ABSTRACTS

1. High-Frequency Imaging

1.1 **High-resolution parametric imaging of the vitreous, retina and choroid,** Ronald H. Silverman,[1,2] Mark J. Rondeau,[1] R. V. Paul Chan[1] and D. Jackson Coleman,[1] *[1]Weill Medical College of Cornell University, New York, NY 10021 and [2]Riverside Research Institute, New York, NY 10038,* s*ilverman@rrinyc.org* (invited overview).

The retina is physically and nutritionally supported by the underlying choroid, a vascular tissue that is part of the uveal tract of the eye. The retina and choroid are each approximately one-quarter millimeter in thickness. The retinal photoreceptors are one of the most metabolically active sites in the human body and thus require a rich microvasculature. The photoreceptors and outer layers of the retina are oxygenated by diffusion from the underlying choroid and the inner retina by the retinal vessels. Diseases of the retina and choroid such as small melanomas, diabetic retinopathy (DR) and age-related macular degeneration (ARMD) may be associated with vascular abnormalities including ischemia, neovascularization, vessel leakage and hemorrhage. This, and vitreoretinal traction, may result in blood and cellular debris entering the vitreous, with potential for subsequent organization of vitreous membranes.

Ultrasound (US) and optical coherence tomography (OCT) are useful and complementary techniques for evaluation of the retina, choroid and vitreous. OCT provides higher resolution (<10 m) than US, but is limited to imaging only the posterior pole (through the pupil) under clear media conditions. It also has limited penetration in depth beyond the retinal pigment epithelium. US can be used to image the central and peripheral retina, choroid and orbital tissues, and is unaffected by optical opacities. The traditional 10 MHz US used in ophthalmology, however, provides inadequate resolution for evaluation of the retina and choroid because of their thinness in respect to wavelength (150 m).

Detection of early changes associated with ARMD, such as retinochoroidal perfusion, reorganization of microvasculature, anatomic changes in the macula (tears, holes, epiretinal membranes) and vitreous debris, would be clinically useful, especially in light of new and effective treatment modalities. The central challenge for US in characterizing these tissues is their thinness and depth. (The axial length of the eye is about 24 mm.) We have been exploring a number of approaches based on postprocessing of radiofrequency data to improve US detection of these changes. Scanning is typically performed using a reverse arc (sector) scan geometry, avoiding the plane of the crystalline lens, using a focused single-element 20 MHz transducer. Postprocessing methods include spectral parameter imaging, nonlinear 20/40 MHz tissue harmonic imaging, wavelet analysis and swept-mode color-flow imaging. We have applied these methods in combination with OCT to visualize the vitreous, retina and choroid and tissue changes associated with disease, including retinochoroidal flow, faint vitreous pathologies such as tractional membranes and debris, and choroidal scattering changes undetectable optically or in conventional US images.

Supported in part by NIH grant EB000238, Research to Prevent Blindness, the Dyson Foundation and an AIUM Education and Research Grant.

1.2 **Comparison of the acoustic beam properties of high-frequency linear and annular arrays,** Sarayu Ramachandran, Ronald H. Silverman and Jeffrey A. Ketterling, *Riverside Research Institute, New York, NY 10038,* s*ilverman@rrinyc.org* (invited).

High-frequency ultrasound transducers provide fine-resolution images and are used in small-animal imaging and ophthalmic imaging. However, the commonly used single-ele-

ment high-frequency transducers are hampered by their limited axial depth of field (DOF). Image quality can be improved by using arrays, and in this study we looked at high-frequency linear and annular arrays. A 40-MHz, 5-ring, annular array was custom built in our laboratory. The transducer had a total aperture of 6 mm, spacing of 100 m between annuli, and a geometric focus of 12 mm. The acoustic field of the array was modeled with a spatial impulse response method and a synthetic-focus technique was used to improve the axial DOF. Next, Field II was used to simulate the field of a 48-element, elevation-focused linear array with a center frequency of 40 MHz and elevation focal length of 12 mm. The synthetic-focus algorithm computed the delays required to shift the transmit and receive focus of each A-line through a specified series of axial depths. A gating function was then employed to extract the focused portions of individual A-lines. A dynamic-receive focusing algorithm was also implemented, in which delays were added only to the received echoes while the transmit focus remained fixed. The simulations of the linear and annular arrays revealed that the performance of the annular array was superior. After application of the synthetic-focus algorithm, the annular array beam had a 6-dB axial DOF of ~6 mm while the DOF of the linear array was only ~4 mm. The lateral beamwidth of the annular array was lower than that of the linear array in the azimuth direction over the extended DOF. Being radially symmetric, the annular array had the same beamwidth in all directions. However, the smallest beamwidth of the linear array in the elevation direction was nearly 50% greater than that of the annular array at the same axial depth. Various imaging strategies were implemented with the annular array using data acquired from eye-bank eyes and mouse embryos.

This work was supported by NIH Grant EY014371 and the Riverside Research Institute Biomedical Research Fund.

1.3 **High-frequency ultrasound scattering from mixtures of two different cells lines: tissue characterization insights,** Michael C. Kolios,[1,2] Anoja Giles[4] and Gregory J. Czarnota,[1-4] *[1]Department of Medical Biophysics, University of Toronto, [2]Department of Physics, Ryerson University, [3]Department of Radiation Oncology, University of Toronto and [4]Sunnybrook Health Sciences Centre, mkolios@ryerson.ca* (invited).

Quantitative ultrasound methods have been developed to provide information about tissue microstructure unavailable to typical ultrasound images. Methods that depend on the analysis of the ultrasonic radiofrequency (rf) spectrum, pioneered by the late Frederic Lizzi at Riverside Research Institute, rely on the frequency dependence of the rf backscatter to infer properties of tissue microstructure. Our group has utilized these methods to analyze the backscatter from cells using high frequency ultrasound imaging. We hypothesize that as the ultrasound wavelength approaches the size of the cell, it is more sensitive to the cell structure and changes in the cell structure due to treatment effects. In this series of experiments, two cells lines with distinct sizes we used to investigate the relationship between the ultrasonic rf spectrum parameters and cell size.

Two cells types, AML cells (~10 m diameter) and PC3 cells (~25 m diameter), were imaged with a high-frequency ultrasound imager (VS40B, VisualSonics Inc., Toronto, Canada) that could store the rf signals associated with an image. Compact aggregates of cells were created by centrifugation (creating a cell pellet). Pellets were made either of pure populations of the two cell lines, or by mixing the cell populations in different proportions (ranging from 1/64 to 1/2 of the cell volume comprised of prostate cells, in steps of 1/2, the remaining volume containing AML cells). Hematoxylin and Eosin (H&E) staining confirmed the appropriate mixing of PC3 cells in the pellets created, with no obvious clustering. An f-2.35 transducer with central frequency of 20 MHz and 10-30MHz bandwidth was used. Regions of interest were chosen and the spectral parameters calculated.

The ultrasound backscatter from cell pellets containing the larger PC3 cells and imaged with the 20-MHz transducer was significantly larger compared to the smaller AML cells (midband fits of 36 dBr vs. 52 dBr, respectively) and the spectral slopes were significantly reduced for the PC3 cells (0.31 dBr/MHz) compared to the AML (0.68 dBr/MHz). The values for the midband fits and spectral slopes of the mixed cell pellets ranged between these two extremes. The midband fit increased by 1-3 dBr and the spectral slope decreased by 0.05 dBr/MHz for every doubling in the volume composition of PC3 cells in the cell pellet (starting at 1/64 of the cell pellet volume occupied by PC3 cells). H&E staining revealed PC3 cells mixed in different proportions among the background AML cells, with no obvious clustering of PC3 cells in the pellet.

The data demonstrate the effect of cell size on ultrasound backscatter in this model system. Despite the fact that there are many more AML cells per unit volume, the scattering strength of the larger PC3 cells dominate the backscatter signal, increasing the backscatter and reducing the spectral slope. The changes in the spectral slope and backscattering strength are consistent with predictions of theoretical models of ultrasound backscatter based on analysis of the normalized rf spectrum.

The authors acknowledge the support of the Canadian Institutes of Health Research (MOP-57592) and the Whitaker Foundation (Transitional grant). The high-frequency ultrasound device was purchased with funds from the Canadian Foundation for Innovation, the Ontario Ministry of Research and Innovation and Ryerson University.

1.4 **High-frequency ultrasound imaging of cell structural changes following radiation therapy,** Roxana Vlad,[1,4] Anoja Giles,[4] Michael C. Kolios[1,2] and Gregory J. Czarnota,[1,3,4] *[1]Department of Medical Biophysics, University of Toronto, [2]Department of Physics, Ryerson University, [3]Department of Radiation Oncology, University of Toronto and [4]Sunnybrook Health Sciences Centre, rvlad@sri.utoronto.ca.*

Objective: The goal of this project is to develop quantitative ultrasound imaging by measuring ultrasound backscatter, speed of sound (SOS), ultrasonic attenuation and estimating effective scatterer size as methods to monitor tumor responses to radiation (XRT). Attenuation-compensated ultrasound integrated backscatter (UIB) using 10-60 MHz frequencies was used to assess the responses of acute myeloid leukemia cells (AML-5) and three different nasopharyngeal carcinoma (NPC) cell lines to radiation.

Method: Cells were exposed to 2, 4 and 8 Gy radiation delivered in one fraction at 200 cGy/minute. Ultrasound images and corresponding radiofrequency data were collected from viable (control) and treated cell samples 48h after irradiation. Two transducers with central frequencies of 20 and 40 MHz and bandwidths of 10-30 MHz and 20-60 MHz were used. A custom-made sample holder was designed to facilitate data collection for ultrasound backscatter, SOS and attenuation coefficient calculations. Changes in nuclear size after radiation treatment were estimated from light microscopy images of Hematoxylin and Eosin (H&E) staining. Changes in cell sizes before and after treatment were measured with a Multisizer 3 Coulter Counter.

Results: An average increase of up to 10% ± 4% in attenuation coefficient was measured from the treated AML cell pellets compared with the control. No significant increase in attenuation coefficient was measured for NPC cell pellets after RT treatment. The SOS generally decreased for the treated cell pellets up to 2% ± 0.7% for AML and NPC cell pellets. The HFUIB increased by 77 ± 1.9 dB for AML, 4.9 ± 1.3 dB for FaDu and 3.1 ± 2.3 dB for CNE-1cell pellets compared with control. No significant variation in HFUIB was measured for C666 cell pellets. Each experiment was performed in duplicate with similar trends. Errors represent the standard deviations calculated for the values measured among sets of nine control samples and nine treated samples. Cell size measurements showed an increase in the

cell size distribution for AML and FaDu cell lines after XRT, quantified by the standard deviation (SD). The relative increase in UIB following XRT correlates well (R = 0.96) with the SD of cell sizes.

Conclusion: HFUIB increased in AML and FaDu cell samples after radiation. The major morphological changes are increase in cells size and distribution of cell sizes, changes in nuclei shape and increase of cell membrane permeability. Future work aims to characterize tissue frequency-dependent properties in a NPC mouse cancer model based on the cells used in this work and correlate these to growth delays from radiation treatments.

AIUM's Endowment for Education & Research Grant and CIHR Strategic Training Fellowship Excellence in Radiation Research for the 21st Century are acknowledged.

1.5 **Quantitative ultrasound analyses of apoptotic cell death *in vivo* and histopathological correlations**, Gregory J. Czarnota,[1-3] William Chu,[1] Behzad Banihashemi,[1] Roxana Vlad,[1, 2] Anoja Giles[1] and Michael C. Kolios,[2, 3] *[1]Radiation Oncology and Imaging Research, Sunnybrook Health Sciences Centre, and Department of Radiation Oncology, University of Toronto, [2]Department of Medical Biophysics, University of Toronto and [3]Department of Physics, Ryerson University, gregory.czarnota@sunnybrook.ca* (invited).

High-frequency ultrasound spectroscopy is a novel method to detect apoptotic cell death based on changes in cell morphology that cause changes in the viscoelastic and consequently the acoustic properties of cell ensembles and tissues. In this study, we have evaluated the use of high-frequency ultrasound to assess tumor responses to photodynamic and radiotherapy *in vivo*.

For photodynamic therapy experiments, solid tumors were grown in SCID mice using a malignant human melanoma cell line (HTB-67). Tumors were treated with 110 J/cm^2 of 633 nm laser light, 24 hours following exposure to 10 mg/kg of Photofrin given intraperitoneally as a photosensitizer. Tumors were examined by 20 and 40 MHz ultrasound prior to treatment and at different times after administration of therapy. For radiotherapy experiments, human PC3 prostate cancer, melanoma, lymphoma and nasopharyngeal carcinoma tumors were grown as xenotransplants in SCID mice. PC3 bearing animals were subjected to 0, 2, 4 and 8 Gy of single fraction using 100 kV X-ray radiation. The other tumor lines were exposed to 0 and 8Gy radiation only. Ultrasound data collection for all therapies consisted of acquiring tumor images in addition to spectroscopic data for quantitative analyses of backscattered ultrasound 24 hours after treatment. Animals were sacrificed immediately after analysis and tumours were excised for histopathologic analysis. Histological sections were examined by haematoxylin and eosin staining in addition to TUNEL for apoptosis. Ultrasound images and corresponding spectroscopic data were analyzed and tested for correlation with histopathological findings.

We observed a time-dependent increase in ultrasound backscatter after photodynamic treatment. Increases in backscatter findings correlated with morphological findings indicating increases in apoptotic cell death, which peaked at 24h after treatment. We observed 0%, 1.48%, 8.25%, 26.83%, 52.52% and 2.12% apoptosis in terms of cross-sectional tumour area from histopathology after 1h, 3h, 6h, 12h, 24h and 48h of PDT, respectively. These corresponded to 1.5%, 4%, 11%, 25.33%, 31.5% and 25% increases in the logarithmically uncorrected mean intensities in ultrasonograms obtained at 20 MHz. Sizes of areas in the ultrasound images demonstrating a 10 dB increase correlated well with those as measured from histopathology. The findings with 40-MHz ultrasound followed the same trend. At 48h, we observed a decrease in ultrasound backscatter that could be explained by an increase in cell lysis and destruction in histology.

For radiation experiments, 30 MHz ultrasound analysis showed an increase in backscatter for the irradiated prostate tumors compared to the control animals. Mid-band fit and spectral

slope were 32 dBr and 0.12 dBr MHz^{-1} for 8Gy samples, compared to 49 dBr and 0.05 dBr MHz^{-1} for controls. Image analysis demonstrated a correlation between radiation dose and the number and size of high intensity patches in irradiated tumors. The mean number (±SD) of high intensity 10 dB patches per image was 1.3 ±1.1, 5.4 ±2.2, 3.9 ±2.1 and 5.3 ±2.5 for the 0, 2, 4 and 8 Gy irradiated tumors, respectively. The average size of these patches (length x width (±SD) in millimeters) was (0.36 ±0.33 x 0.25 ±0.18), (0.55 ±0.48 x 0.49 ±0.38), (0.65 ±0.53 x 0.58 ±0.43) and (1.10 ±1.18 x 0.69 ±0.55) for the 0, 2, 4 and 8 Gy irradiated tumors, respectively. The size and location of these areas correlated with histological areas of increased apoptosis. For the nasopharyngeal carcinoma, melanoma and lymphomas tumours ultrasound results indicated relative radioresponsiveness with good correlation to histopathological results. Histopathological analyses of TUNEL staining indicated areas of cell death were coincident with hypervascular areas as indicated by CD31 staining. That staining procedure also indicated a vascular effect elicited by 8Gy doses of radiation.

In summary, spectroscopic ultrasound analyses can detect dose-dependent, photodynamic- and radiation-induced cell death. Ultrasound results correlated with histological evidence of increased apoptosis with progressing time after photodynamic therapy or with higher-doses of radiation therapy. Our results indicate that high-frequency ultrasound may be used to noninvasively monitor effects of therapy in animal models of human tumours.

