2 **An approach for measuring the cyclic variation of backscatter in fetal human hearts at mid-gestation**, Mark R. Holland, Gautam K. Singh, Agnieszka Kulikowska, Carol A. Kirschner and Achiau Ludomirsky, *Washington University, St. Louis, MO, james.g.miller@wustl.edu*

Measurements of the systematic variation of backscattered ultrasonic energy from the myocardium over the heart cycle (i.e., cyclic variation of backscatter) may represent a useful approach for investigating intrinsic characteristics of the developing fetal heart. The objective of this investigation was to demonstrate the feasibility of measuring the cyclic variation of backscatter from the hearts of human fetuses at mid-gestation from analyses of

two-dimensional grayscale images acquired with a commercial echocardiographic imaging system. Echocardiographic images of mid-gestational fetuses were obtained using a Siemens/Acuson Sequoia imaging system configured to give a linear relationship between the displayed grayscale value and the level of ultrasonic backscatter expressed in decibels. Transverse (long axis) cross-sectional images of the fetal heart consisting of approximately 6 heart cycles were stored as 8-bit digital cineloops. These image data were analyzed offline using NIH ImageJ™ analysis software by placing regions-of-interest the mid-myocardium of the walls of the left and right ventricles. Cyclic variation data was generated by determining the mean grayscale level within the region-of-interest for each of the acquired image frames. Changes in the measured mean grayscale levels over the heart cycle were expressed in decibels using previously-determined calibration data. The measured cyclic variation data were characterized in terms of the magnitude and normalized time delay relative to the systolic interval. Results demonstrate successful measurements of the cyclic variation of backscattered ultrasound from both the left and right ventricular myocardium of fetal hearts. These data suggest that it is feasible to obtain measurements of the intrinsic properties of the developing fetal heart based on analyses of cyclic variation data.

4.3 **Some potential improvements in ultrasonic tissue characterization achieved by reducing phase aberration effects**, James G. Miller, Kirk D. Wallace and Mark R. Holland, *Washington University, St. Louis, MO, james.g.miller@wustl.edu*

The focus of this presentation is on the consequences of phase cancellation at the face of phase sensitive piezoelectric receiving apertures and the resulting phase aberration artifacts on ultrasonic tissue characterization measurements. One goal is to explore potential improvements in tissue characterization that arise as a consequence of imaging techniques that are designed to reduce such sources of potential error. Ultrasonic tissue characterization represents an approach that complements and extends presently available high-resolution imaging. Because high-resolution images are capable of providing good anatomical detail, tissue characterization measurements, such as backscatter and attenuation, can be reported with less spatial resolution in order to achieve more robust quantitative values. Such modest spatial averages of the intrinsic material properties of normal and pathologically altered tissues are obtained from local measurements derived from the same signals that are used to form the ultrasonic images. Hence, improvements in high resolution imaging such as those associated with phase aberration reduction translate directly into improvements in tissue characterization. In this presentation, we focus on examples drawn primarily from echocardiography. Current echocardiographic images are frequently acquired with harmonic mode (nonlinear) imaging and exhibit substantial resolution of anatomical detail. The use of myocardial tissue characterization to identify alterations in local tissue properties arising from specific pathologies offers the promise of enhancing the diagnostic information available from echocardiographic imaging. Among the challenges to be overcome in meeting this goal are approaches for dealing with the intrinsic anisotropy of the heart and for overcoming limitations that arise as a result of phase and amplitude aberrations associated with propagation through an intrinsically inhomogeneous medium.

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4.4 **Multimodality/multimode characterization of breast tissues**, P.L. Carson, G.L. LeCarpentier, M.M. Goodsitt, R.C. Booi, Sumedha Sinha, Ganesh Nayaransami, M.A. Helvie and M.A Roubidoux, *University of Michigan, Ann Arbor, MI, pcarson@umich.edu*

Clinical breast imaging and numerous quantitative studies have shown that gray scale ultrasound provides different, complementary information to that of mammography and is itself complemented by color flow and strain imaging. The judged value of the added

diagnostic information from ultrasound for various clinical roles is still in flux. Combination of ultrasound and digital mammography in the same view offers the potential of precisely identifying the region of the mammogram corresponding to identified ultrasound masses but the x-ray display is only the line integral of the attenuation coefficient through the entire breast thickness. Hence, tissues are superimposed in the x-ray images, which can result in the camouflaging of lesions and/or the appearance of false lesions. X-ray tomosynthesis substantially resolves this problem by producing 3D images of the breast. Anecdotal information from the first 20 breasts studied with multimode ultrasound and X-ray tomosynthesis at our institution is presented. Solid/cyst differentiation might still be important and best done with ultrasound, particularly in the dense breast. From two cancers studied to date, the large apparent dark, then bright rings seen around some or most breast cancers in X-ray tomosynthesis is larger than the usual hypoechoic ultrasound core. Comparison of spatial extent and, possibly vessel morphology, in X-ray tomosynthesis with that in gray scale ultrasound and strain and color flow images of these lesions is tantalizing.