1.6 **Tissue characterization by harmonic band spectrum analysis of backscattered ultrasound,** Robert Muratore, Ronald H. Silverman, Shreedevi Dasgupta and S. Kaisar Alam, *Riverside Research Institute, New York, NY, muratore@rrinyc.org.*

Spectrum analysis of backscattered rf ultrasound echo signals has proven to be a remarkably robust technique for tissue characterization. Here, we explore the possible benefits of applying spectrum-analysis techniques to the harmonic portion of backscattered echo signals to improve visualization of lesions produced by high-intensity focused ultrasound (HIFU).

HIFU-generated lesions in tissue are important to monitor, but sometimes are difficult to evaluate with conventional video (B-mode) images. To gain insight into the possible benefits of harmonic spectral-parameter images for HIFU-lesion monitoring, we formed lesions in a variety of mammalian *ex vivo* tissues including bovine myocardium. Broadband ultrasound diagnostic transducers were used to probe normal and lesioned tissue. the ultrasound rf data were digitized. Acquired data were digitally bandpass-filtered to evaluate spectral results in the fundamental- and harmonic-frequency ranges. To do this, the data were spectrum analyzed over the full available bandwidth (typically 5 to 25 MHz): a sliding Hamming window was applied to each scan vector across the scan region of interest; each windowed portion of the echo signal was Fourier-transformed; and the tissue spectrum was normalized by a glass-plate spectrum. The portions of the resultant spectra outside the bands of interest were excluded from analysis. The in-band portions of the normalized spectra were linearly parameterized. Parameter values then were converted to pixel values in the scan region of interest.

The resulting parameter images (midband fit or integrated backscatter, intercept, and slope) for the harmonic and fundamental frequency bands were compared to conventional envelope-detected video images in terms of signal/noise and resolution. We found that harmonic-frequency parameter images can improve the detectability of tissue lesions, consistent with previously-reported results.

This research was supported in part by Bioengineering Research Partnerships grant 5R01 CA084588 from the National Cancer Institute and the National Heart, Lung, and Blood In-

stitute (USA), and by the Riverside Research Institute Fund for Biomedical Engineering Research.

1.7 **Pulse-compression imaging with a 40-MHz annular array,** J. Mamou and J.A. Ketterling, *Lizzi Center for Biomedical Engineering, Riverside Research Institute, New York, NY 10038,mamou@rrinyc.org.*

Very-high-frequency (>30 MHz) ultrasound allows fine-resolution imaging at the expense of depth-of-field and acoustic penetration depth. Mechanically-scanned annular arrays have demonstrated that they can significantly extend the depth-of-field. This study investigates chirp coded-excitation to increase the signal-to-noise ratio (SNR) and consequently increase acoustic penetration depth.

In this study, a 40-MHz, five-element annular array with a focal length of 12 mm and a total aperture of 6 mm was used. The transducer was excited with an optimized, custom design, 4- s, linear chirp spanning 15 to 65 MHz that was optimized from *ex vivo* experiments and computer simulations. The chirp was tapered by a Tukey window in order to limit post-pulse-compression axial side-lobe artifacts.

Images of a 12- m wire were generated to quantify lateral and axial resolutions. All 25 transmit/receive signal combinations were digitized and post-processed for compression and synthetic focusing. Compression consisted of linearly filtering the signals with the time-reversed excitation chirp modulated by a Dolph-Chebyshev window.

Results showed that resolution was not significantly degraded when compared to a conventional monocycle excitation and that SNR was improved by more than 14 dB. The increased SNR allowed imaging 2 mm deeper in scattering phantoms containing 10- m glass beads. Images of mouse embryos and low-contrast phantoms also showed marked improvements in image-quality.

This research was supported by NIH grants EB006509, EY014371 and the Riverside Research Institute Fund for Biomedical Engineering Research.

2. Breast-Cancer Imaging

2.1 **Tutorial/overview of breast disease with a focus on breast-cancer biology,** E.J. Feleppa, *Lizzi Center for Biomedical Engineering, Riverside Research Institute, New York, NY 10038, feleppa@rrinyc.org* (invited tutorial).

An estimated 180,510 new cases of invasive breast cancer will be detected in the US during 2007; of those, an estimated 2,030 will be detected in men. An estimated 40,910 deaths will occur due to beast cancer in the US during 2007; of those, 450 deaths will occur in men. Breast cancer is the second leading cause of cancer death in American women. Although incidence and mortality have dropped slightly in the last few years, breast cancer is an important disease that warrants attention in terms of improved understanding of causes, prevention, treatment, and for the purposes of this symposium, detection and monitoring through imaging. To gain a better understanding of the properties of breast cancer that are related to imaging it using ultrasound, this presentation will provide an overview of the complex normal breast architecture, and the biology and structure of various benign and malignant conditions in the breast. The discussion will include an introduction to conditions such as in situ and invasive ductal adenocarcinoma, fibroadenoma, fibrocystic disease, cysts, intraductal papillomas, lipomas, hematomas, etc. It also will include a brief introduction to common methods of treating breast cancer. This presentation will set the stage for subsequent talks concerned specifically with ultrasonically imaging the breast and will show how ultrasound

may have important advantages over radiographic methods when imaging densely glandular breasts.

2.2 **Breast ultrasonography: current and future roles for this increasingly powerful tool**, Brian S. Garra,[1] Louise M. Mobbs[2] and Sally D. Herschorn,[1] *[1]Department of Radiology, University of Vermont College of Medicine, Burlington, VT 05405 and [2]Radiology Health Care Service, Fletcher Allen Health Care, Burlington, VT 0540,bgarra@uvm.edu* (invited overview)

Breast lesion detection was the first clinical application attempted with ultrasound in 1951. For a time, noncontact water bath immersion scanners were tried with limited success. Since that time, it has undergone several major changes and improvements. With the advent of real-time scanning around 1978, contact B-scanning of the breast gradually became the preferred method for US imaging of the breast. For a very long time after that however, US was relegated to distinguishing solid from cystic masses in the United States even though great progress was made in developing criteria for solid mass diagnosis in other countries. In 1989, the Japan Society of Ultrasonics in Medicine published criteria for the diagnosis of solid masses quite similar to those used today. By the late 1990's, ultrasound had become an accepted method of diagnosing solid masses even in the USA. New advances such as harmonic imaging, sensitive color-Doppler imaging, 1.5D arrays and speckle reduction have resulted in increases in spatial and contrast resolution that have increased the ability of users to detect small masses using US and to accurately characterize larger ones.

New technologies that promise to further increase the value of ultrasound for detection and diagnosis of breast lesions include 2D arrays, new speckle reduction algorithms, image enhancement algorithms, volume scanning with precise registration with CT, MRI and PET, ultrasound elastography and new techniques for performance of screening breast US examinations. However, these new advances will have competition. Other new methods of breast imaging have been quite successful, including full field digital mammography, computer-aided detection and diagnosis, MRI, breast tomosynthesis, electrical impedance imaging, infrared imaging and now Positron Emission Mammography (PEM).

Determining the proper role for each modality in the diagnosis of breast cancer will be the challenge for the next decade. It is quite possible that different diagnostic algorithms will work equally well and regional preferences and regional economics will determine which modalities are used in diagnostic workups. Currently, the major role for US is as a biopsy guidance tool and as an adjunct diagnostic tool to mammography. A future role for US in combination with PET and PEM is possible, as is a stronger screening role – especially if algorithms for microcalcification detection by US can be perfected.

2.3 **Recent experience with ultrasound computed tomography for breast imaging,** Michael Andre,[1, 2] Chad Barker,[1, 2] Navdeep Sekhon,[2] Linda Olson,[2] David Borup[3] and James Wiskin,[3] *[1]Dept. of Radiology, San Diego VA Healthcare System, San Diego, CA 92161, [2]Dept. of Radiology, University of California, San Diego, CA 92093 and [3]Techniscan Medical Systems, Inc., Salt Lake City, UT 84117, mandre@ucsd.edu.*

Laboratory and *in vivo* measurements have suggested that normal breast tissue, benign lesions and cancerous lesions may be indentified by their acoustic properties (particularly sound speed and attenuation). Over the past 20 or more years, transmission ultrasound imaging of the breast has been applied to this problem by several researchers with varying degrees of success. A brief historical perspective on these pioneering works will be presented, many of which first were reported at this very conference.

In general, these earlier methods used two-dimensional linearization techniques to solve what is inherently a nonlinear three-dimensional problem. It is now clear that the range of tissue properties encountered in the breast is sufficiently large that linear approximations lead to severe artifacts and inadequate spatial resolution. Until recently, the engineering technology and mathematical methods for full-wave inverse-scattering 3D tomography have been so complex that practical results in humans were not realized. Techniscan Medical Systems, Inc. (Salt Lake City, UT) has developed a scanner for breast imaging that uses a multifrequency, nonlinear, 3D, inverse-scattering algorithm. The system is installed at the University of California, San Diego to evaluate clinical feasibility of using Ultrasound CT (USCT) to analyze and detect breast masses.

Operation and performance of this pre-clinical prototype system, especially with respect to sound speed measurements, was examined for this report. The accuracy and linearity of sound speed measurements by USCT was very high ($R^2 = 0.988$) over the range of 1418 2.1 to 1606 5.0 m/s. Patients with known findings on conventional breast sonography and mammography have been scanned ranging in age from 20 to 78. Sample case studies with mammography, ultrasound and the multiplanar reconstructed USCT images of speed of sound and sound attenuation will be presented. Detailed reports of the inverse-scattering algorithm and current pre-clinical results in patients will be presented in two companion papers. A second-generation scanner with 1 mm slice thickness and improved in-plane resolution is being constructed.

This work was supported in part by NIH/NCI 1 R44 CA 110203-01 and UCSD CTA #20060960.

2.4 **Multifrequency, fully nonlinear, acoustic inverse scattering: theory and breast tissue characterization,** J. Wiskin, D. Borup, S. A. Johnson, M. Berggren, F. Setinsek, B. Hanover, S. Olse and K. Callahan, *TechniScan Medical Systems, Inc., Salt Lake City, UT, 84117 and Department of Bioengineering University of Utah, Salt Lake City, UT, jwiskin@techniscanmedical.com.*

Inverse scattering is a mathematical technique that has been applied, in investigational studies, to breast transmission ultrasound imaging for several years. Usually, a linearization technique is applied to this inherently nonlinear and numerically ill-conditioned problem. Unfortunately, the breast tissue parameters of speed of sound propagation and sound attenuation are of sufficiently strong variation that the linear approximation leads to serious artifacts.

The full nonlinear inversion was thought to be intractable due to its size, solving for ~20 million unknowns for the 3D problem, as well as the presence of local minima, again resulting in image artifacts. We present the theoretical background for a multifrequency, nonlinear, Ribiere-Polak conjugate gradient-based minimization. This approach has resulted in high resolution 3D representations of speed and attenuation with in-plane resolution of ~1.5 mm and vertical resolution of ~4.5 mm.

For data collection and image generation, either a phantom breast or a patient's breast hangs pendant in a 30 C water bath surrounded by an array consisting of a transmitter and a receiver array to generate and collect ultrasound wave data. The data consists of 180 tomographic views, encompassing a full 360 aperture. Each view consists of 960 time signals collected on a specially-designed 6 row array of transducer elements. Depending on breast size, 50 or so levels of data, spaced 2 mm apart constitute full breast data. We discuss the shortcomings of the 2D algorithm which assumes that acoustic energy is confined to a single plane. To overcome these limitations, a fully 3D algorithm that simulates wave propagation in 3D, and inverts for a 3D representation of sound speed and attenuation, is then presented. Significantly, one level of data is used in the 2D algorithm, whereas all levels of data are used simultaneously in the 3D inversion

In addition, studies were conducted in an attempt to improve image resolution without incurring insurmountable algorithmic problems. These include geometric array tilt, shading and relative rotation of the receiver. Images will be presented of known phantoms (3D) and 3D breast reconstructions from subjects and the differences in image quality with these various approaches will be compared.

This research was funded by NCI SBIR Fast-Track Grant 1 R44 CA 110203-01A2, and TechniScan, Inc., Salt Lake City, UT.

2.5 **Representative patient case studies of speed of sound and attenuation of sound images from transmission ultrasound imaging of the breast**, K.S. Callahan, J.W. Wiskin, D.T. Borup, B. Hanover, S.A. Johnson and Y.R. Parisky, *TechniScan Medical Systems, Inc., Salt Lake City, UT 84117 and Mammoth Hospital, Mammoth Lakes, CA, kcallahan@techniscanmedicalsystems.com*.

Transmission ultrasound imaging for implementation in breast diagnostics has been investigated over the past several decades with varying degrees of success. In general, the resolution of breast features has not been sufficient for introduction into the clinical arena. TechniScan Medical Systems has developed a transmission ultrasound computed tomography (USCT) imaging system utilizing inverse scattering for computing the speed and attenuation of sound traveling through breast tissue. This scanning system is comprised of an examination table wherein a patient lays prone with her breast suspended in a warmed water bath system. An ultrasound array consisting of emitting and receiving transducers is mounted on a yoke that moves through an axis to circle the breast, similar to an X-ray CT system, although no radiation is involved in the scan. During each 360 horizontal rotation, a transmitter emits ultrasound plane waves (300 kHz-2 MHz) every 2 while an opposing parallel 960-element, six-row receiver array intercepts the resulting scattered waveforms. The collected discrete frequency domain data are then used to generate 2-D images of each vertical coronal slice. After completion of the entire vertical slice, the arrays move up the breast in 2 mm increments until the entire breast has been scanned. Finally, a proprietary 3-D algorithm considers multiple scattering interactions between the planes resulting in a quantitative map of the speed of sound and the attenuation of sound throughout the entire breast.

Under IRB-approved study protocols, women who were undergoing conventional breast imaging with mammography and/or reflection hand-held ultrasound were recruited for imaging with the USCT system. The inclusion criteria for enrollment were age 18 or above, scheduled for mammography and/or ultrasound imaging, not pregnant or nursing, no nipple discharge or open breast wounds, and a weight of less than 400 lbs. Collected data on the patients included breast history, mammography and ultrasound information, and biopsy and pathology records. Representative case studies with mammography, ultrasound and the multi-planar reconstructed USCT images of speed of sound and sound attenuation will be presented. The collected cases to be shown include those with benign outcomes such as cysts, seroma, fibroadenoma and biopsy-proven malignant outcomes including Grades I through III invasive ductal carcinomas.

2.6 **Breast lesion characterization using contrast enhanced subharmonic and cumulative maximum intensity breast images,** Mridul S. Mall,[1, 2] Flemming Forsberg,[1] Rahul Soparawala,[1, 2] Daniel A. Merton[1] and Catherine. W. Piccoli,[1] *[1]Department of Radiology, Thomas Jefferson University, Philadelphia, PA 19107 and [2]School of Biomedical Engineering and Health Systems, Drexel University, Philadelphia PA 19104, flemming.forsberg @jefferson.edu.*

This project was undertaken to demonstrate that quantitative contrast enhanced subharmonic imaging (SHI) can be used to characterize breast lesions. Moreover, cumulative maximum intensity (CMI) imaging, which is a composite imaging mode depicting vascular architecture and blood flow constructed through maximum intensity capture of temporal data in consecutive images, was developed.