Supported in part by NIH Grants 1RO1CA91713 and 1P01CA87634. Work performed in cooperation with GE Global Research Laboratories and Healthcare.

4.5 **Acoustic backscatter changes in the corneal stroma associated with hydration**, Ronald H. Silverman,[1, 2] Monica Patel,[2] Omer Gal, Mark J. Rondeau,[2] Harriet O. Lloyd,[2] Tatiana Raevski[2] and D. Jackson Coleman,[2] *[1]Frederic L. Lizzi Center for Biomedical Engineering, Riverside Research Institute, New York, NY and [2]Weill Medical College of Cornell University, New York, NY, rsilverman@rrinyc.org*

The human cornea is approximately a half millimeter in thickness. The 50 m thick epithelium overlays the stroma, which is an avascular tissue composed of collagen lamellae with sparsely distributed keratocytes. The stroma, which comprises the bulk of the cornea, is internally limited by Descemet's membrane and an endothelial cell layer. The endothelium is responsible for maintenance of stromal dehydration. Impairment of the endothelium results in corneal edema and lost of transparency.

Our aim was to investigate the effect of corneal edema on acoustic backscatter. We performed experiments on fresh bovine eyes. We removed the cornea along with a border of intact sclera from the globe. The cornea was then submerged for a period of 45 minutes in corneal preservation medium and then scanned. The cornea was then successively placed for 45 minutes in hypotonic media at concentrations of 75%, 50%, 25% and 0% (water) and scanned at each concentration.

The scanning system consisted of three linear stages (1 m positional resolution) controlled by a National Instruments PCI-7354 motion controller. A spherically-focused lithium niobate transducer with a 6 mm aperture and 12 mm focal length was used in combination with a Panametrics 5900 pulser receiver. Radiofrequency (rf) echo data were acquired using an Acqiris DP310 digitizer at a sample rate of 400 MHz (12-bits/sample).

Spectral parameter images of the corneal stroma were produced by manually delineating the anterior stroma in the B-mode image and analyzing a region of fixed depth (0.5 mm or 1.0 mm) beneath this boundary. A floating sample region 3 vectors wide by 32 samples in depth was rastered throughout the region-of-interest (ROI) and calibrated power spectra determined at each position. Calibrated power spectra were computed by multiplying the rf data by a Hamming function, performing a Fast Fourier Transform (FFT), dividing by the FFT of a focal-plane glass plate reflection, and expression of the squared magnitude in decibel units. Spectral slope, intercept and midband fit were determined from the linear best fit to the calibrated power spectrum within its 15 dB bandwidth. Attenuation coefficients were determined by measuring slope (dB/MHz) as a function of tissue depth (cm) within the ROI.

Results showed statistically-significant changes in slope, midband fit and attenuation with hydration. Slope and midband fit increased and attenuation decreased as the normality of the immersion medium was decreased.

Our findings suggest that stroma edema produces intralamellar fluid spaces that act as small scatterers. The 'dilution' of the stroma by fluid may be responsible for the observed decrease in attenuation.

These findings may be applicable for noninvasive characterization not only of corneal edema, but biomechanical changes in the stroma associated with disease (e.g., keratoconnus) or refractive surgery.

This work was supported in part by NIH grant EB000238 and Research to Prevent Blindness.

## 5. Bone

5.1 **Ultrasonic characterization of cancellous bone using apparent integrated backscatter**, Brent K. Hoffmeister,[1] David A. Johnson,[1] John A. Janeski,[1] Daniel A. Keedy,[1] Brian W. Steinert[1] and Sue C. Kaste,[2] *[1]Rhodes College Department of Physics, 2000 North Parkway, Memphis, TN 38112 and [2]St. Jude Children's Research Hospital, Department of Diagnostic Imaging, Memphis, TN 38105, hoffmeister@rhodes.edu*