A modified Logiq 9 scanner (GE Healthcare, Milwaukee, WI) operating in grayscale SHI mode (transmitting/receiving at 4.4/2.2 MHz) was used to perform *in vivo* SHI on 14 women with 16 breast lesions (10 benign and 4 malignant confirmed by biopsy). Following baseline scans of grayscale ultrasound and power Doppler imaging (PDI), contrast was administered for PDI and grayscale SHI. Digital clips were acquired for each injection and a SHI time-intensity curve was plotted for each lesion using Image ProPlus (Media Cybernetics, Silver Spring, MD). The slope of the initial uptake was obtained from time intensity curves. SHI perfusion estimates (Q) were determined using a linear relationship ($Q = 0.47rFBV+1.62$) previously established in a canine model,[(1)] where rFBV is the slope of the initial SHI uptake. Perfusion was determined within three regions of interest (ROIs) encompassing the center, periphery or entire lesion. The mean transit time and degree of anastamosis were calculated for each lesion. Results were compared using t-tests and linear regression. Results of automatically aligning CMI images using the sum-absolute-difference algorithm, developed in MATLAB (The MathWorks Inc, Natick, MA) will be compared to manually-aligned CMI images.

In SHI, there was almost complete suppression of tissue signals, allowing the lesion vascularity to stand out. The internal morphology of the vascularity associated with the breast masses was visualized better with SHI than with PDI. Perfusion estimates in the whole lesion were significantly different for malignant and benign tumors ($p = 0.04$) but not for central and peripheral ROIs ($p > 0.32$). CMI imaging provided a better depiction of the tortuous angiogenic vascular morphology associated with breast lesions. The mean transit time was lower in malignant than in benign masses (0.72 vs. 1.32, $p = 0.02$). Comparisons of automatically and manually aligned CMI images will be presented.

In conclusion, new quantitative methods for analyzing *in vivo* grayscale SHI have been tested in breast lesions. Preliminary results indicate that perfusion and mean transit time may improve the characterization of malignant and benign breast masses. However, the current patient population is very small and further studies are required to substantiate these findings.

Supported in part by the U.S. Army Medical Research Materiel Command under DAMD17-00-1-0464 and by GE Healthcare.

(1) Forsberg F, et al. *J Ultrasound Med 25,* 15-21 (2006).

2.7 **Blinded reading of breast elastograms – updated clinical results,** 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, bgarra@uvm.edu.*

Our study evaluating the clinical efficacy of ultrasound elastography as an adjunct to ultrasound and mammography is continuing. As part of that study, two observers performed blinded reviews of the elastograms to determine the ability of elastography alone to distinguish benign from malignant breast masses. So far, 185 biopsy proven masses have been examined. The elastograms were acquired with a Philips HDI 1000 scanner using a 7.5 MHz linear array transducer. Up to 28 frames of radiofrequency (rf) data were acquired to generate each elastogram. Both frame-held and hand-held elastograms were acquired. Each elastogram was enhanced using wavelet filtration to suppress noise and artifacts and was presented for review alongside its corresponding sonogram. The reviewers were blinded to

the sonographic, mammographic and biopsy results. A level of suspicion (LOS) score was assigned to each lesion using a 100 point scale based on subjective evaluation of three features. 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 diameter of each lesion on both elastograms and sonograms was measured and compared. ROC analysis was used to evaluate the performance of features and observers.

For the most experienced observer, the overall LOS for cancer scores resulted in an area under the ROC curve of 0.85 ±0.04 in the first143 patients. Limiting the evaluation to patients whose lesions were visible on elastography, the ROC area increased to 0.91 ± 0.03 for 135 patients. The overall LOS score performed significantly better than using any one feature such as hardness score (Az = 0.83), size difference score (Az= 0.81) or border irregularity score (Az = 0.76).

Combinations of two features did not greatly improve performance. Two invasive lobular carcinomas and one invasive ductal carcinoma measured smaller on the elastogram than on the sonogram making it difficult to use this criterion to classify a lesion as "definitely benign." Hardness score performed better in this respect than size difference but this situation may change as image quality improves and lesion borders become easier to identify.

Our findings are generally consistent with that achieved by others and suggest that elastography will be useful as an adjunct tool for distinguishing breast cancer from benign masses. With improved image quality, we are hopeful that the percentage of lesions not seen elastographically will decline and that the size difference criterion will increase in usefulness for mass classification.

2.8 **Breast tissue characterization by means of surface stress patterns analysis,** Vladimir Egorov and Armen Sarvazyan, *Artann Laboratories, Trenton, NJ 08618, vegorov@artannlabs.com.*

The objective of this study is the development and validation of tissue characterization algorithms for Breast Mechanical Imager (BMI), an elasticity imaging device based on measurement of stress patterns on the surface of the breast. BMI provides real-time imaging of breast tissue abnormalities and their quantitative characterization. Temporal and spatial changes in the stress pattern provide detection of lesions having different elastic properties and allow three-dimensional reconstruction of these lesions and assessment of their mechanical properties.

We developed and implemented real-time computational procedures for assessment of breast lesion features such as size, cross-section area, shape, hardness, strain hardening and mobility. Laboratory testing on the tissue models and breast phantoms demonstrated accuracy of Young's moduli of the phantom bulk material and of inclusions measurement to within 5 -35% and reproducibility of elasticity measurement in the range of 5 - 15%. Accuracy of evaluation of the geometrical parameters of inclusions is within 5 -10%. Results of ongoing clinical studies indicate that a set of mechanical parameters of the breast lesions calculated using developed algorithms may be potentially used for breast tissue pathology characterization and classification.

This work was supported by NIH grant 5 R44 CA091392.

3. Tissue Parameters 2

4.1 **Combining magnetic-resonance spectroscopy and ultrasound spectral parameters to improve tissue-type imaging of prostate cancer,** Shreedevi Dasgupta, Ernest Feleppa,

Christopher Porter, Sarayu Ramachandran, Andrew Kalisz, Jeffrey Ketterling, Marc Lacrampe and Christina Isacson, *Riverside Research Institute, New York, NY and Virginia Mason Medical Center, Seattle, WA, dasgupta@rrinyc.org.*

Purpose: Our aim is to improve upon our existing prostate-cancer tissue-type imaging by making use of independent prostate tissue properties sensed by multiple imaging modalities. Combining properties such as the choline-to-citrate ratio detected by magnetic-resonance (MR) spectroscopy with ultrasonic (US) echo-signal spectral parameters and clinical variables in our classifier will enhance our ability to successfully visualize cancerous regions in the prostate.

Method and Materials: US radiofrequency (rf) echo-signal data and clinical variables including prostate-specific antigen (PSA) were acquired during biopsy examinations. A neural-network classifier was trained using spectral-parameter values computed from the rf data and PSA values. Biopsy-core histology was used as the gold standard. Classifier performance was assessed using ROC analysis. Tissue-type images (TTIs) were generated using a look-up table that returned cancer-likelihood scores for various combinations of US spectral parameters and PSA values.

In order to combine US and MR spectral-parameter values, spatial coregistration of the values is essential. Therefore, volume renderings of the prostate were generated from transverse MR and US scans to determine the feasibility of combining the two imaging modalities in 3-D. To compensate for the distortions introduced by the larger endorectal probe used in MR imaging, the MR volume was warped in 3-D using the US volume as a reference. Both 3-D volume renderings were compared to 3-D renderings of histology for validation.

Results: The ROC-curve area for US neural-network-based classification was 0.84 compared to a curve area of 0.64 for B-mode-based classification. Cancerous regions that were not visible in conventional US images were revealed in TTIs generated using the classifier. Coregistration of 3-D prostate US and warped MR renderings was successful.

Conclusions: TTIs based on neural-network classification of US and clinical parameters show promise for improving the detection of prostate cancer. Warping 3-D renderings of the prostate to compensate for the different degrees of gland deformation caused by different transrectal probes appears to be feasible. Consequently, we will be able to produce accurately coregistered 3-D data derived from US and MR to improve methods for visualizing prostate-cancer foci. Success in combining the two imaging modalities will be valuable for better depiction of cancerous regions in the prostate for biopsy and treatment planning and treatment monitoring.

Supported in part by NIH grant CA053561

3.2 **Targeted detection and treatment of prostate cancer,** William A. Steelman[1,2] and William D. Richard[1], *[1]Washington University in St. Louis and [2]Envisioneering Medical Technologies, wsteelman@envisioneeringmedical.com.*

With prostate cancer as the most-common cancer, other than skin cancer, among men in America, developing better methods to diagnose and treat prostate cancer is of vital importance. In order to meet this need the TargetScan® system was developed to allow physicians to pinpoint specific sites in the prostate for targeted biopsy or targeted (focal) therapy. Targeting sites within the prostate is done by first generating a 3-dimensional model of the prostate with the aid of ultrasound. This 3-D model can then be used to define biopsy sampling sites or focal treatment sites such as seed implant locations for brachytherapy. Finally the 3-D model is used in conjunction with image guided needles to execute the biopsy or treatment plan.

The key to the TargetScan® system is the software-directed transducer motion control system coupled with PC-based ultrasound imaging. The motion control system allows the

probe to image at any transverse plane in a 60 mm window or any sagittal plane in a 180 window without moving the probe. Imaging in this manner ensures that the prostate remains stationary during the procedure and allows the exact location of each image to be known. Using the image locations and the boundaries of the prostate, which are input by the user, the software can generate the 3-D model. Furthermore, PC-based imaging enables the images to be gathered, the boundaries to be defined and the model to be generated all from one integrated software interface. The integrated motion control and imaging systems also make it possible to execute a biopsy or treatment plan using the same stationary probe. With the ability to model the prostate and perform targeted biopsies and treatments, physicians will be able to better detect and manage prostate cancer.

This talk provides an architectural overview of the motion control and imaging subsystems as well as a functional overview of the TargetScan® system. Sample images and biopsy plans generated by the system will also be presented.

3.3 **Change in ultrasonic backscattered energy for temperature imaging: factors affecting temperature accuracy and spatial resolution,** R. Martin Arthur,[1] Jason W. Trobaugh,[1] Yuzheng Guo,[1] William L. Straube[2] and Eduardo G. Moros,[3] *[1]Electrical & Systems Engineering, [2]Radiation Oncology, Washington University in St. Louis, St. Louis, MO, 63130, USA and [3]Radiation Oncology, University of Arkansas, rma@esewustl.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 for multiple porcine, bovine and turkey tissues and *in vivo* in living normal murine tissue with implanted tumors (HT29 colon cancer line) on nude-mouse preparations. Measured changes were consistent with predictions for certain subwavelength scatterers and with results from simulations for images of populations of temperature-dependent scatterers. Application of temperature imaging to monitoring of tumor heating requires accurate temperature estimation over small volumes, e.g., to within 0.5 ºC for tissue volumes of 1 cm^3, requiring consistent and predictable measurements of the temperature dependence of CBE.

Using simulation studies, we have studied the impact of various factors on the variation of measurable CBE with temperature. In these simulations, we represented the imaging system by its point-spread function and the tissue medium by discrete scatterers with a variable range of temperature dependence. Images were simulated to represent temperatures from 37 to 50 ºC by changing the scatterer amplitudes according to curves predicted previously for single scatterers, and CBE was computed for regions based on the means and standard deviation for CBE over all pixels in the region. CBE computed from simulation showed the same monotonic increase and decrease as in experimental results and covered ranges similar to both prediction and experiment. We used multiple simulations to characterize temperature-dependent CBE statistically and found that the region size, type and distribution of scatterers in a population, and image signal-to-noise ratio (SNR) all had a significant impact, i.e., each could change the mean and/or standard deviation of the temperature-dependent CBE by 0.5-1dB resulting in potential temperature estimation errors of 1-2 ºC. With a consistent scatterer population and image SNR, however, a region size equivalent to a 1cm^3 tissue volume produced estimation error less than 0.5 ºC.

We are currently conducting 3D *in vitro* heating experiments with turkey tissue to apply these simulation findings to experimental measurements and investigate temperature accuracy and spatial resolution. 2D images are acquired with a Terason 3000 (Teratech Corp., Burlington, MA), laptop-based, phased-array system using a 7-MHz linear probe (model 12L5). 3D images are generated by translating the probe in the elevation dimension using a stepper motor system and are acquired at temperatures from 37.0 to 50.0 ºC in 0.5 ºC steps.

Apparent motion in the images is compensated using a 3D nonrigid motion-compensation algorithm. The 3D motion field is approximated as varying linearly over the tissue volume and is estimated by maximizing the 3D normalized cross-correlation using standard optimization techniques available in MATLAB®. Initial CBE measurements are consistent with previous results. We expect that by using a consistent region size and accounting for SNR, CBE can be calibrated in this tissue to provide estimation of temperature to 0.5 °C for a 1 cm^3 volume.

Support: R21-CA90531, R01-CA107558 and the Wilkinson Trust at Washington University, St. Louis.

3.4 **Attenuation estimation using spectral cross-correlation,** Hyungsuk Kim and Tomy Varghese, *Department of Medical Physics, Department of Electrical and Computer Engineering, The University of Wisconsin-Madison, Madison, WI 53706, hyungsukkim @wisc.edu.*

Estimation of the local attenuation coefficient in soft tissue is important both for clinical diagnosis as well as for further analysis of ultrasound B-mode images. However, it is difficult to extract spectral properties in a small region of interest from noisy backscattered ultrasound radiofrequency (rf) signals. Diffraction effects due to transducer beam focal properties also have to be corrected for accurate estimation of the attenuation coefficient. In this talk, we propose a new attenuation estimation method using spectral cross-correlation between consecutive power spectra obtained from the backscattered rf signals at different depths. Since the spectral cross-correlation method estimates the spectral shift by comparing the entire power spectra, it is more robust and stable to the spectral noise artifacts in the backscattered rf signals. A diffraction-compensation technique using a reference phantom with a known attenuation coefficient value is also presented. Hamming-gated window sizes required for obtaining accurate and stable power spectra using short-time Fourier analysis techniques are also discussed.

Simulated ultrasound rf data for both the reference and the sample phantom with various attenuation coefficients and transducer properties are generated using an ultrasound simulation program. With appropriate choice of block size, the simulation results show that local attenuation coefficient estimates obtained using spectral cross-correlation are within 2.3% of the actual value with small estimation variances. Experimental results using a tissue-mimicking phantom also illustrate that the spectral cross-correlation algorithm estimates attenuation coefficients accurately with small estimation variances.

3.5 **Hybrid spectral domain method for attenuation estimation,** Hyungsuk Kim and Tomy Varghese, *Department of Medical Physics, Department of Electrical and Computer Engineering, The University of Wisconsin-Madison, Madison, WI 53706, hyungsukkim @wisc.edu.*

Classical spectral shift approaches for estimating ultrasound attenuation are more sensitive to local spectral noise artifacts and have difficulty in compensating for diffraction effects due to beam focusing. Spectral difference approaches, on the other hand, fail to estimate attenuation coefficients at tissue boundaries that also possess variations in the backscatter property. However, spectral difference methods are relatively insensitive to ultrasound transducer parameters including diffraction effects. In this talk, we propose a new hybrid attenuation estimation method in the frequency domain that incorporates advantages of both the spectral difference and spectral shift based algorithms to reduce limitations associated with both these methods. The proposed hybrid method initially utilizes the spectral difference approach to obtain normalized block power spectrum using the reference phantom method. Most transducer or system-dependent parameters including diffraction are ef-

fectively reduced by this procedure. The power spectrum that includes variations due to backscatter changes are then filtered using a Gaussian filter centered at the transmit center frequency of the system. A spectral shift method, namely spectral cross-correlation, is then utilized to compute the spectral shift from these filtered power spectra to estimate the attenuation coefficient.

Ultrasound simulation results demonstrate that the estimation accuracy of the hybrid method is significantly better than the centroid downshift method (spectral shift method) in uniform attenuating regions and is also stable at boundaries with variations in the backscatter when compared to the reference phantom method, (spectral difference method). Experimental results using a tissue-mimicking phantom also illustrate that the hybrid method is more robust and provides accurate attenuation estimates in both uniformly-attenuating regions and regions with backscatter variations. The proposed hybrid method preserves the advantages of both the spectral shift and spectral difference approaches while eliminating the disadvantages of both these methods, thereby improving the estimation accuracy and robustness of attenuation estimation.