Apparent Integrated Backscatter (AIB) is a measure of the frequency averaged (integrated) backscattered power contained in a portion of a backscattered ultrasonic signal. AIB has been used extensively to study soft tissues but its usefulness as a tissue characterization technique for human cancellous bone has not been demonstrated. To address this, we performed measurements on 25 specimens of human cancellous bone over five different frequency ranges using broadband ultrasonic transducers with center frequencies of 1, 2.25, 5, 7.5 and 10 MHz. Specimens were obtained from the femoral heads of 7 donors and prepared in the shape of cubes (15 mm side length) with faces oriented along principal anatomic directions (anterior, posterior, proximal, distal, superior and inferior). A mechanical scanning system was used to measure AIB at multiple sites on each specimen along each orientation. The average AIB values from the specimens were plotted as a function of the following properties of the specimens: bone mineral density, mechanical modulus, yield strength and ultimate strength. A linear regression analysis was performed to determine the degree of correlation between AIB and these properties. The correlation coefficients ranged from $R = 0.35$ (AIB at 10 MHz vs. mechanical modulus) to $R = 0.88$ (AIB at 7.5 MHz vs. bone mineral density). The correlation improved progressively with transducer frequency up to 7.5 MHz, and then decreased for 10 MHz. We conclude that AIB may be a useful tissue characterization technique for human cancellous bone, especially in a frequency range around 7.5 MHz.

5.2 **Ultrasonic scattering from parallel nylon wire cancellous bone phantoms,** Keith A. Wear, *Food and Drug Administration, Rockville, MD*

*Background:* Ultrasound is now a widely-accepted modality for diagnosis of osteoporosis. It is important to study scattering of ultrasound by cancellous bone because scattering (1) has shown diagnostic potential and (2) is a component of attenuation, which has been shown to be highly correlated with bone mineral density. Previously, scattering measurements from single wires were used to compare to measurements from cancellous bone. The comparison required the assumption of incoherent scattering to extrapolate scattering from a single cylinder to scattering from a network of cylinders. *Objective:* To extend the experimental model by the use of arrays of wires instead of single wires. *Methods*: Scattering coefficients were measured in seven phantoms that consisted of parallel nylon fishing lines (simulating trabeculae) in two-dimensional arrays (custom-built by CIRS, Norfolk, VA).

Line diameters were 152, 203, 254 and 305 m. (Mean trabecular thickness for human calcaneus is 127 m.) Scattering coefficients were predicted using Faran's theory of elastic scattering from cylinders. *Results:* Good agreement between theory and experiment was found. *Conclusion:* Parallel nylon-wire phantoms are useful for simulating the scattering properties of cancellous bone.

This work was supported by a grant from the FDA Office of Women's Health.

5.3 **An alternative interpretation of the paradoxical 'negative' dispersion reported in bone**, James G. Miller and Karen Marutyan, *Washington University, St. Louis, MO, james.g.miller@wustl.edu*

Reports from many laboratories of measurements of the phase velocity of ultrasonic waves propagating in cancellous bone indicate that in a substantial number of specimens the velocity decreases with increasing frequency. In addition, these and other studies typically report that bone is characterized by an attenuation coefficient that varies with frequency in a fashion that could be crudely approximated as linear with frequency. Under such circumstances, some approximations to the (exact) Kramers-Kronig relations suggest that an increase of velocity with frequency would be expected, in contrast with the decrease with frequency that is often reported. If the attenuation coefficient were strictly proportional to frequency, the dispersion would increase logarithmically with frequency. In this presentation, we propose an alternative explanation for the observed 'negative' dispersion in cancellous bone. Our hypothesis is that the apparent negative dispersion is actually the result of the interference between the fast wave and the slow wave modes that characterize the composite structure of bone. Treatments such as Biot theory and its modifications have been used successfully to model composite media consisting of solid and liquid-like components. Such treatments predict two longitudinal modes, a fast mode in which the liquid and solid components move in phase, and slow wave in which the liquid and solid components move out of phase. Using such models, we demonstrate that the observed 'apparent negative dispersion' can result from the interference of these two modes. Apparently negative dispersions result even though the actual dispersions for the both fast and slow waves are positive.

Supported in part by NIH R37HL40302

## 6. Elasticity 2/Imaging

6.1 **Image quality, tissue heating and frame-rate trade-offs in ARFI imaging**, Richard Bouchard,[1] Jeremy Dahl[1] and Gregg E. Trahey,[1,2] [1]*Department of Biomedical Engineering, Duke University, Durham, NC and* [2]*Department of Radiology, Duke University, Durham, NC, rrb@duke.edu*

As Acoustic Radiation Force Impulse (ARFI) imaging continues to develop into a clinically-viable technique, we strive towards its real-time implementation. The real-time use of ARFI imaging requires both shorter acquisition times for a single ARFI displacement map and repetitive acquisition of these frames. Due to the high energy of pulses required to generate appreciable radiation force, however, repetitive acquisition could result in substantial tissue heating. In an effort to reduce both acquisition time and tissue heating, novel beam sequencing along with parallel-receive acquisition can be employed. These techniques reduce the total number of ARFI impulses needed to generate an image as well as minimize the time between successive impulses. We present an analysis of the trade-offs in image quality — quantified by resolution, CNR and SNR — resulting from these various acquisition schemes. Our results indicate that these techniques yield a significant improvement in frame rate with only moderate decreases in metrics of image quality. The tissue heating resulting from these schemes is also assessed through FEM modeling.