3.6 **Estimation of local ultrasound attenuation from broadband echo signals using narrow bandpass filtering,** Hyungsuk Kim,[1,2] J.A. Zagzebski[1] and Tomy Varghese,[1,2] *Department of [1]Medical Physics and [2]Electrical and Computer Engineering, The University of Wisconsin-Madison, Madison, WI 53706, hyungsukkim @wisc.edu.*

The video-signal analysis method for computing the attenuation coefficient estimates the ratio of mean echo intensities from a sample to those from a reference phantom scanned using the same transducer settings. This ratio is relatively independent of transducer and system parameters including diffraction effects, thereby yielding the attenuation coefficient of the sample. A problem with video-signal analysis, however, is that the relative echogenicity versus depth curves computed in this manner are distorted when broadband data commonly utilized in pulse-echo systems are utilized. In this talk, we present the accuracy of attenuation coefficient estimates computed from image data derived after bandpass filtering the backscattered echo signals. Simulated ultrasound radiofrequency signals of objects having different attenuation properties were generated using an ultrasound simulation program. Narrowband filtering and amplitude detection were applied at different frequencies around the center frequency of the broadband signal. Envelope or B-mode signals derived from the narrow bandpass data are processed to estimate attenuation using the video signal analysis method.

Bandpass filtered signals using a 1 MHz filter, with center frequencies lower than or at the center frequency of the broadband echo signal, produced unbiased attenuation estimates. However, when the attenuation coefficient of the sample was significantly different than that of the reference, bandpass filtered signals centered at higher frequency components exhibit larger errors in attenuation estimations, particularly at large depths. Local attenuation coefficient estimates using the video-signal analysis method with narrow bandpass filtering provides improved results when compared to video-signal analysis on broadband envelope signals. In addition, the accuracy of the attenuation estimation using narrowband video signal analysis was comparable to other spectral methods for attenuation estimation while maintaining computational efficiency for real-time implementation.

3.7 **Cancer detection and classification using multiparameter quantitative ultrasound,** M.L. Oelze, *Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, oelze@uiuc.edu.*

Quantitative ultrasound (QUS) has been used successfully to differentiate benign from malignant solid tumors in animal models of breast cancer. In these studies, QUS made use of

estimates of the average scatterer diameter (ASD) and average acoustic concentration (AAC) from the ultrasonic backscatter. However, initial attempts to classify different kinds of malignant breast tumors based on their ASD and AAC estimates were not successful when using ultrasonic frequency ranges from 10 to 24 MHz. Later examination of the backscattered power spectra from the malignant tumors revealed that statistically-significant differences could be observed for ultrasonic frequencies above 16 MHz. In addition, examination of optical photomicrographs of the tumors suggested that cells and their organizational patterns within the tumors were important to ultrasonic backscatter.

Based on observations from the initial QUS analysis, new models for ultrasonic backscatter were created by considering the cytoskeletal structure of cells. Estimates of ASD and AAC were obtained using only frequency ranges above 16 MHz, and envelope statistics of the backscatter were used to quantify the underlying organizational structure of the tumors. The homodyned-K distribution was used to model the amplitude of the envelope from regions-of-interest in the malignant tumors. The homodyned-K distribution yielded two parameters: the *S* parameter, which quantified the randomness of the scatterer spacings, and the parameter, which quantified the amount of clustering of the scatterers in the interrogated tissue. Statistically-significant differences ($p < 0.05$) were observed between the average *S* and parameters from the malignant tumors. Furthermore, statistically-significant differences ($p < 0.05$) were observed between ASD and AAC estimates from the malignant tumors using the new scattering models at ultrasonic frequencies above 16 MHz. The use of four parameters, as opposed to two, improved the ability to uniquely classify different kinds of malignant tumors.

This work was supported by start-up funds from the University of Illinois at Urbana-Champaign.

4. Tissue Parameters 2

4.1 **Validating and expanding the theoretical frameworks that relate ultrasonic backscatter to scatterer properties,** Shreedevi Dasgupta, Ernest Feleppa, Jonathan Mamou, Mark Rondeau and Harriet Lloyd, *Riverside Research Institute, New York, NY and Weill Medical College of Cornell University, New York, NY, dasgupta@rrinyc.org.*

Purpose: To experimentally validate existing theoretical frameworks relating ultrasonic (US) spectral parameters to scatterer properties and to asses the validity of assumptions that underlie the frameworks.

Method and Materials: US radiofrequency (rf) echo signals were acquired from uveal melanoma cells suspended in minimum essential medium (MEM). The concentration of cells in suspension ranged from 8x106 cells/ml to 2.5x105 cells/ml, and the average cell diameter was m. The acoustic impedance of the cells was estimated, using cell pellets, as the product of pellet density and propagation velocity. Standard Fourier methods were used to compute spectral parameters for these cells from the rf data. The spectra were normalized in two ways. In the first method, a glass plate calibration spectrum expressed in dB was used to define the system transfer function; it was subtracted from the log power spectrum of the cell-scattered echo signals to correct for system effects. In the second method, the spectrum derived from scanning a suspension of microscopic spherical scattering beads of known diameter, concentration and acoustical impedance was compared to the spectrum predicted by Faran's theory for such spheres; the difference between expected and experimental spectra was attributed to system effects. Predicted normalized spectral-parameter values were calculated for two theoretical frameworks using estimated scatterer sizes, concentrations and

relative acoustic impedance values. The theoretical gating function was varied by changing the window type and size. Predicted spectra were compared to those obtained from the experimental rf data.

Results: The normalized parameter values obtained experimentally agreed closely with the parameter values predicted by the theoretical frameworks. However, the predicted values computed using different frameworks differed slightly. In general, midband and intercept values decreased with decreasing cell size and concentration whereas slope values increased with decreasing cell size as expected.

Conclusion and Future Directions: We plan to continue these studies using other cell types, sizes, concentrations, and shapes (including nonisotropic scatterers). Success will provide an improved basis for quantitative determination of tissue-scatterer properties and for diagnosing and monitoring disease progression or response to therapy in tissues with nonisotropic or densely-packed micro-architectures.

Supported by NIH grant EB006894.

4.2 **Instrument for determining complex shear moduli of soft-tissue-like materials from 10 through 300 Hz,** E.L. Madsen, H.A. Hobson, G.R. Frank and T.J. Hall, *Medical Physics Department, University of Wisconsin-Madison, elmadsen@wisc.edu.*

Two elastography modalities involve generation and tracking of shear waves in soft tissues, viz, Acoustic Radiation Force Impulse (ARFI) imaging[1] and (dynamic) MR elastography (MRE). Knowledge of the range of complex shear modulus, $G = G + iG''$, as a function of frequency for organ tissues can be very useful information. [G' is the (real positive) shear storage modulus and G'' is the (real positive) shear loss modulus.] Also, realistic phantoms can profit from such knowledge. Current MRE involves imaging sinusoidal shear waves generated by an external source. Some MRE labs[2] reconstruct a "shear stiffness" (approximately G) and one reconstructs both G and G''.[3] ARFI, however, involves a broad spectrum of shear-wave frequencies generated by an impulsively-displaced small volume at the focus of an ultrasound (US) transducer; shear wave fronts are tracked with ordinary B-mode US pulses following the impulse (pushing pulse) yielding a spatial distribution of shear-wave speeds followed by computation and display of the shear modulus distribution. In real soft tissues, where the loss factor = tan G''/G can be 0.25 to 0.7 and perhaps larger, there is significant shear wave attenuation and corresponding speed dispersion.

Simulation of realistic tissue-like loss factors in phantoms could aid MRE and ARFI researchers in assessing the trade-off between better resolution and higher attenuation as the frequency increases. (ARFI researchers might fashion pulses to yield higher or lower frequency contents of shear waves generated.) Also, realistically large loss factors could aid ARFI researchers in testing algorithms to account for dispersion; extent of dispersion/attenuation could itself be diagnostically significant. Current phantoms used in MRE and ARFI are essentially lossless. Even if the loss were significant, the complex shear moduli at higher frequencies would likely not be known because a suitable instrument for making accurate measurements is not available. For example, we have learned through experience that the commercial instrument in our lab for measuring the complex Young's modulus, $E = E + iE''$, does not yield believable values for E' above about 50 Hz or for E'' above about 10 Hz. The frequency range involved in MRE is 50 to 300 Hz, and perhaps higher and that for ARFI could be similar.

We have built an instrument for measuring G with mechanical components that reproduce one developed at the University of Pennsylvania (U. of PA) by Arbogast et al.[4] The U. of PA instrument has been shown to make accurate determinations of the absolute values of G $||G||$ from 20 through 160 Hz. That system has not been operational for years, however, and electronic circuit diagrams are not available. Measurement samples are 1-mm thick and

about 1.5 cm^2 in area. Each sample is adhered to two parallel platens. The system produces linear sinusoidal oscillations on one platen using a linear actuator and the displacement is monitored via a linear variable differential transformer (LVDT). A shear-force detector is attached to the other platen. We assembled our own electronic components and did rigorous testing to assure that the phase lag, , of displacement relative to force was accurately determined. We also correct for inertial effects (shear-wave propagation) which can become significant above 200 Hz for soft tissues. Our values of $\|G\|$ agree with Arbogast's over the 20-160 Hz range using silicone samples of the same make and model. Unlike previous studies, a major test of the accuracy of our system in determining G and G'' in the 10-300 Hz range is requirement of conformity with the Kronig-Kramers relations, corresponding to the causality requirement, for a variety of soft-tissue-like materials with a broad range of loss factors.

(1) Nightingale K, McAleavey S, Trahey G. *Ultrasound Med Biol 29,* 1715-1723 (2003).
(2) Muthupillai R, et al. *Science 269,* 1854-1857 (1995).
(3) Sinkus R, et al. *Magn Reson Imaging 23,*159-165 (2005).
(4) Arbogast K, et al. *J Biomechanics 30,*757-759 (1997).

4.3 **Regional variation in the attenuation properties of mid-gestational fetal pig hearts,** Allyson A. Gibson, Gautam K. Singh, Joseph J. Hoffman, Achiau Ludomirsky and Mark R. Holland, *Laboratory for Ultrasonics, Washington University, St. Louis, MO, mrh@wuphys.wustl.edu.*

During fetal heart development, both the left and right sides of the heart are subjected to similar loading conditions; however, studies suggest that the left- and right-ventricular myocardium develop differently. The intrinsic composition and myofiber orientation of the heart can profoundly affect measured ultrasonic properties. As a result, measurements of the attenuation coefficient and its frequency dependence can provide an approach for assessing regional differences in myocardial properties.

The goal of this study was to characterize and compare attenuation properties of the left and right ventricles in fetal pig hearts through measurements of the mid-bandwidth attenuation coefficient and its frequency dependence. Sixteen excised, formalin-fixed fetal pig hearts, representing 53-63 days of gestation, were investigated. Approximately 1.0 mm thick slices were obtained from each specimen by cutting perpendicular to the long axis of the heart at the mid-papillary level. Spatially-localized measurements of the attenuation coefficient and slope of the linear attenuation coefficient with frequency were acquired using a 50-MHz single-element transducer with insonification perpendicular to the face of the myocardial specimen.

Measurements of the attenuation coefficient at 45 MHz and slope of the attenuation coefficient from 30-60 MHz demonstrate regional differences between the left- and right-ventricular myocardium. These differences appear to be consistent with the anisotropy of the fiber orientation observed in histological assessment and previously reported apparent backscatter measurements of the same specimens. For regions representing perpendicular insonification relative to the local myofiber orientation, the mean attenuation coefficients at 45 MHz were found to be 46.9 7.5 dB/cm and 38.0 8.1 dB/cm (mean ± SD; $p < 0.001$; $N =$ 16) for the right- and left-ventricular myocardium, respectively. The slope of a linear fit to the measured attenuation coefficients from 30-60 MHz showed a similar result with the right-ventricular myocardium demonstrating a larger value (1.49 0.24 dB/cm/MHz; mean SD) than the left-ventricular myocardium (1.21 0.22 dB/cm/MHz; mean SD; $p <$ 0.001). This study suggests an intrinsic difference in the myocardium of the left and right ventricles in fetal pig hearts at mid-gestation in spite of exposure to similar prenatal loading conditions during development.

4.4 **Observed differences in the measured magnitude of cyclic variation of backscatter in fetal human left- and right-hearts at mid-gestation,** Mark R. Holland, Gautam K. Singh, Agnieszka Kulikowska, Carol A. Kirschner, Deborah Hicks and Achiau Ludomirsky**,** *Washington U. University, St. Louis, MO, mrh@wuphys.wustl.edu.*

Background: 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. Previously-reported studies from our Laboratory on excised fetal pig hearts have demonstrated that the apparent backscatter level from the myocardium of right ventricle to be greater than that from the left ventricle, suggesting an intrinsic difference in the myocardium of the left and right ventricles at mid-gestation. Furthermore, recently published results from our Laboratory[(1)] examining systematic variations in the relative intracellular and extracellular acoustic impedance differences over the heart cycle indicate that the predicted magnitude of cyclic variation can be directly related to the overall myocardial backscatter level. An increase in the overall myocardial backscatter level is associated with a concomitant decrease in the predicted magnitude of cyclic variation.

Objective: The objective of this investigation was to compare measurements of the magnitude of cyclic variation from the left and right ventricular free walls from the hearts of human fetuses at mid-gestation and interpret the results in the context of previous measurements showing a difference in the level of backscatter between the left- and right-hearts of fetuses and the relationship between overall backscatter level and the magnitude of cyclic variation.

Methods: Echocardiographic images of 12 fetuses (17 to 29 weeks gestation) with structurally normal hearts were obtained using an imaging system configured to give a linear relationship between the displayed grayscale value and the level of ultrasonic backscatter expressed in decibels. Long-axis images of the fetal hearts were analyzed by placing regions-of-interest in the walls of the left and right ventricles. Cyclic variation data were generated by measuring the mean backscatter level within each region-of-interest for each of the acquired image frames over several heart cycles.

Results: Results demonstrate that the magnitude of cyclic variation is greater for the left ventricular free wall than for the right ventricular free wall, with measured mean magnitudes of cyclic variation of 4.5 ± 1.0 dB and 2.3 ± 1.0 dB (mean ± SD; $p < 0.001$, paired t-test) for the left and right ventricular free walls, respectively.

Conclusion: Results show a significant difference in the measured magnitude of cyclic variation in the left and right ventricular myocardium of developing fetal hearts consistent with previously observed differences in the level of backscatter between the left- and right-hearts of fetuses and with the predicted relationship between overall backscatter level and the magnitude of cyclic variation. The results of this study suggest cyclic variation measurements may offer a useful approach for investigating fundamental differences in myocardial properties of the two ventricles during fetal heart development.

(1) *J Am Soc Echocardiogr 17,* 1131-37 (2004)

4.5 **Anisotropic myocardial backscatter characterized using the Riverside Research Institute parameters: 'midband fit', 'spectral slope' and 'intercept,'** Min Yang, Todd M. Krueger, James G. Miller and Mark R. Holland, *Washington University, St. Louis, MO, mrh@wuphys.wustl.edu.*

Background: Previous studies from our Laboratory[(1)] have demonstrated a significant relationship between the measured apparent backscatter properties of myocardium and the angle of insonification relative to the predominant myocardial fiber orientation. Maximum levels of backscatter were found for perpendicular insonification and minimum levels for parallel insonification. An approach introduced by investigators at Riverside Research In-

stitute[2] provides a method for characterizing aspects of tissue microstructure underlying the observed scattering properties based on a set of parameters (spectral slope, intercept and midband fit) obtained from analyses of normalized spectra.

Objective: The objectives of this investigation were to measure the anisotropy of backscatter from myocardium using the Riverside Research Institute approach and to use the extracted parameters (spectral slope, intercept and midband fit) to characterize apparent scatterer size, spatial concentration and acoustic impedance properties as a function of the angle of insonification. The anisotropy of the measured integrated backscatter values is compared with the corresponding midband fit values.