This work has been supported by NIH 1R01HL075485, NIH 1R01CA114075, NIH 1R01EB002132, NIH 1R01CA114093 and the NSF-GRFP. We thank Siemens for in kind support.

6.2 **A finite element model of an integrated indenter/acoustic radiation force impulse (ARFI) imaging system**, Liang Zhai, Mark Palmeri, Richard Bouchard, Roger Nightingale and Kathryn Nightingale, *Department of Biomedical Engineering, Duke University, Durham, NC, liang.zhai@duke.edu*

Acoustic Radiation Force Impulse (ARFI) imaging is an imaging technique that provides information about the local mechanical properties of tissues. For lesion-stiffness characterization, the ratio of the mean ARFI displacement inside the lesion to that outside the lesion is related to the corresponding tissue elastic modulus ratio and lesion geometry. To validate ARFI derived surface lesion detection and stiffness characterization of *ex vivo* tissue samples, such as excised colon cancer, a customized indenter system was designed and constructed. This system is capable of automated quantification of indenter loads and displacements across a surface, with concurrent ARFI imaging. To evaluate the relationship between lesion/tissue indenter displacement ratio and lesion geometry, an FEM model has been developed.

A three-dimensional FEM model has been created to simulate the indentation response of a linear, isotropic, elastic solid. Both the indenter tip and the elastic solid have a cylindrical shape and are positioned coaxially. The indenter tip is modeled as steel with a radius of 0.1 cm and a height of 0.2 cm. The elastic material has a Young's modulus of 1Kpa, a radius of 1.5 cm and a height of 1.5 cm. A frictionless contact surface is defined between the tip and the material. There are 111,055 nodes and 103,995 elements in the model. Sizes of the elements vary spatially with the smallest elements (25 m) around the edge of the indenter, to reduce the numerical error. In the absence of lesions, the stress simulated shows good agreement (within 3.5%) with that calculated from Timoshenko's analytic solution for indentation of a semi-infinite homogenous elastic media. Cylindrical lesions of varying size and stiffness were incorporated into the simulations. Relative stiffness was estimated to be the ratio of displacement inside to that outside the lesion under a given stress. Results show that indenter measured stiffness depends on both the elastic modulus ratio and lesion geometry.

This work is supported by NIH R01 CA114075 and R01 EB002132.

6.3 **Preliminary investigations into real-time cardiac acoustic radiation force impulse imaging,** Stephen J. Hsu, Richard R. Bouchard, Douglas M. Dumont, Patrick D. Wolf and Gregg E. Trahey, *Duke University, Durham, NC*

Acoustic radiation force impulse (ARFI) Imaging has been demonstrated to be a suitable imaging modality in visualizing variations in local stiffness within soft tissue. Recent advances in multiplexed and parallel ARFI imaging have shortened acquisition times and lessened transducer heating to a point where realtime ARFI imaging has become a viable avenue of exploration.

In this work, we explore the application of cardiac ARFI imaging at frame rates approaching realtime imaging. *In vivo* parallel ARFI images of a canine heart were acquired at a frequency of 10 Hz for 3 seconds. The matched eletrocardiogram (ECG) was also recorded. When registered with the ECG, the changing displacements within the sequence of ARFI images reflected the stiffness changes of the myocardium during the entire cardiac cycle. Sequences with the radiation force pulse amplitude set to zero were also acquired to measure variations within the ARFI images due to physiological motion.

Raw ARFI displacement data included an appreciable amount of cardiac motion artifact. Linear motion filters were generally able to remove this motion. However, motion

artifacts remained during periods of vigorous heart contraction and expansion. Higher order motion filters were investigated to filter this motion more effectively. The results show great promise for realtime cardiac ARFI imaging.

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6.4 **Multifrequency vibro-acoustography: theory and imaging applications**, Matthew W. Urban, Mostafa Fatemi and James F. Greenleaf, *Mayo Clinic College of Medicine, Rochester, MN 55905*, *urban.matthew@mayo.edu*

Vibro-acoustography is a method that uses the dynamic radiation force of ultrasound to harmonically vibrate tissue. This tissue vibration causes the creation of a sound field called acoustic emission that is measured by a nearby hydrophone. In current practice, two ultrasound beams of slightly different frequencies, $f_0$ and $f_0 + f$, where $f_0$ and $f$ are in the megahertz and kilohertz ranges, respectively, are used. The beams intersect at the focus of the transducer and interfere, creating the dynamic radiation force.