Methods: In vitro backscatter measurements were performed on eight cylindrical formalin-fixed lamb myocardial specimens using a 5 MHz focused transducer. The measured backscatter power spectrum corresponding to each angle of insonification relative to the myocardial fiber direction investigated was compensated for the effects of attenuation and analyzed over the frequency range from 4 to 6 MHz to provide estimates of spectral slope, intercept, and midband fit values. Integrated backscatter measurements were obtained over the same frequency bandwidth.

Results: Measurements of the (5 MHz) midband fit and intercept values demonstrated significant anisotropy with maxima for insonification perpendicular to the predominant myofiber orientation and minima for parallel insonification. Midband fit values showed excellent agreement with the corresponding integrated backscatter values at each angle of insonification. Values of the slope did not exhibit a significant dependence on the angle of insonification within the uncertainties of the measurements.

Conclusion: These data suggest that measurements of spectral slope, intercept and midband fit can provide insights regarding aspects of tissue microstructure underlying the observed anisotropy of myocardial scattering properties. Measurements of the slope parameter suggest no significant change in effective scatterer size with angle of insonification. The observed anisotropy in midband fit and intercept parameters suggest an angle of insonification dependence arising from the combined effective spatial scatterer concentration and acoustic impedance properties without a significant contribution from changes in effective scatterer size.

(1) *J Clin Invest 88,* 438-46 (1991).

(2) *IEEE Trans Ultrason Ferroelec Freq Contr 34*, 319-329 (1987)

5. Statistics for Experiment Design

5.1 **Some fundamental principles of study design for the assessment of diagnostic imaging and multiple-feature tissue classification,** Robert F. Wagner, *Office of Science and Engineering Labs/CDRH/FDA, Silver Spring MD 20993, robert.wagner@fda.hhs.gov* (invited overview).

The general principles to be reviewed here apply to the assessment of diagnostic modalities, in particular, the estimation of sensitivity, specificity and their trade-off as summarized in the receiver operating characteristic (ROC) curve and the total or partial area under the ROC curve. The sizing of any such assessment study requires estimation of the size of the expected or mean effect(s), the variances of the random effects in the study and the correlations of the random effects across competing modalities. First, we assume a simple diagnostic test, like the PSA assay, with no human clinician in the loop. Then, there is only one so-called random effect, namely, patient variability. We review the basic statistical issues and requirements on number of patient samples for this common study. If a human clinician

is included in the loop (e.g., reading diagnostic ultrasound images), there is an additional random effect, namely, reader variability. This leads to the so-called multiple-reader, multiple-case (MRMC), ROC paradigm. We will review the major advances in MRMC analysis over the last decade, and the implications for study design. If a statistical-learning machine (e.g., a classical or neural classifier) must fuse multiple diagnostic features in order to provide a diagnostic score, the problem requires a higher level of analysis because of the finite-sample effects of limited numbers of patients for both training and testing. We will therefore review the fundamental concepts of Cover's theorem — the pathway to classifier capacity and complexity — and their connection with bias and variance of classifier assessment. A strategy for a pilot study to estimate the size of a pivotal study to achieve a desired level of confidence in the assessment scorecard of a diagnostic classifier will be reviewed.

5.2 **Metrics to evaluate multiple correlated ROC data and their uncertainties**, Frank Samuelson, *FDA, frank.samuelson@fda.hhs.gov* (invited.)

Many kinds of information from our imaging system(s) may be used in conjunction with sophisticated software to mark and score locations on patients that are most suspicious of disease. As in ROC analysis, we assume that these marks will fall into two populations; some marks will be at locations truly of interest (e.g. disease) and all others will be false positives. Like ROC analysis, we want to measure the ability of our system to discriminate between these types of marks via their scoring and we want to know of the uncertainty in this measure. Unlike usual ROC analysis, any single patient may have any number of either type of mark. This type of analysis is often called FROC analysis, or Free Response ROC analysis. This talk will look at metrics that we can use for this type of problem and, most importantly, how we can estimate uncertainties in them.

5.3 **Basics of sample size calculation,** Ronald H. Silverman, *Weill Medical College of Cornell University, New York, NY and Riverside Research Institute, New York, NY,* s*ilverman@rrinyc.org* (invited).

A crucial stage in the planning of a scientific study is determination of the sample size required to reach statistical significance. There are four requirements that must be satisfied to determine this: (1) definition of the hypothesis, (2) specification of the level of the effect that would be of clinical or scientific interest, (3) specification of the significance and power of the test and (4) estimation of the statistical distribution of the test variable. Requirement 1, definition of the hypothesis, may in some cases be obvious, but, in other situations ,can require more thought. For instance, in a project designed to produce a system that provides 'better' images, it would be necessary to establish a quantitative means of defining 'better.' It would also be necessary to have a standard against which to compare the new improved method. Hypotheses may be framed in many ways, including: the means of the experimental and control groups will be different; the mean of the experimental group will be higher than that of the control; or the proportion of cases meeting some criterion will be higher in the experimental than the control group. Requirement 2 is more a philosophical than statistical issue. It may be framed as a question: 'What would be considered to be a significant improvement conferred by my method?' In this case, the word 'significant' is meant in the nonstatistical sense, i.e., that the improvement would be meaningful in terms of improved patient care, etc. Requirement 3 involves defining the level of confidence for the sample size calculation. Values of sample size are computed for specific conditions of alpha (Type I error) and beta (Type II error), where Type I error refers to incorrectly rejecting the null hypothesis (where p 0.05), and Type II error refers to erroneously accepting the null hypothesis (where $p > 0.05$). Statistical power is defined as 1 – . A moderate criterion would set = 0.05 and power = 80%. A more stringent criterion would be = 0.01 and

power = 90%. As and become more stringent, the sample size required to prove the hypothesis increases. The last requirement involves having some knowledge of the expected statistical distributions. In cases where two means are to be compared (e.g., with Student's *T*-test), we need to have estimates of the values of the experimental variable in the known control population and the value we hope to achieve using our new method. In addition, we need an estimate of the standard deviation. Sample size calculations may also be determined for comparison of two proportions, for instance, the fraction of time a feature is detected using the standard method versus the experimental method. These values may come from a pilot study or from historical data. Sample size calculation can help focus the mind regarding what a study hopes to achieve and is often a crucial aspect in a hypothesis-based grant proposal in terms of defining the goals of the study and what can realistically be achieved within the time and budgetary constraints of the project.

6. Bone Evaluation

6.1 **An approach for applying Bayesian probability theory to experimental ultrasonic signals transmitted through bone potentially arising from mixed fast and slow wave propagation,** Christian C. Anderson, Keith A. Wear, Karen R. Marutyan, Mark R. Holland, James G. Miller and G. Larry Bretthorst, *Washington U. in St. Louis and FDA, jgm@wuphys.wustl.edu.*

Background: Recent studies from our laboratory suggested that the widely-reported decrease in phase velocity with frequency (negative dispersion) for ultrasonic waves propagating through cancellous bone can arise because of the interference of fast and slow mode signals, each of which exhibits a positive dispersion.[1] Results of simulations suggested that Bayesian probability theory can be employed to recover the material properties linked to these two interfering waves, even when the waves overlap sufficiently strongly that visual inspection cannot distinguish the two modes.[2]

Objective: The goal of the present study was to examine representative experimental bone data to assess the ability of Bayesian inference to first determine whether one or two modes are propagating (a model selection problem) and then to recover the slope of attenuation (*nBUA*) and phase velocity underlying the propagation of each mode (a parameter estimation problem).

Methods: The data analyzed had previously been acquired on human calcaneus samples that were defatted and prepared with flat and parallel sides such that they were approximately 18 mm thick. The samples were insonified in a water tank using two focused, coaxially aligned, 500 kHz center-frequency broadband transducers in a through-transmission arrangement. Analysis performed on the received broadband pulses revealed approximately linear-with-frequency increases in attenuation coefficient but modest negative dispersions over a bandwidth of 300-700 kHz. The received signals were used as inputs to a Bayesian inference algorithm that used Markov chain Monte Carlo with simulated annealing to calculate joint posterior probabilities for one- and two-mode propagation models. Each model incorporated monotonically increasing, linear-with-frequency attenuation coefficients, and monotonically increasing, logarithmic-with-frequency phase velocities for all ultrasonic waves, consistent with the requirements of causality imposed by the Kramers-Kronig relations for media with linear-with-frequency attenuation coefficients. The same algorithm also evaluated marginal posterior probabilities for the individual ultrasonic parameters of interest in each model.

Results: Methods for implementing the Bayesian analysis for the one and the two mode models, and issues arising in those implementations, will be presented and illustrated using

experimental data. Results of (more conventional) amplitude and phase spectroscopy analysis will be compared with the results of the Bayesian analysis. Evidence suggesting that a two-mode model is preferred over a one-mode model will be presented.

Conclusions: Bayesian methods show promise for extracting the true material properties of bone from the mixed-mode signals that appear to exhibit negative dispersion. For media that exhibit a linear-with-frequency increase in attenuation coefficient, such a decrease in phase velocity with frequency (negative dispersion) appears to violate the causality-induced Kramers-Kronig relations. The mixed-mode hypothesis resolves this inconsistency. Bayesian methods appear to permit the extraction of true material properties that could potentially be even better predictors of fracture risk than those derived from the currently employed one-mode analysis.

(1) *J Acoust Soc Am 120,* EL55-EL61 (2006).
(2) *J Acoust Soc Am 121,* EL8-EL15 (2007).

6.2 **Effect of phase cancellation on estimates of calcaneal broadband ultrasound attenuation in adult women,** Keith A. Wear, *FDA, kaw@cdrh.fda.gov.*

Broadband Ultrasonic Attenuation (BUA) is a clinically-accepted measurement for diagnosis of osteoporosis. Typical clinical BUA measurements are performed with phase sensitive receivers and therefore can be affected by phase cancellation. In order to separate the effects of conventional attenuation (absorption plus scattering) from phase cancellation, BUA was measured on phantoms with acrylic wedge phase aberrators and on 73 women using both phase sensitive (PS) and phase insensitive (PI) reception. A clinical bone sonometer (GE Lunar Achilles Insight®) with a two-dimensional receiver array was used. PI BUA measurements on phantoms with acrylic wedge phase aberrators were found to be far more resistant to phase cancellation than PS BUA measurements. In data from 73 women, means and standard deviations for BUA measurements were 81.4 ± 21.4 dB/MHz (PS) and 67.2 ± 9.7 dB/MHz (PI). The magnitude of the discrepancy between PS BUA and PI BUA tended to increase with bone mineral density (BMD).

6.3 **Attenuation sensitive backscatter technique for ultrasonic bone assessment,** Brent K. Hoffmeister,[1] David P. Johnson,[1] John A. Janeski,[1] Brian W. Steinert,[1] Daniel A. Keedy,[1] Ann M. Viano[1] and Sue C. Kaste,[2] *[1]Rhodes College Department of Physics, Memphis, TN and [2]St. Jude Children's Research Hospital, Department of Diagnostic Imaging, Memphis, TN, hoffmeister@rhodes.edu.*

Osteoporosis is a major public health problem that affects an estimated 44 million Americans. Ultrasonic techniques may provide a safe and efficient means for detecting the early onset of this degenerative bone disease. Most techniques rely on through transmission or axial measurements of the speed of sound and/or attenuation. A practical disadvantage of these techniques is that they can not be used easily at the hip and spine where most osteoporotic fractures occur. To address this problem, we are developing single transducer techniques based on apparent backscatter. The term "apparent" means that the frequency dependent effects of diffraction and attenuation are not removed from the backscattered signal. In previous studies, we found that the frequency averaged apparent backscattered power correlated well with bone density. Interestingly, the apparent backscattered power decreased with increasing bone density, suggesting that attenuation effects play an important role. Based on this idea, we have developed a parameter called Time Slope of Apparent Backscatter (TSAB) that is designed to be especially sensitive to attenuation effects. This parameter measures the apparent backscattered power as a function of the depth (or equivalently time) of penetration of the ultrasonic wave into the bone.

We performed *in vitro* backscatter measurements on 23 specimens of human cancellous bone prepared from the femoral heads of seven donors. A mechanical scanning system was used to measure each specimen at multiple sites, and the resulting values of TSAB were spatially averaged to obtain a single representative value for each specimen. Ultrasonic measurements were repeated using five different ultrasonic transducers with center frequencies ranging from 1 to 10 MHz. The spatially averaged TSAB values were correlated with the density and the mechanical properties of the specimens. The mechanical properties were determined through direct mechanical testing of the specimens. We observed significant linear correlations between TSAB and the density and mechanical properties of the specimens. The best correlation coefficients generally were obtained with the two highest frequency transducers (center frequencies 7.5 and 10 MHz) with R^2 values ranging between 0.55 and 0.85. These results suggest that TSAB may be a useful parameter for ultrasonic bone assessment.

Supported by NSF MRI/RUI 0320043

6.4 **Hierarchical modeling of bone as a material/structural composite,** J. Lawrence Katz, *School of Computing & Engineering and School of Dentistry, University of Missouri-Kansas City, Kansas City, MO, katzjl@umkc.edu.*

In the late 1960s and early 1970s, I began, with my colleagues and students, a series of ultrasonic wave propagation (UWP) studies to measure the elastic properties of bone and teeth, as well as of apatites. In 1971, based on these measurements, I was able to model both the anisotropic elastic properties of hydroxyapatite (HAp) as well as of bone as a simple collagen/HAp material composite. The failure of the simple composite model to predict quantitative values for bone and teeth elastic properties led me to initiate a series of optical, SEM, UWP and mechanical measurements of the microstructural organization of cortical bone. These experiments and calculations led me to assert in 1976 that to understand the mechanical properties of bone it was necessary to view it as a hierarchical material/structural composite. More sophisticated composite modeling and measurements of viscoelastic and electrical properties of cortical bone confirmed this view. Further confirmation of the importance of the structural organization of bone in determining its mechanical properties was provided by our comparison of the UWP measurements of anisotropy in both plexiform and haversian bovine cortical bone. Additional confirmation was provided by the Tulane BME group's measurements of elastic anisotropy as a function of position in human femoral cortical bone. The fact that the tensor properties of cortical bone from various bones and between various researchers do not generally scale led to problems in correlating the relationships between such measurements. This led me to adapt a calculation from crystal physics that provides two scalar anisotropic constants, shear and compressive anisotropy, based on appropriate mixtures of the tensor constants. To bring the research up-to-date, this calculation has been used recently to develop a master curve for the UWP measured anisotropic elastic properties of both bone and teeth. Also, multiscale mechanics of hierarchical structure/property relationships in calcified tissues has been recently modeled.

7. Elastography

7.1 **Progress and prospects of elastographic imaging,** Jonathan Ophir,[1] Raffaella Righetti,[1] Arun ThitaiKumar,[1] Thomas Krouskop[1] and Brian Garra,[2] *[1]University of Texas Medical School, Houston, TX and [2]University of Vermont, Burlington, VT, Jonathan.Ophir@uth.tmc.edu* (invited overview).

The idea of measuring the stiffness of soft tissues using ultrasound was suggested in the literature some 25 years ago. Since then, the measurement and later imaging of elastic parameters of tissues have progressed from this idea to a commercial reality that is based on solid fundamentals. Today, it is possible to obtain high-resolution real-time images of the axial strain components in soft tissues that are subjected to an external or internal mechanical load. These images have shown that new and potentially useful information can be obtained *in vivo* from such images, far beyond that which is available from sonograms alone. The road ahead involves several additional possibilities of gleaning substantially more information from soft tissues. These include the calculation and imaging of the elastic modulus, imaging the Poisson's ratio and its temporal evolution for the study of fluid flow in tissues that are affected by diseases such as lymphedema, and the imaging of the shear strain characteristics of tissue boundaries that characterize the bonding strength between tissue layers that may be specific for various disease states. This talk will illustrate some of the progress in the field and will demonstrate some of the diverse future possibilities.