The acoustic emission signal from the object is inherently related to the frequency response of the object and its viscoelastic properties. However, in most cases there is no *a priori* knowledge about this frequency response. To explore this frequency response adequately, the patient or specimen may have to be scanned several times with different values of $f$. Because scanning time is finite, this leads to a lower rate of information gain and lower patient throughput.

Multifrequency vibro-acoustography is an extension of the current method in which multiple ultrasound beams with different frequencies are used to encode the radiation force with multiple frequencies for simultaneous excitation. This allows the acquisition of multiple images with different low-frequency content in a single scan.

We present the theoretical background for multifrequency excitation and image formation with this multifrequency radiation force. Using four carefully-chosen ultrasound frequencies provides six low-frequency components in the radiation force. We will show results from a vibrometry experiment for quantifying the material properties of a viscoelastic medium using a spherical inclusion. We will also present imaging results of a breast phantom.

This work was supported by grants EB002640, EB002167, and EB00535-04 from the National Institutes of Health.

6.5 **Improvements in the synthetic-focusing technique for a high-frequency annular array,** Sarayu Ramachandran, Jonathan Mamou and Jeffrey A. Ketterling, *Riverside Research Institute, Frederic L. Lizzi Center for Biomedical Engineering, 156 William St., New York, NY 10038, sarayu@rrinyc.org*

We previously showed that a synthetic-focus technique can significantly expand the axial depth of field (DOF) of a high-frequency, 5-ring, annular array. However, use of the annular array for real-time imaging is limited by the acquisition time and quantity of data required for a complete set of digitized pulse/echo A-lines. We reduced the amount of data collected by capturing echoes on only a few transmit/receive ring combinations and by using a lower sampling rate for digitizing the A-lines. We then applied a digital synthetic-focus algorithm to the acquired data during post-processing and constructed an image with an improved DOF and small lateral beamwidth (LBW).

The transducer used in this study was a 40-MHz, concave, 5-ring, annular array, fabricated in-house. The array had a 6 mm total aperture, 12 mm focal length and five equal-area annuli with 100 m spacing between annuli. Pulse/echo data captured by the transducer

were digitized and then processed using a synthetic focus algorithm. The algorithm calculated the delays needed to shift the focus of each individual A-line through a range of specified axial depths. Time delays were added to the A-lines and a gating function was used to isolate the focused portions. Focused sections were extracted and then summed to produce the final focused image. The algorithm was tested on simulated pulse/echo data, and the 6 dB axial DOF was found to be ~6 mm. Different transmit/receive ring combinations were selected to assess which grouping of annuli provided the same low LBW over the extended axial DOF while cutting down the amount of data to be captured. The transducer was then used to scan a wire phantom consisting of nine 25 m diameter wires spaced diagonally at 1mm-by-1mm intervals and the DOF, after applying the synthetic focus technique, was comparable to the results obtained from simulations. This system successfully generated high-quality images from 3D scans of mouse embryos at various stages of development. Comparisons of signal-to-noise ratios and contrast-to-noise ratios were made before and after applying the synthetic focus algorithm.

This work was supported in part by NIH Grant EY014371.

6.6 **Towards a stand-alone compact ultrasound tissue characterization system**, N. Botros and J. Shell, *Department of Electrical and Computer Engineering, Southern Illinois University, Carbondale, IL 62901-6603, botrosn@siu.edu*

This paper presents a work in progress to develop a stand-alone (no need for computer) compact system for soft tissue ultrasound tissue characterization system. The system digitizes the backscattered ultrasound signal from a selected region of the tissue using a data acquisition unit built by the authors. The digitized data is stored in a compact electronic chip; the chip in this preliminary study is Xilinx Field Programmable Gate Array (FPGA) XC4005. The FPGA chip is a compact electronic chip of approximate size of 1" 1" 0.1"; it can be easily interfaced to external signals or stimuli, external devices or another chip through the input/output pins. The stored design on the chip can be easily modified, even by the user, by just re-downloading the new design or by taking advantage of the reconfigurable nature of the chip. Because it is dedicated hardware without a host computer, the chip can operate in real-time applications where higher speed of operation is needed. The attenuation coefficient and backscattering coefficient are calculated in the frequency domain using the Fast Fourier Transform. The values of these two coefficients represent the features that carry the signature of the tissue. A pattern-recognition algorithm based on implementation of Hidden Markov Models (HMMs) is used to differentiate between normal and abnormal tissues and to classify the abnormality (if any). HMMs are statistical pattern recognition algorithms with training capabilities. Hidden Markov Models use Markov process to model the signal (the ultrasound back-scattered signal in our case) into a state-transition network with a small number of states, $N$. The signal is modeled with the following parameters: $O = \{ O_1, O_2, ..... O_t ..... O_T \}$, the observation sequence, $= [\ _1]$, the initial state probability for state I, this probability is 1 for this study; $A = [\ a_{ij}]$, the state transition probability matrix that describes how the new state $j$ may be reached from old state $i$, and $B = [b_j(x)]$, the state output observation probability matrix, which corresponds to the output of each state. The model ( ) is represented by the triple notation $= (A, B, \ )$. The data base of this study is generated by simulating the backscattered process. The elements of the observation sequence in this study are the elements of a feature set that carry the signature of the signal. These elements are values of the attenuation coefficient and backscattering coefficient in the frequency domain. The model is optimized by using training data. The model is trained by first initializing its elements $(A, B, \ )$ to arbitrary values and then inputting the observation sequence of known signal (normal tissue, abnormal type 1, ..) and updating the value of the elements until the output of the model matches the class of the input data. The

model of each feature set is stored in a reference template (file). To recognize any unknown signal, its model is computed and compared to the files in the reference template; the model that has the least-square distance from the unknown is declared the match of the unknown.

Xilinx Computer Aided Design (CAD) package that includes Hardware Description Language (HDL) is used to simulate and then synthesize on the FPGA the different components of the system mainly the acquisition unit, the Fast Fourier Transform, and the HMM.

Our work is in progress. We have built the FFT processor; we are at the final stage of building the HMM.

## 7. Prostate Cancer Management

7.1 **Overview of state of the art in the detection, diagnosis and treatment of prostate cancer**, Ernest J. Feleppa, *F.L. Lizzi Center for Biomedical Engineering, Riverside Research Institute, New York, NY, feleppa@rrinyc.org*

Excluding basal and squamous-cell skin cancers, cancer of the prostate (CaP) is the most-common cancer of men in the United States and is estimated to be the third leading cause of cancer deaths here in 2006. The American Cancer Society estimates that 234,460 new cases of CaP will be detected and 27,870 deaths will be caused by CaP this year; these numbers respectively represent 33% of new cancers detected in men and 9% of male cancer deaths in the US. Clearly, this is an important cancer, and one that is of great concern nationally.

CaP is definitively diagnosed using biopsies guided by transrectal ultrasound (TRUS). These biopsies are not targeted because CaP lesions rarely are reliably depicted in TRUS images. Many CaP cases are incorrectly determined to be cancer free because of the current inability to guide biopsies into ultrasonically visible lesions. In fact, often the decision to perform a biopsy is based on blood tests that measure levels of prostate-specific antigen (PSA) and that have very low sensitivity and specificity for CaP. Furthermore, because no current standard clinical imaging modality reliably depicts cancerous lesions, imaging cannot be used effectively for staging localized CaP, or for planning, targeting or monitoring its treatment.

However, if CaP is detected at an early stage, i.e., when it is gland confined, then the chances of a complete cure are excellent. Unfortunately, CaP that is detected at an advanced stage, i.e., when distant spread has occurred, is very difficult to manage. Treatment options include radical surgery, various forms of implanted radiation, radiation from external sources, cryotherapy, microwave therapy and high-intensity focused ultrasound.

This talk will provide a tutorial overview of current practices and problems in detecting, diagnosing, treating and monitoring CaP and will serve as an introduction for subsequent talks related to advanced topics in prostate-cancer imaging and treatment.

7.2 **Latest developments in multimodality imaging of prostate cancer**, Shreedevi Dasgupta, Jeffrey Ketterling, Andrew Kalisz, Christopher R. Porter, Marc Lacrampe and David Dail, *Riverside Research Institute and Virginia Mason Medical Center, dasgupta @rrinyc.org*

Ultrasonic spectrum analysis applied to radiofrequency ultrasonic echo signals has proven to provide a promising basis for distinguishing among different types of tissue based on sometimes subtle differences in tissue microarchitecture and scattering properties. In the prostate, spectrum analysis combined with artificial-neural-network (ANN) classification tools has enabled encouraging differentiation between cancerous and non-cancerous tissue. These methods have produced an ROC-curve area of 0.84 compared to an area of 0.64 for conventional B-mode based determinations of suspicion levels for identical regions of the gland. Based on the shape of these ROC-curves, ultrasonic spectrum-analysis alone seems

to be potentially capable of improving the sensitivity of ultrasound guided biopsies by more than 50% by using tissue-type images (TTIs) derived from ultrasound spectra and ANNs to target the biopsy needle. Such TTIs potentially can depict regions showing cancerous properties in 2 or 3 dimensions for biopsy guidance, disease evaluation, treatment planning and targeting, and therapy monitoring.