This work was supported by National Cancer Institute Program Project Grant P01-CA64597-10 and by a fellowship grant from the John Dunn Foundation

7.2 **Challenges, opportunities and recent progress in quantitative elastography,** Jeffrey Bamber,[1] Paul Barbone,[2] Gearoid Berry,[1] Nigel Bush,[1] Aabir Chakraborty,[3] Louise Coutts,[1] Remo Crescenti,[1] Francis Duck,[4] Ricardo Liederman,[2] David MelodeLima,[1] Naomi Miller,[1] Assad Oberai,[5] Jacqueline Shipley,[4], Miranda Skurczynski[4] and Lijun Xu,[1] *[1]Institute of Cancer Research and Royal Marsden Hospital, Sutton, Surrey, UK, [2]Boston University, Boston, MA, [3]Royal Free Hospital, London, UK, [4]Royal United Hospital, Bath, UK and [5]Rensselaer Polytechnic Institute, Troy, NY, jeff@icr.ac.uk* (invited).

The first conference in this series was held with optimism that quantitative analysis of signals from ultrasound scattered or transmitted by tissues would lead to clinically-valuable measures of tissue composition, function or state. Similar enthusiasm now exists for measuring mechanical properties of tissues using the techniques of elastography, which involve processing time-varying echo data to extract the spatial and/or temporal variation of a stress-induced tissue strain. Many of the challenges facing those working towards quantitative elastography are, however, quite similar to those already experienced with earlier forms of ultrasonic tissue characterization, such as the tendency for results to be sensitive to experimental conditions that are not easy to know, and the existance of a wide range of mechanical properties that interact but that one would like to separate as measured variables. The second of these points presents both challenges and opportunities. Insufficient knowledge exists to tackle a full multivariate inverse problem or to know which variables can be ignored/taken advantage of so as to simplify the problem. We have therefore begun work to gain a better understanding of how to solve specific elastographic inverse problems, at the same time as studying, experimentally and theoretically, the relative importance of a number of mechanical characteristics in a variety of situations. This paper reports a selection of such studies.

Methods for solving the inverse problem to image shear modulus and nonlinearity from quasi-static surface loading are being investigated and an iterative algorithm, based on an adjoint equation, was shown in simulation and with experimental data on phantoms, to be a good candidate for clinical application. We are currently exploring the application of such methods to quantitative imaging of radiation dose distribution, where we have already documented the increase in Young's modulus with increasing dose, for gels that polymerise on exposure to ionising radiation. Clinically, we have briefly explored the use of a calibrated elastic stand-off to measure the stress profile across the surface of the tissue and were able to

detect differences in the stiffness of breast tissue, as well as its distribution with tissue type, between unirradiated and irradiated breasts in cases of post-treatment radiation fibrosis.

Tissues are not just elastic, but are poroelastic; when they are squeezed, the free fluid that they contain may be induced to move. Under sustained compression, this causes a heat conduction-like spatio-temporal distribution of strain. For homogeneous biphasic media (solid matrix with a single fluid compartment), we have been able, in simulation and phantom experiments, to recover (from time-dependent strain images) information related to the Young's modulus and Poisson's ratio of the solid matrix, its permeability to the pore fluid, the volume of mobile fluid affected and the direction of fluid flow. In general, this requires measurement of volumetric strain, although we have been able to utilize cylindrical symmetry in experiments to avoid this measurement complexity and have shown that for simple types of layered media, useful information can be inferred from measurements of the spatio-temporal dependence of axial strain only. Indeed, in clinical tests, the spatio-temporal pattern of axial strain predicted for a three-layer elastic-poroelastic-elastic sandwich is seen during sustained compression of the forearm and appears to be exaggerated in lymphoedema cases. Finally, theoretical modelling of a multicompartmental poroelastic medium containing a tumor in a homogeneous background, with estimated values for stiffness, resistance to fluid flow within and between the interstitial and microvascular compartments, and microvessel density, has indicated that fluid drainage into the local microvasculature should be the dominant flow-related stress/strain relaxation mechanism and that the magnitude of strain relaxation should be measurable by elastography.

The study of tissue anisotropy is also important in the context of quantitative elastography and we have chosen skin as an anisotropic tissue to study in the first instance. Having learned how to avoid confounding effects of the viscoelastic and nonlinear behaviour of skin, we have used elastography to show that surface tensile loading generates both lateral normal strain and lateral shear strain deep into the subcutaneous fat but not easily into the underlying muscle. Application of the tensile load in different directions has shown that normal forearm skin possesses a stiffness anisotropy of about 2, with 90 angular periodicity, but for arms affected by lymphoedema, the stiffness is approximately isotropic, the lateral normal strain propagates more easily beyond the fat-muscle boundary and more lateral shear may exist at the fat-muscle boundary.

For the full inverse problem to be solved, account would eventually have to be taken not only of the fact that tissue is, in general, mechanically nonlinear, viscous, porous and anisotropic but may also be mechanically discontinuous. In clinical elastography, we have noted strain behavior consistent with slip boundaries, e.g., between subcutaneous fat and muscle and between tumor and background. Quantifying the amount of adhesion at such boundaries should have clinical utility, which has led us to develop and evaluate in phantoms a new method that we call slip elastography, to noninvasively assess frictional resistance to slip at such tissue interfaces. The images depict the locations of slip boundaries in tests using gelatine phantoms and provide quantitative force values that are proportional to those expected to overcome boundary friction.

Finally, we have developed a method for imaging the transient strain generated at the site of impulsive and highly-focused acoustic radiation force. The method measures a highly local value of strain sampled before neighbouring stiffness values and boundaries have had time to influence the stress distribution. Advantages over surface-loaded quasistatic strain imaging appear to include better resolution, signal and contrast to noise ratio and contrast transfer efficiency, especially for soft inclusions in a stiff background or for objectives placed beyond a slip boundary.

Our encouraging results to date suggest that the next step in the future study and development methods such as these would certainly be worth taking. This involves moving to

three-dimensional measurement of time-varying displacement and strain, taking advantage of ongoing development of 4D ultrasound imaging technology.

This work has been funded from various sources, including the EPSRC, DoH NEAT, the ICR NIH, and CenSSIS.

7.3 **Recent progress in prostate elastography studies,** S. Kaisar Alam,[1] Ernest J. Feleppa,[1] Christopher R. Porter,[2] Andrew Kalisz,[1] Sarayu Ramchandran[1] and Shreedevi Dasgupta,[1] *[1]Riverside Research Institute, New York, NY and [2]Virginia Mason Medical Center, Seattle, WA, kalam@rrinyc.org.*

Over half of all prostate cancers cannot be detected by current clinical imaging modalities. In contrast, transrectal palpation is routinely used by physicians to detect masses that may reveal the presence of prostate cancer. Palpation is effective for detecting cancerous lesions because many diseases can alter tissue elasticity. However, palpation requires lesions to be near enough to an accessible surface for the internal mass to be felt. In addition, the lesions also need to have adequate elasticity contrast. The known clinical usefulness of manual palpation of the prostate for detecting masses that can be felt through the rectal wall suggests that ultrasonic elastography may be effective for imaging prostate cancers throughout the entire gland. Therefore, we performed a preliminary study to assess the feasibility of elastographic depiction of prostate cancer and to determine whether a handheld approach to prostate elastography is workable.

We digitally acquired radiofrequency (rf) ultrasound-echo data from prostate-cancer patients scheduled to undergo radical prostatectomy. A hand-held transrectal ultrasound (TRUS) probe was used for deforming as well as imaging the prostate. The probe face that was in contact with the rectal wall was manually pushed against it in a gentle manner to apply a compression force to the immediately adjacent prostate and to induce a small strain in the gland. We acquired rf echo-signal data at each of fifteen, closely spaced, transverse scan planes at the scanner frame rate as the deformation force on the rectal wall was continuously increased. We computed strain from consecutive scans using 1D and 2D rf cross-correlation analyses.

The acquired rf data produced low-noise elastograms that clearly displayed the macroscopic prostate architecture. "Suspicious," low-strain (i.e., relatively stiff) areas correlated well with histological findings of cancer. Our results suggest that prostate cancers potentially can be made visible in prostate elastograms, and prostate elastography potentially may be able to depict prostate cancers more reliably than conventional imaging, including B-mode ultrasound imaging.

In summary, elastography appears to show a potential for detecting and evaluating prostate cancers that, for the most part, are occult in all conventional imaging modalities. A larger clinical study is required and is being planned to verify this potential.

This work was supported in part by NIH grant CA84274.

7.4 **Development and testing of a real-time elasticity imaging system,** Timothy J. Hall, *Medical Physics Department, University of Wisconsin-Madison, Madison, WI, tjhall@wisc.edu* (invited).

Ultrasound has been used to estimate tissue elasticity since the early 1980's. A substantial improvement in technology came with the ability to form images of tissue elastic properties ("elastography") developed by Cespedes and Ophir. Since that time, there has been rapid development in technology leading to at least two ultrasound system manufacturers marketing elasticity imaging software packages on their premium systems. These systems implement freehand scanning techniques for quasi-static tissue deformation. This presentation

will review some of the key developments and highlight strategies for near-term future development.

Among the key developments in real-time elasticity imaging were improvements in strategies for motion tracking. Early developments demonstrated that 2-D tracking allowed accurate motion estimates with larger deformation resulting in higher elasticity image signal to noise ratios. Another key development was the demonstration that an optimal motion tracking kernel size exists, but that size depends on the deformation field. Further, predictive-search strategies were developed to reduce the computational cost of motion-tracking algorithms. These developments in motion-tracking strategies will be reviewed.

Several groups have performed observer studies to test the utility of elasticity imaging for breast tumor diagnosis. The information gleaned from these experiments depends on experiment design and execution. This presentation will review previous observer performance studies and highlight key aspects and results of our own recent work where elasticity imaging, combined with B-mode ultrasound, was demonstrated to provide a statistically-significant increase in breast abnormality classification over B-mode imaging alone. From this work, we also learned that some improvements in tools available to the observers would likely improve their ability to extract and use elasticity image information.

Finally, this presentation will discuss some of the developments we are working on that will likely open new opportunities for elasticity imaging in the near future. For example, we know from *in vitro* tissue measurements that most breast tissues have nonlinear stress-strain relationships. Consistent with those measurements, we have demonstrated deformation-dependent strain image contrast for fibroadenomas and relatively constant contrast for cancers, as expected. Methods for studying and imaging this elastic nonlinearity will be discussed. Recent results, and the implications, of elasticity imaging with a 2-D CMUT array will also be discussed.

We are grateful for the grant support from NIH/NCI R01-CA100373.

7.5 **Mechanical and electromechanical imaging of the cardiovascular system,** E. Konofagou, J. Luo, W-N Lee, I. Zervantonakis, K. Fujikura, S. Wang, S. Homma and J. Coromilas, *Columbia U., ek2191@columbia.edu* (invited).

Myocardial elastography has been validated regarding its capability of detecting abnormal myocardial function, due to ischemia or infarction, through estimation and imaging the myocardial deformation during the natural contraction of the myocardium. We have previously proposed a theoretical framework that shows good performance of the angle-independent myocardial elastography using an ultrasonic image formation model based on well-developed 3D finite-element canine left ventricle models in both normal and left-circumflex ischemic cases. In this paper, we show how angle-independent myocardial elastography can be employed as well as validated *in vivo* to assess the contractility of normal and pathological myocardia compared with the theoretical framework. The angle-independent measurements are also compared against tagged Magnetic Resonance Imaging (tMRI) *in vivo*. Finally, at higher frame rates, e.g., at approximately 320 fps, we show the capability of visualizing the conduction wave propagating in the cardiac muscle during the depolarization and repolarization phases through electromechanical coupling.

Angle-independent myocardial elastography, based on radiofrequency (rf) signal processing at high frame rates, consists of three main techniques. First, in-plane (lateral and axial) cumulative displacements during systole are iteratively estimated using 1D cross-correlation and recorrelation techniques in a 2D search using a 1D matching kernel of 7.7 mm and 80% overlap. Second, in-plane finite strains were calculated from the cumulative motion using a least-squared strain estimator. Third, angle-independent measures, principal strains, were further computed from the finite strains by solving an eigenvalue/eigenvector problem

with a classification strategy. A GE-Vivid FiVe system with a standard probe (FPA 2.5MHz 1C) was used to acquire rf signals for the clinical study at 135 fps. A 2D short-axis view of the left ventricle was considered both in simulations and *in vivo*.

The elastographic estimates, including motion and principal strains, in normal and pathological human subjects were validated in short-axis views. Similar to the theory, the elastographic estimates in normal clinical cases showed wall thickening radially and shortening circumferentially except for the septal wall, which is hypoechoic. Principal strains further characterized and differentiated abnormal from normal myocardia in short-axis views. Preliminary comparison with tMRI estimates in four normal subjects indicated that the elastographic estimates are within 4% of the tMRI estimates over the entire cardiac cycle. At higher frame rates, in the displacement images, waves were depicted propagating along the septum and posterior wall in a long-axis view, from apex to base (during systole), at both end-diastole and end-systole.

The feasibility of angle-independent myocardial elastography was shown through imaging of the myocardial motion and in-plane principal strains throughout the entire cardiac cycle, which was proven essential in the reliable depiction of disease. This capability was demonstrated *in vivo* and in close agreement to tMRI estimates. Finally, by employing higher frame rates, the contraction waves in the heart were clearly visualized on the displacement images, indicating the onset of activation of different ventricular regions.

This study was supported in part by the American Heart Association (SDG 0435444T), the Wallace H. Coulter Foundation (CU02650301) and the National Institutes of Health (R01 EB006042-01).

7.6 **Clinical experience of real-time tissue elastography in breast, prostate and abdominal desease,** Tsuyoshi Mitake,[1] Takeshi Matsumura,[1] Takuji Oosaka,[1] Akiko Tonomura,[1] Makoto Yamakawa[2] Naotaka Nitta[3] and Tsuyoshi Shiina,[2] *[1]Hitachi Medical Corp., [2]U. Tsukuba and [3]National Inst. Advanced Industrial Science and Technology, ciao_mitake @nifty.com* (invited talk).

We have developed a real-time tissue elastography imaging system for visualizing the tissue hardness/softness to detect lesions such as cancer. Our system is based on autocorrelation by combining envelope and phase for the special benefit of avoiding aliasing errors, high-speed processing, accuracy and a wide dynamic range. And, when using the system clinically under freehand compression, it is important to avoid errors due to decorrelation caused by the lateral direction. To overcome this issue, the combined autocorrelation is applied in axial and lateral directions. The frame rate of the system that is integrated into ultrasound scanner is more than 15 fps at 40 mm (axial) by 30 mm (lateral). Strain images are superimposed on 2D image with a translucent color map.

Using the integrated system, we have been investigating its clinical usefulness for several clinical abnormalities, e.g., breast cancer, prostate cancer, abdominal disease, etc. With respect to breast cancer, we have gathered more than 1,500 cases in screening usage. As a result, the consultation rate of detailed examination was reduced from 3.59% to 1.51%. During the study, we found some tips and hints about how to produce the compression and so on. We will provide technical details of the system and show our clinical experiences and hints with some statistical result.

7.7 **Clinical elasticity estimation: methods and applications on the verge of clinical adoption,** Brian S. Garra, *U. Vermont, bgarra@uvm.edu* (invited).

Elasticity imaging and estimation, an outgrowth of the ancient technique of palpation, is gaining wider acceptance as an important clinical tool and is being applied to more tissues and diseases every year. Although images of elastic properties may be generated using any

imaging tool capable of monitoring tissue displacements over time, ultrasound (US) and magnetic resonance imaging (MRI) have become the dominant modalities for imaging and estimating elasticity in living tissues.