Like conventional ultrasound B-mode images, conventional magnetic-resonance images cannot reliably depict cancerous regions of the prostate. However, as in ultrasound spectral methods, magnetic-resonance spectroscopy (MRS) shows an encouraging ability to distinguish cancerous from noncancerous prostate tissue based on its depiction of chemical constituents of tissue. In noncancerous prostate tissue, the level of citrate tends to be higher than that of choline or creatine. However, in cancer of the prostate, the situation is reversed and creatine, choline, or both tend to be elevated with respect to citrate. MRS can depict the ratios of these constituents and, based on the ratios, can distinguish cancerous from noncancerous prostate tissue. As is the case with ultrasonic spectrum analysis, classification of prostate tissue by MRS produces ROC-curve areas having values ranging from 0.70 to 0.80.

Because these two modalities sense fundamentally different properties of tissue, i.e., mechanical properties for ultrasound and chemical properties for MRS, we anticipate that combining the two modalities will markedly improve classification performance. We describe current efforts to register ultrasonic and MRS data in 3-D and to correlate TTIs with prostatectomy histology.

This research is supported in part by NIH/NCI grant CA053561.

7.3 **A signal-processing strategy for ultrasonic imaging of brachytherapy seeds**, J. Mamou and E.J. Feleppa, *F.L. Lizzi Center for Biomedical Engineering, Riverside Research Institute, New York, NY, feleppa@rrinyc.org*

A new signal-processing strategy applied to the envelope of the backscattered ultrasound signal is proposed. This strategy employs singular spectrum analysis (SSA) and shows promise for reliably imaging radioactive seeds implanted in the prostate gland. Brachytherapy using small titanium-shelled radioactive seeds is proving to be a well-accepted means of treating prostate cancer. Such seeds typically are extremely difficult to image during the ultrasound-guided implantation procedure. Knowledge of seed locations during the procedure would be invaluable because it would allow dosimetry errors to be corrected immediately in the operating room. Preliminary studies discovered that seed signals contain repetitions. The algorithm uses these repetitions for detection. Seed-specific signal repetitions are identified by selecting eigenvalue pairs of the autocorrelation matrix of the envelope-detected radiofrequency echo signals. A signal then is reconstructed from the selected eigenvalues and its power spectrum is computed to derive a 'P-value' indicative of the likelihood of the presence of a seed at the location of that repetitive signal. P-values are color-coded and superimposed over a conventional, 2D, B-mode image to display seeds with ample sensitivity and specificity. 3D renderings further aid visualization of the seeds. These new ultrasound images can be used readily by clinicians to locate seeds. Simulations to assess performance as a function of different levels of white and speckle noise and the presence of signals at repetition periods not associated with seeds were conducted and showed robustness of the algorithm to noise; that the algorithm can be tuned to be sensitive only to seed-specific repetitions. Experiments with seeds implanted in beef as well as in an ideal scattering environment were conducted. Seeds were detected in each case; however, some ambiguous (falsely positive) regions appeared in the beef experiment. The SSA strategy shows great potential for imaging directly in the operating room. In particular, the SSA algorithm uses envelope-detected signals that are available on every clinical scanner.

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7.4 **Noninvasive prostate lumpectomy using tissue type imaging and high intensity focused ultrasound**, Russell Fedewa,[1] Ernest J. Feleppa,[2] Ralf Seip,[1] and Narendra T. Sanghvi,[1] *[1]Focus Surgery, Inc., 3940 Pendleton Way, Indianapolis, IN 46226 and [2]Riverside Research Institute, Frederic L. Lizzi Center for Biomedical Engineering, 156 William Street (9th Floor), New York, NY 10038-2609*

The long-term goal of this work is to reduce the treatment time of current minimally-invasive, localized prostate cancer treatments by performing targeted treatments via the use of tissue type imaging (TTI) with high-intensity focused ultrasound (HIFU). This approach is comparable to the use of a lumpectomy for early stage localized breast cancer.

HIFU permits precise ablation of tissue through noninvasive surgery. The addition of TTI to the HIFU system will permit the identification of prostate regions likely to contain cancer resulting in a noninvasive targeted treatment of prostate cancer.

Cancer of the prostate (CAP) is the most-common non-skin cancer occurring in men in the United States and it is the second leading cause of cancer death for men behind lung cancer. In 2006, an estimated 234,460 new cases of prostate cancer will be diagnosed and 27,350 men will die of CAP in the United States and, world wide, approximately 269,000 people died of prostate cancer in 2002. The changes discussed above for lowering the PSA threshold could result in upwards of 680,000 men diagnosed with prostate cancer each year with many of these men diagnosed with asymptomatic cancer. Most instances of CAP are multifocal, which demands the treatment of the entire prostate gland to insure effectiveness since the current cancer diagnostic tests (biopsy and PSA) are limited regarding the precise location and extent of cancer within the prostate. However, for men with early stage CAP where the extent of the cancer can be limited using an invasive saturated biopsy approach, targeted treatment of CAP is being performed.

TTI is able to provide a mapping of the likelihood of CAP based on analysis of the rf backscatter from the prostate tissue and clinical measurements (PSA). Implementing TTI on the Sonablate® 500 system (SB-500, Focus Surgery, Inc., Indianapolis, IN) will permit the targeting and treatment of regions of cancer within the standard HIFU treatment. HIFU treatment of the prostate is composed of positioning of the probe under ultrasonic image guidance, capture of an image set depicting the entire prostate volume, treatment planning and treatment monitoring. Each HIFU treatment is built on systematically placing lesions (3 mm 3 mm 10 mm) next to each other within the prostate to ablate the targeted tissue. Following each treatment, the treated site is imaged in the transverse direction (sector image) and the sagittal direction (linear image), which permits the user to monitor and adjust the treatment based on the image feedback. Current capabilities of the SB-500 include rectal wall detection, reverberation detection for insuring proper coupling with the rectal wall, reflectivity index measurements, NVB detection (Doppler) and 3D visualization of the prostate and treatment plan.

The precision of HIFU lends itself to targetted prostate cancer treatment based on TTIs that are integrated into the imaging (2D and 3D) of the SB-500 platform. The image feedback following treatment at each site presents the potential to use the TTI approach to provide treatment verification as well as treatment planning.

## 8. ROC Analysis

8.1 **A tutorial review of approaches for assessing the quality of diagnostic tests leading to ROC analysis with illustrations from ultrasonic tissue characterization**, James G. Miller, *Washington University, St. Louis, MO, james.g.miller@wustl.edu*

This presentation is designed to illustrate some of the features of approaches for characterizing the quality of diagnostic tests based on original contributions by Charles Metz of the University of Chicago and members of the ultrasonic tissue characterization community who have presented at this Symposium in the past, including Robert Wagner and Keith Wear. We will illustrate with concrete examples many of the well known approaches for characterizing diagnostic tests including accuracy, sensitivity (true positive fraction), specificity (true negative fraction), false positive fraction, false negative fraction, positive predictive value, negative predictive value and others. We will illustrate the use of the receive operator characteristic (ROC) approach as a method that overcomes limitations associated with many of these measures arising from the influence of the arbitrary choice of decision threshold. Some examples will be based on a hypothetical test to determine whether an individual is 'male' or 'not male' based on the height of that individual. Data from 1328 individuals in which the 'disease prevalence' (that is, being 'male') is 0.498. Issues such as the 'cost' of a false positive will be addressed in the context of appropriate choices for the operating point on the ROC curve. Differences in the appropriate values for false positive fractions for a screening test (usually applied to a population with a low disease prevalence), as opposed to a diagnostic test (usually applied to a population with a moderate disease prevalence), will be illustrated. One goal of this presentation is to illustrate the potential value that ultrasonic tissue characterization studies exhibiting specific areas under the ROC curve might provide.

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8.2 **'Complexity' of a multiple-biomarker classifier and its implications for assessment,** R.F. Wagner, *Center for Devices & Radiological Health, FDA, Rockville MD 20850*

This talk will review the way in which the complexity of a multiple-biomarker classifier propagates into bias and variance in measures of the performance of the classifier. We begin with some contemporary anecdotes in the fields of bioinformatics and linguistics. The most celebrated landmark of modern bioinformatics has been the sequencing of the human genome. Early in the project it was commonly believed that humans have about 100,000 genes and as the project neared completion the estimates came down into the neighborhood of 25,000-30,000. Hidden Markov Models (HMM) are used to carry out statistical parsing of the 'linguistics' of such bioinformation. Such massively-complex analysis has been facilitated by modern developments in massively complex hardware and software — but such analysis is naturally accompanied by great uncertainties. At a lower level of complexity are the algorithms we use for tissue characterization or computer-aided diagnosis in medical imaging (~ 5-20 image features and at an intermediate level are the tools under current development for fusing multiple clinical laboratory biomarkers (> 20) — for example, from a large number of spectral lines in mass spectroscopy of protein fragments in blood samples and other mutliplex data from protein and gene microarrays. This talk will review the uncertainties in measured performance of such diagnostic tests as a function of the sample sizes available for training and testing as well as the dependence on the number of fused biomarkers and the complexity of the associated statistical learning algorithm. A strategy for designing large trials based on our pilot studies will be outlined.