US elasticity imaging can be performed by compressing tissue while monitoring tissue displacement (elastography) or by transmitting an acoustic wave through tissue and monitoring tissue motion (sonoelastography). Both superficial and deep organs can be examined using elastography. In the case of deeper organs, more external pressure must be applied, but this has not proven difficult clinically. Another option for deeper organs is to use the transmitted pulsations of the heart or major arteries to produce the required tissue displacements. The development of acoustic radiation force methods will further enable the imaging of elasticity in deeper organs.

Specific structures that have been examined so far include breast masses, thyroid nodules, lymph nodes and prostate nodules. The goal for evaluation of masses and nodules has been to improve our ability to distinguish cancerous tissue from benign nodules. Commercial clinical trials to study breast mass elastography are about to begin. Entire organs that have been studied include the breast, thyroid, kidney, liver, uterus, and pancreas. The focus in many organs is to detect and grade diffuse disease — for example, cirrhosis in the liver or rejection in renal transplants. In addition, skeletal muscle has been extensively studied along with the myocardium, and blood vessel walls including atheromatous plaque. The characterization of atheromatous plaque to detect unstable or vulnerable plaque is currently an area of great clinical interest.

Another promising area of application is in the monitoring of ablation therapy. Ablative therapies destroy tumors by application of heat (laser, radio frequency, HiFU) or by cold (cryoablation) but all methods significantly change tissue hardness. This change is easily imaged using elasticity imaging. Yet another promising area of investigation is the monitoring of fluid movement in tissues using poroelasticity imaging. This method has great potential for the evaluation of lymphedema.

Commercial manufacturers are moving forward with incorporating elasticity imaging in their clinical systems. All major US equipment vendors either have announced elasticity imaging capability in their systems or have it in development. As these systems move into clinical trials and processing methods are further refined, the role of elasticity estimation, imaging and nonimaging, will increase and become better defined. Exciting times are ahead!

8. ARFI

8.1 **Transthoracic cardiac acoustic radiation force impulse imaging: a feasibility study,** Stephen Hsu, Brian Fahey, David Bradway and Gregg Trahey, *Duke University, sjh6@duke.edu.*

Acoustic radiation force impulse (ARFI) imaging has been demonstrated to be capable of visualizing variations in myocardial stiffness through the cardiac cycle. With the transducer placed directly on the exposed heart, ARFI images have shown differences between systolic and diastolic tissue displacements that were greater than the measured displacement artifacts from cardiac motion. However, in order to be a viable clinical real-time system, a noninvasive method of ARFI image acquisition is necessary.

In this work, we explore the feasibility of transthoracic cardiac ARFI imaging. We imaged the hearts of two live porcine subjects, weighing approximately 20 kg with heart rates up to 150 bpm. A transthoracic approach poses several challenges, such as increased tissue

depth, vigorous cardiac motion and limited viewing angles. An abdominal low-frequency (2.2 MHz) probe was used with an extended radiation force pulse length (360 s) to produce tissue displacements at depths up to 8 cm. Several physiological motion filters and ARFI acquisition sequences were created to reduce cardiac motion artifacts. Passive ARFI acquisitions, where the radiation force pulse amplitude was set to zero, were also acquired to assess the levels of cardiac motion artifact within the images. Single line M-mode and two-dimensional ARFI images of the heart were formed from intercostal and subapical viewing angles. Although a significant amount of cardiac motion artifact is present at systole, the ARFI displacement images of the heart reflect the expected myocardial stiffness changes through the cardiac cycle.

8.2 **Excitation enhanced imaging: *in vitro* and *in vivo* results,** Flemming Forsberg,[1] Raymond J. Ro,[1,2] William T. Shi,[1,3] Michael K. Knauer,[4] Kausik Sarkar,[5] Anne L. Hall,[3] Chris Vecchio[4] and Richard Bernardi,[4] *[1]Department of Radiology, Thomas Jefferson University, Philadelphia, PA 19107, [2]School of Biomedical Engineering, Science and Health Systems, Drexel University, Philadelphia, PA 19104, [3] GE Healthcare, Milwaukee, WI 53219, [4]Spectrasonics Imaging, Inc., Wayne, PA 19087 and [5]Department of Mechanical Engineering, University of Delaware, Newark, DE 19716, flemming.forsberg@jefferson.edu.*

To improve contrast imaging, a novel technique called Excitation Enhanced Imaging (EEI) has been developed. EEI employs two acoustic fields: a low-frequency, high-intensity ultrasound field (the excitation field) to actively condition (or increase the size of) contrast microbubbles; and a second higher-frequency, lower-intensity regular imaging field applied shortly afterwards to detect the enhanced contrast scattering.(1) We have investigated the efficacy of EEI *in vitro* and *in vivo.*

Four different ultrasound contrast agents were tested *in vitro*: Sonazoid (GE Healthcare, Oslo, Norway), Definity (BMS Medical Imaging, N Billerica, MA), Therimage (Focus Therapeutics, Media, PA) and Optison (GE Healthcare, Princeton, NJ). An excitation frequency of 1.1 MHz at an amplitude of 1.2 MPa was used with a 16 cycle pulse length at prf of 2 Hz. Imaging frequencies of 2.5 MHz and 7.5 MHz were investigated for concentrations between 0.02 l/l and 80 l/l at ambient (22 C) and physiological (37 C) temperatures to determine the change in scattered signal strength before and after the excitation pulse (i.e., the enhancement obtained with EEI) at fundamental and harmonic frequencies. A new zero-thickness interface model was used to simulate the dual pulse imaging mode associated with EEI and compared to the *in vitro* measurements. A Logiq 9 scanner (GE Healthcare, Milwaukee, WI) with a 3.5C curved linear array and an AN2300 digital ultrasound engine (Analogic Corporation, Peabody, MA) with a P4-2 phased array transducer (Philips Medical Systems, Bothell, WA) were modified to perform EEI on a vector-by-vector basis in fundamental and pulse inversion harmonic grayscale modes. *In vivo* cardiac EEI was tested in four dogs.

At a 2.5 MHz imaging frequency, Sonazoid produced 10 dB of enhancement at 22 C, which reduced to 5 dB at 37 C. Conversely, Optison created 1 dB of enhancement at 22 C, which increased to 9 dB at 37 C. This enhancement reduced to 3 dB when the concentration was increased from 0.05 l/l to 0.5 l/l. While no enhancement was found for the contrast agent Definity at any of the concentrations studied, Therimage produced approximately 5 dB of enhancement at both the fundamental and the harmonic frequencies (7.5 and 15 MHz) at a 20 l/l concentration. Initial simulation results indicate that the shell elasticity plays a vital role in the growth as well as dissolution of the bubbles. While results at an imaging frequency of 7.5 MHz were somewhat in agreement with measurements, the enhancement was

unrealistically high (20-35 dB). Further work is ongoing to improve upon the model. Somewhat disappointingly no enhancement produced by EEI was observed *in vivo.*

In conclusion, up to 10 dB of enhancement can be achieved in EEI mode *in vitro* at lower imaging frequencies (with less enhancement occurring at higher frequencies). However, EEI appears to be quite sensitive to changes in temperature and microbubble concentration and this may explain the disappointing *in vivo* results. Further research is needed to clarify these issues.

This work was supported in part by U.S. Army Medical Research Materiel Command under DAMD17-00-1-0662 and by NIH HL62830.

(1) Forsberg F, et al. *Ultrasonic Imaging 27,* 65-74 (2005).

8.3 **On the adherence of targeted bubbles to bloods clots *in vitro*,** Savitha Fernandes,[1, 2] Sergiy V. Shevchuk,[3] Samuel C. Gilmore,[3] Terry O. Matsunaga[3] and Flemming Forsberg,[1] *[1]Department of Radiology, Thomas Jefferson University, Philadelphia, PA 19107, [2]School of Biomedical Engineering, Science and Health Systems and [3]ImaRx Therapeutics, Tucson, AZ 85719, flemming.forsberg @jefferson.edu.*

The ability of targeted bubbles to adhere to fresh platelet clots was assessed *in vitro*. Whole blood from healthy volunteers (25 ml) was collected and centrifuged at 1,100 rpm for 15 min to separate platelet-rich plasma (PRP). Then the PRP was separated and 2 ml of it centrifuged at 3,000 rpm for 5 min to get platelet poor plasma (PPP). Calcium was added followed 3 min later by 15-20 μl of Thrombin from human plasma to form a fresh blood clot. MRX802-0221 (ImaRx Therapeutics, Inc., Tucson, AZ) is a fibrin-targeted contrast agent and these targeted bubbles were added to 8 PRP clots and 7 PPP clots (dose: 10 μl). As a control, bubbles with no targeting ability were added to 9 PRP clots and 5 PPP clots. Following 3 washes, the number of bubbles attached relative to clot area was determined using an SMZ-10A microscope (200x magnification; Nikon, Melville, NY) and ImagePro Plus software (Media Cybernetics, Silver Spring, MD). The adherence of targeted and control bubbles was compared using unpaired t-tests. Radiation force will also be employed using a single-element, 2.25 MHz transducer (Panametrics, Waltham, MA) with continuous wave ultrasound (100 Hz prf, 30 s exposure, 38.4 kPa p-p pressure) to gently push the bubbles onto the clots and increase the number of adhered bubbles.

The average number of MRX802-0221 bubbles attached (per 1,000 μm^2 of clot area) in PRP clots was 70 25 bubbles and in PPP clots it was 35.8 13.7 bubbles. The control bubbles had a mean adherence of 17.6 6.6 bubbles and 6.08 1.73 bubbles in PRP and PPP clots, respectively. The difference in adherence rates was statistically significant for PRP clots ($p = 0.0242$) and marginally significant for PPP clots ($p = 0.0504$). The outcome of the radiation force experiments will be compared with these values and results reported.

In conclusion, the attachment of MRX802-0221 targeted bubbles to PRP clots was found to be significantly higher than the control.

Supported by NIH HL71433.

8.4 **Measuring elastic and viscous moduli from radiation force induced tissue motion,** James. F. Greenleaf, X. Zhang and S. Chen, *Ultrasound Research Laboratory, Mayo Clinic College of Medicine, jfg@mayo.edu.*

Radiation force produced by momentum transfer from traveling ultrasound waves into materials can be used to physically displace tissue. Measurements of the resulting displacement can be used to estimate intrinsic mechanical properties of the tissue such as shear storage and loss moduli. Focused ultrasound beams can be used to place force distributions at selected regions deep in tissue and the same beams used in pulse echo can be used to measure the resulting displacement response to the force. In isotropic and homogeneous tissues,

shear wave speed and dispersion can be used to solve for the elastic and viscous moduli. Other tissues are anistotropic, but homogeneous, such as muscle in which the force application and subsequent measurements must be related through a suitable model to the anisotropic material properties. Judicious choice of vibration modes and resulting motions can greatly aid in solving the very complex motion for the related material properties in complex structures such as vessels. Using remote application of force and measurement of resulting motion we have measured the complex shear modulus in (1) isotropic tissue such as liver, (2) anisotropic tissue such as muscle and (3) structures such as vessels. The goal of this program is to relate the measured fundamental properties to onset and extent of disease.

Supported in part by grants EB 02167 and EB 02640 from NIH.

8.5 **High shear loss modulus tissue-mimicking materials for ARFI imaging and MR elastography,** E.L. Madsen, M.A. Hobson, G.R. Frank and T.J. Hall, *University of Wisconsin, Madison, WI*, *elmadsen@wisc.edu.*

Two elasography modalities involve generation and tracking of shear waves in soft tissues, viz, Acoustic Radiation Force Impulse (ARFI) imaging[1] and (dynamic) MR elastography (MRE).[2, 3] The complex shear wave number at frequency f (Hz) is given by $k = (2 \quad f)(\quad /G)^{-1/2}$, where is the mass density of the propagating medium and G is the complex shear modulus at frequency f. $G = G' + iG''$ where G' is the (real positive) shear storage modulus and G'' is the (real positive) shear loss modulus. In soft tissues, where the loss factor = tan $= G''/G'$ can be 0.25 to 0.7 [2, 4, 5] and perhaps larger, there is significant shear wave attenuation and corresponding speed dispersion. For example, reasonable values of G' and tan for breast fat might be 1 kPa and 0.25 at 50 Hz and might be 2 kPa and 0.5 at 300 Hz. The resulting wavelengths are 2 cm and 0.5 cm at 50 Hz and 300 Hz, respectively, while the propagation distances for the shear wave amplitude to decrease by a factor of 1/e are 2.6 cm and 0.35 cm at 50 Hz and 300 Hz, respectively.

Simulation of realistic tissue-like loss factors in phantoms could aid MRE and ARFI researchers in assessing the trade-off between better resolution and higher attenuation as the frequency increases. (ARFI researchers might fashion pulses to yield higher or lower frequency contents of shear waves generated.) Also, realistically large loss factors could aid ARFI researchers in testing algorithms to account for dispersion. Extent of dispersion/attenuation could itself be diagnostically significant. Current phantoms used in MRE and ARFI are essentially lossless.

Thus, there is a need for high loss tissue-mimicking (TM) materials with realistic values of G' and G''. One type of low loss TM material for elastography consists of oil in gelatin dispersions.[6] We have modified these materials by adding a high molecular weight polysaccharide to the aqueous gelatin component resulting in TM materials with representative values of G' and G'' in the 50 to 300 Hz frequency range. The loss factor (G''/G') is a strong function of polysaccharide concentration. Following are some numbers for the case for one polysaccharide concentration with 0% (no oil) and 70% oil by volume. At 0% oil, G' is about 5 kPa at 50 Hz and 7.5 kPa at 300 Hz, while tan is 0.2 at 50 Hz, increases to 0.4 at 200 Hz and levels off above 200 Hz. For the 70% oil version, G' values are about half of those for the 0% oil material from 10 through 300 Hz, and tan values are about 3/4 of those for the 0% oil material from 10 through 300 Hz.

As in the case where no polysaccharide is present,[6] it is expected that geometrically and chemically stable heterogeneous phantoms can be made from the new high loss materials. The maximum elastic contrast = (G' of inclusion)/(G' of surroundings) is about 2 for the high loss materials.

(1) Nightingale K, McAleavey S, Trahey G. Shear-wave generation using acoustic radiation force: *in vivo* and *ex vivo* results, *Ultrasound Med Biol 29,* 1715-1723 (2003).

(2) Sinkus R, Tanter M, Xydeas T, Catheline S, Bercoff J, Fink M. Viscoelastic shear properties of *in vivo* breast lesions measured by MR elastography, *Magn Reson Imaging 23,* 159-165 (2005).

(3) Muthupillai R, Lomas DJ, Rossman PJ, Greenleaf JF, Manduca A, Ehman RL. Magnetic resonance elastography by direct visualization of propagating acoustic strain waves. *Science 269,* 1854-1857 (1995).

(4) Sinkus R, Tanter M, Catheline S, Lorenzen J, Kuhl C, Sondermann E, Fink M. Imaging anisotropic and viscous properties of breast tissue by magnetic resonance-elastography. *Magn Reson Med 53,* 372-387(2005) .

(5) Abrogast and Margulies. Material characterization of the brainstem from oscillatory shear tests, *J Biomechanics 31,* 801-807(1998).

(6) Madsen EL, Hobson MA, Shi H, Varghese T, Frank GR. Stability of heterogeneous elastography phantoms made from oil dispersions in aqueous gels, *Ultrasound Med Biol 32,* 261-270 (2006).

Supported in part by NIH grants R01EB000459, T32CA009206 and R01CA100373.

8.6 **Measurement of axial and lateral resolution in acoustic radiation force impulse imaging,** Manoj Menon, Tony Broyld and Stephen McAleavey, *University of Rochester, Rochester, NY 14627, menon@bme.rochester.edu*.

Acoustic Radiation Force Impulse (ARFI) imaging is the measurement of the mechanical properties of tissue by the generation of local impulsive acoustic radiation forces using a standard diagnostic ultrasound scanner. Short duration (30 s), high intensity (600-1000 W/cm^2) ultrasound pushing pulses induce micron-scale tissue displacements related to tissue stiffness. The displacements are tracked using ultrasound tracking pulses and are quantified using conventional correlation-based methods.

ARFI imaging is used to image objects of various shapes and sizes that characterize pathologies; therefore, it is important to quantify its resolution capability. The resolution of the ARFI imaging system was found using the step response of the system. The step response can be found by imaging an object with adjacent light and dark regions. The derivative of the step response results in the point response of the system. The full width, half maximum (FWHM) of the point response may be reported as the lower resolution limit.

The elastic contrast necessary for a step response was provided by a hard tissue-mimicking phantom with a soft central core (greater than 30 kPa, and less than 4 kPa, respectively). The phantom was created from a solution of gelatin (300 bloom at a concentration of 99 g/L for the hard portion and 100 bloom at a concentration of 41.3 g/L for the soft portion), 13.75 mL of n-propanol to adjust the speed of sound close to 1,540 m/s, 285 mL of water, 45 g of graphite powder to create a homogenous field of scatterers, and 3 mL of gluteraldehyde to increase the melting point. The phantom was imaged in two orientations with regard to the soft core in order to measure both axial and lateral resolutions. The resolution measurement was limited by undersampling in typical ARFI images in the lateral direction (13.4 lines/cm). In order to increase the line density, the transducer was positioned above the sample and images were taken in 100, 7.4 m steps. By combining the images taken, an image with a higher lateral line density (1,340 lines/cm) was created. The axial and lateral step responses were found by choosing lines in the image that included the interface between the hard and soft regions of the phantom. The region of the step was chosen by inspection and a cubic function was fit to the data. The derivative of the fit function was calculated and the FWHM resolution was measured. Measurements of axial resolution and lateral resolution were taken in various locations for resolution measurements of 0.439 ± 0.425 mm ($n = 10$), and 1.559 ± 0.747 mm ($n = 19$), respectively.

Grants: S ARMY/CDMRP W81XWH-04-1-0034, Wallace H. Coulter Foundation Early Career Award and in-kind and technical support from Siemens Medical Solutions USA, Ultrasound Group.

8.7 **Estimation of shear modulus using spatially-varying acoustic radiation force,** Stephen McAleavey and Menoj Menon**,** *Department of Biomedical Engineering, University of Rochester, Rochester, NY 14627, stephenm@bme.rochester.edu.*

The limitations and diagnostic utility of palpation have led to an interest in elastography, the imaging of tissue stiffness or a related parameter. These images are useful because disease or therapeutic processes may cause a significant change in tissue stiffness without a concomitant change in ultrasound echogenicity or x-ray density. Quantitative methods for estimating tissue shear modulus are especially desirable for evaluation of diffuse diseases, e.g., liver fibrosis, because the lack of local contrast in diffuse disease severly limits the utility of nonquantitative methods.

We present a method for estimating the shear modulus of an elastic material using the radiation force of short bursts of ultrasound with a deliberate spatial variation in intensity. This spatially-varying acoustic radiation force impulse is used to generate a shear wave of known spatial frequency (wavelength). The propagation of this shear wave is measured using ultrasound tracking methods and the temporal frequency of the shear wave estimated. Given the known wavelength and material density, and the measured estimate of temporal frequency, the shear modulus at the point of excitation may be calculated easily from the relationship $G = (\ f)^2$. Because the temporal, rather than spatial, frequency of the shear wave is estimated, observations of the tissue displacement can be made rapidly at a single point. The proposed method avoids the use of difficult-to-obtain estimates of spatial derivatives of tissue motion as needed in inversion methods.

We present finite element simulations of tissue motion in response to spatially-modulated radiation force and demonstrate good agreement with our analytical model. We also present the results of *in vitro* measurements of the shear modulus of graphite/gelatin phantoms. A Siemens Antares scanner was used to generate the spatially-varying pushing beams and track motion in the phantoms. We estimated the gelatin phantom shear moduli to be 1.4 and 5.8 kPa using this method, in good agreement with the 1.5 and 5.6 kPa values measured with an MTS mechanical testing system.

9. Imaging

9.1 **Imaging with reconfigurable transducer arrays,** Rayette Fisher, Scott Cogan, David Mills, Robert Wodnicki and Kai E Thomenius, Imaging Technologies, *GE Global Research, Niskayuna, NY, thomeniu@crd.ge.com.*

Recent advances in piezoceramic acoustic stack design, capacitive micromachined ultrasound transducer (cMUT) electronics and transducer-to-electronics integration are enabling the fabrication of highly integrated reconfigurable ultrasound arrays. Reconfigurability in this context refers to the ability to reorganize the array elements in any configuration deemed desirable. Configurations that we find attractive are an annular array, which can be translated electronically along a 2D array surface, or a phased array whose element orientation and pitch can be varied to optimize an image.

Further, the annular array configuration enables 3D-enabled miniaturized systems by reducing the channel count, system size and power consumption. In addition to such fabrication-related benefits, the annular array will also provide dynamic axisymmetric focusing; something that previously has only been possible with mechanically-scanned devices. We

have developed a switch matrix using application specific integrated circuits (ASICs) that change the interconnections between transducer subelements. These circuits, when interconnected to array elements, are able to dynamically combine the subelements to form larger elements and ideal apertures for a given target (e.g., annular and phased array apertures with various ring widths).[1-6]

While the switch matrix ASIC can be used with both piezoceramic transducers and cMUTs, the monolithic nature of the latter facilitates stacked sensor integration with the switch matrix ASIC. We have built an array of switch matrix ASICs in bare die form; they provide electronic control of several thousand transducer subelements. Description of the interconnect methodology will be provided along with initial phantom imaging results.

In conclusion, the use of novel packaging methodology to stack the array with its electronics array opens the door further front-end electronics miniaturization. The relocation of electronics into the probe handle combined with aperture agility will have a great impact on our ability to make highly portable ultrasound systems. We believe that these developments will broaden the range of ultrasound applications to new areas such as use by a primary care physician or for measurements of physiological parameters for patient monitoring.

This work was supported in part by US Army Medical Research Acquisition Activity DAMD17-02-0181 (820 Chandler Street, Fort Detrick MD 21702-5014) and by NIH (NIBIB) R01 EB002485, "Low Cost Ultrasound Using Silicon Transduction", as well as the General Electric Company. The content does not necessarily reflect the policy of the U.S. Government.

(1) Cogan S, et al. Solutions for reconfigurable arrays in ultrasound, in *Proc IEEE Ultrason Symp* (2006).

(2) Thomenius K, et al. Mosaic arrays using micromachined ultrasound transducers, *US Patent 6,865,14*0 (2005).

(3) Hazard D, et al. Annular array beamforming for 2D arrays with reduced system channels, in *Proc IEEE Ultrason Symp,* pp. 1859-1862 (2003).

(4) Bailey D. A computer controlled transducer for real-time three-dimensional imaging," in *Acoustical Imaging 18*, Lee H, Wade G, eds., pp. 543-552.

(5) Bele R. Echography probe and apparatus incorporating such a probe, *US Patent 4,641,660* (1987).

(6) Fisher R, et al. Reconfigurable arrays for portable ultrasound, in *Proc IEEE Ultrason Symp* (2005).

9.2 **Development of variable-depth HIFU (high intensity focused ultrasound) applicators for remote acoustic hemostasis under ultrasound image guidance,** Joel Mobley,[1] Jason L. Raymond,[1] David Woolworth,[1] Sara Davis,[1] Charles Church[1] and Peter Kaczkowski,[2] [1]*Jamie Whitten National Center for Physical Acoustics, University of Mississippi, University, MS 38677 and* [2]*Center for Industrial and Medical Ultrasound, University of Washington, Seattle, WA 98105, jmobley@olemiss.edu.*

With continuing clinical experience and engineering advances, high intensity focused ultrasound (HIFU) will soon provide the means to achieve hemostasis remotely, without direct access to the site of the wound. One of the milestones in the evolution of this technology is to provide the practitioner with the ability to both observe and treat the tissue of interest ultrasonically within a single handheld probe. Our approach is to combine a commercial phased-array imaging transducer with a coaxial annular HIFU device capable of variable depth targeting. In this work, we describe the development of annular HIFU probes with variable focal depths, including phased arrays and single-element transducers with interchangeable Fresnel lenses.

Phased array system: Our current phased array system consists of five annular elements with a central opening (20 mm) designed to accommodate an intracavitary imaging probe coaxial with the HIFU beam. The HIFU array operates at 2.5 MHz, and driving signals are produced in five channels of a 32-channel signal generator. Each element is driven by an amplifier that is capable of delivering 100 watts of rf power. The focal region can be moved from 6.0 to 9.5 cm by electronically focusing the annular elements. Results of preclinical trials show that electronically focusing the annular HIFU array successfully permits the clinician to target the zone of injury in depth under ultrasound guidance. Furthermore, therapeutic power levels appear to be adequate for treating open bleeds.

Fresnel lens system: In an attempt to provide a more economical approach to the construction of HIFU applicators, we have also developed single-crystal devices that employ interchangeable, low-profile Fresnel lenses to provide for variations in the focal depth. Two lens types have been tested: arc lenses whose refractive surfaces are at oblique angles and step lenses whose profile contains only surfaces parallel and normal to the transducer plane. Both Schlieren and phase sensitive beam profiling have been performed to assess the performance of these two lens designs. The step Fresnel is found to be most efficient for this application because of the mode conversion in the outer rings of the arc design.

9.3 **Investigations into clutter reduction methods in abdominal ultrasonic imaging,** Muyinatu Lediju, Michael Pihl, Stephen Hsu, Jeremy Dahl, Caterina Gallippi and Gregg Trahey, *Duke University and University of North Carolina, gregg.trahey@duke.edu.*

In ultrasonic imaging, clutter is known to degrade image quality. It is caused by a number of acoustic phenomena, including reverberation in tissue layers and off-axis scattering due to side and grating lobes inherent in ultrasonic imaging systems. Clutter arising from the abdominal wall often clouds the image of structures underneath the abdomen; a primary example occurs during fetal imaging in obese women. Reducing abdominal clutter will enhance the ability to clearly observe abdominal structures.

We propose to ascertain the source and extent of abdominal clutter by inducing slight motion of the abdomen during ultrasonic imaging. We used the transducer to slightly move the abdomen while imaging the *in-vivo* bladder; the bladder was used as a substitute for a uterus containing amniotic fluid. We also conducted matched experiments with abdominal phantoms that mimicked the observed acoustic and geometric properties of the bladder. Successive frame image subtraction and two-dimensional speckle tracking algorithms were developed and applied to the bladder and phantom data sets. Additionally, Field II simulations were developed to model the effectiveness of our experimental methods. We also report on blind source separation and wall-filtering methods to reduce clutter. The results provide insight into the magnitude and sources of the clutter.

9.4 **Backscatter and scatterer size estimates using a 2D CMUT transducer,** W. Liu[1], J. Zagzebski,[1], T. Hall,[1] T. Varghese,[1] T. Herd,[1] S. Panda,[2] S. Barnes[2] and C. Lowery,[2] *[1]Department of Medical Physics, University of Wisconsin-Madison, Madison, WI 53706 and [2]Siemens Medical Ultrasound Systems, Issaquah, WA 98029, wuliu@wisc.edu*

Compared to conventional piezoelectric transducers, new capacitive microfabricated ultrasonic transducer (CMUT) technology is expected to offer a broader bandwidth, higher resolution, and advanced 3D/4D imaging inherent in a 2D array. For ultrasound parametric imaging, such as scatterer-size imaging, a broader frequency range provides more information on frequency-dependent backscatter, and, therefore, better size estimates. Elevational compounding, which can significantly reduce the large statistical fluctuations associated with parametric imaging, becomes readily available with a 2D array.

In this work, we show phantom and *in vivo* breast tumor scatterer size image results using a Siemens V3 2D CMUT transducer (9 MHz center frequency) attached to a Siemens SONOLINE

Antares clinical scanner with a research interface. A uniform phantom with two 1cm-diameter spherical inclusions of slightly smaller scatterer size was submerged in oil and scanned by both the V3 and a conventional VFX13-5 linear array transducer. The attenuation and scatterer size of the sample were estimated using a reference phantom method. Rf correlation analysis was performed using the data acquired by both transducers. The V3 results indicate that at a 2 cm depth (near the 3-D focus for both transducers) the correlation coefficient reduced to less than 0.2 for 0.2 mm lateral or 0.3 mm elevational separation, which are better than the 0.3 mm lateral or 0.8 mm elevational separation for the same decorrelation using the VFX13-5 transducer.

Angular or/and elevational compounding is often used to reduce the variance of scatterer size estimates. The V3 2D array transducer acquired rf signals from 140 planes over a 2.8 cm elevational direction. Power spectra were estimated in each plane by using a 3 mm gated window (~ 13 wavelengths) with 75% axial overlap. Spectra from adjacent beam lines (3 mm laterally) with 75% lateral overlap were then averaged. If no elevational compounding is used, the fractional standard deviation of the size estimates is about 12% for both the spherical inclusion and the background. Elevational compounding of 11 adjacent planes reduces it to 7% for both media. Scatterer size estimates on two *in vivo* breast tumors also demonstrate the improvements using elevational compounding with data from the V3 transducer.

The new CMUT transducer offers better image resolution than the conventional array, the convenience of elevational compounding and the ability to perform 3D/4D ultrasound parametric imaging.

9.5 **A low-cost B-mode USB ultrasound probe,** William D. Richard,[1] David M. Zar[1] and Roman Solek,[2] *[1]Z&R Technologies, L.L.C. and [2]Interson Corporation, Inc., wdr@zandrtech.com.*

The Universal Serial Bus (USB) is now the ubiquitous interface bus of choice for connecting peripherals to personal computers and laptops. USB 2.0 is a half-duplex bus running at 480 Mb/s and each peripheral can draw as much as 500 mA of current at a nominal 5 V from the USB connector.

We have developed a USB-based B-mode probe family that connects directly to a personal computer or laptop without the need for additional interface boxes or power supplies. One member of the family draws as little as 250 mA from the 5 V supply (1.25 W) while forming ten (10), 20 cm-deep, 5.0 MHz images/second. The pulser/receiver, high voltage supply, analog-to-digital converter, servo and USB interface are all contained inside the probe body.

There are several advantages to this architectural approach to B-mode imaging, including low cost and portability. In addition, placing the pulser/receiver within a few inches of the transducer eliminates signal loss in long cables and provides optimal signal-to-noise performance. After raw data are transferred to the computer, gain compensation, interpolation, filtering and other data processing are performed by the host processor. This gives flexibility to developers and allows enhancements to the system to be incorporated via software updates. In addition, the raw data are available for storage and later postprocessing.

This talk describes the advantages of the architecture of the probe family, discusses the hardware/software division of the required processing steps, and presents example images and ciné loops from several different imaging applications.

10. Review, Priorities and Funding of NIH and NSF Programs

10.1 **What's new in peer review for imaging technology at NIH,** Lee Rosen, *Scientific Review Administrator for Biomedical Imaging Technology, Center for Scientific Review, NIH, rosenl@csr.nih.gov* (invited).

10.2 **Latest developments and funding opportunities in the National Cancer Institute,** Barbara Y. Croft, *Program Director, Cancer Imaging Program, National Cancer Institute, NIH, croftb@mail.nih.gov* (invited).

10.3 **Latest developments and funding opportunities in the National Institute for Biomedical Imaging and Bioengineering,** Hector Lopez, *Program Director, Division of Applied Science and Technology, National Institute for Biomedical Imaging and Bioengineering, NIH, lopezh@mail.nih.gov* (invited).

10.4 **Latest developments and funding opportunities in the National Science Foundation,** Semahat S. Demir, *Program Director, Biomedical Engineering and Collaborative Research in Computational Neuroscience, NSF, sdemir@nsf.gov* (invited).

Panel Discussion

Moderator: J.G. Miller
Participants: B.Y. Croft, S.S. Demir, H. Lopez, L. Rosen