

College of Engineering Biomedical Research Day

Poster Presentation Abstracts

#81 Abstract Title: A Nth-order Linear Algorithm for Extracting Diffuse Correlation Spectroscopy Blood Flow Indices in Heterogeneous Tissues

Author(s): Y. Shang, Dept of Biomedical Engineering, U of Kentucky
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Abstract: Conventional semi-infinite analytical solutions of correlation diffusion equation may lead to errors when calculating blood flow index (BFI) from diffuse correlation spectroscopy (DCS) measurements in tissues with irregular geometries. Previously, we created an algorithm integrating a Nth-order linear model of autocorrelation function with the Monte Carlo simulation of photon migrations in homogenous tissues with arbitrary geometries for extraction of BFI (i.e., α DB). The purpose of this study is to extend the linear algorithm for extracting BFI in heterogeneous tissues with arbitrary geometries. BFIs in different types of tissues are simultaneously extracted by the proposed linear algorithm through utilizing DCS data at multiple source-detector separations. We compared the proposed linear algorithm with the semi-infinite homogenous solution in a computer model of adult head with heterogeneous tissue layers of scalp, skull, cerebrospinal fluid, and brain. For validation purpose, we assigned ten levels of α DB in the brain layer with a step decrement of 10% while maintaining α DB values constant in other layers. Simulation results demonstrate the accuracy (errors < 3%) of high-order ($N \geq 5$) linear algorithm in extracting BFIs in different tissue layers and extracting relative changes of cerebral blood flow (rCBF) in deep brain. By contrast, the semi-infinite homogenous solution resulted in substantial errors in rCBF ($34.5\% \leq \text{errors} \leq 60.2\%$) and BFIs in different layers. The Nth-order linear model simplifies data analysis, thus allowing for online data processing and displaying. Future study will test this linear algorithm in in vivo heterogeneous tissues with different levels of blood flow variations and noises.

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College of Engineering Biomedical Research Day

Poster Presentation Abstracts

#82 Abstract Title: Noncontact Diffuse Correlation Tomography of Human Breast Tumor

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Abstract: Background: Since aggressive cancers are frequently hypermetabolic with angiogenic vessels, quantification of blood flow (BF) can be vital for cancer diagnosis. Our laboratory has developed a noncontact diffuse correlation tomography (ncDCT) system for 3-D imaging of tumor-to-normal BF contrast, which has been verified by computer simulations and tissue-like phantoms. In this study, we report our first step to adapt the ncDCT system for in vivo imaging of human breast tumors. Methods: Twenty-eight female patients with breast tumors were recruited from University of Kentucky Comprehensive Breast Care Center. The patient lied in a supine position and the tumor location was determined by ultrasound technologists. A line-shape ncDCT probe with 2×15 source-detector pairs was driven by a motorized stage to rotationally cover the region of the breast tumor. The measured boundary BF data were used to reconstruct tumor-to-normal flow contrasts. Results: Higher tumor-to-normal BF contrasts were observed in the majority of patients measured by the ncDCT. The central locations of the reconstructed tumors matched ultrasound images well when the tumors located in the sensitive region of light penetration. Discussion and Conclusions: These preliminary in vivo imaging results demonstrate the feasibility of ncDCT for detecting breast tumors. More breast tumors will be imaged to investigate the possibility using BF contrasts to differentiate benign from malignant tumors.

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College of Engineering Biomedical Research Day

Poster Presentation Abstracts

#83 Abstract Title: **Diffuse Optical Measurements of Head and Neck Tumor Hemodynamics for Early Prediction of Radiation Therapy**

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Abstract: Radiation therapy is a principal modality for the treatment of head and neck cancers and its efficacy depends on tumor hemodynamics. Our laboratory developed a hybrid diffuse optical instrument allowing for simultaneous measurements of tumor blood flow and oxygenation. In this study, the clinically involved cervical lymph node was monitored by the hybrid instrument once a week over the treatment period of seven weeks. Based on treatment outcomes within one year, patients were classified into a complete response group (CR) and an incomplete response group (IR) with remote metastasis and/or local recurrence. A linear mixed model was used to compare tumor hemodynamic responses to the treatment between the two groups. Interestingly, we found that human papilloma virus (HPV-16) status largely affected tumor hemodynamic responses. For HPV-16 negative tumors, significant differences in blood flow index (BFI, $p = 0.007$) and reduced scattering coefficient (μ_s' , $p = 0.0005$) were observed between the two groups; IR tumors exhibited higher μ_s' values and a continuous increase in BFI over the treatment period. For HPV-16 positive tumors, oxygenated hemoglobin concentration ([HbO₂]) and blood oxygen saturation (StO₂) were significant different ($p = 0.003$ and 0.01 , respectively); IR group showed lower [HbO₂] and StO₂. These results are physiologically reasonable since higher rate of oxygen consumption associated with higher density of vasculature (μ_s') and lower tissue oxygenation level (lower StO₂ and [HbO₂]) are often observed in more aggressive tumors. Overall, our diffuse optical measurements show the great potential for early prediction of radiotherapy in head and neck cancers.

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College of Engineering Biomedical Research Day

Poster Presentation Abstracts

#84 Abstract Title: Speckle Contrast Diffuse Correlation Tomography for Flow Contrast Imaging of Complex Turbid Media

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Abstract: Microvascular hemodynamics has an important role in pathogenesis and the detection and characterization of disease for enhancing prognosis. Abnormal tissue blood flow, for example, may be altered in contrast to surrounding healthy tissues due to circumstances such as uncontrolled angiogenesis or vascular damage. Near infrared (NIR) light provides a noninvasive mechanism for probing microvasculature flow up to several centimeters deep. Currently, deep tissue NIR flow techniques are minimally effective at 3D flow contrast tomography. Modalities such as laser speckle contrast imaging (LSCI) are capable of 2D flow contrasts with charge-coupled device (CCD) detection but are generally only sufficient for superficial tissues using wide-field light sources. This study developed a robust technique combining CCD detection of spatial speckle contrast with a point source, a finite element method (FEM) based reconstruction scheme for incorporating complex geometries and optical property distributions, a uniquely encountered smear correction, and reflectance-based measurements. This speckle contrast diffuse correlation tomography (scDCT) technique features potentially swift and robust flow contrast imaging for the realistic situations encountered in vivo. Homogeneous liquid phantom measurements verified scDCT flow was within 12% of the standard technique. The smear correction was found to be a substantial and requisite factor when using reflectance-based speckle contrast measurements of deep tissue with a point source. Measurement by scDCT following placement of a solid phantom anomaly below the liquid phantom surface resulted in successful 3D flow contrast reconstructions based on the anomaly center and dimensions recovered. These results were also validated against computer simulations.

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Poster Presentation Abstracts

#85 Abstract Title: **Noncontact Diffuse Optical Assessment of Blood Flow Changes in Head and Neck Free Tissue Transfer Flaps**

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Abstract: Understanding how tissue blood flow (BF) changes after free tissue transfer may enable head and neck surgeons to predict early when thrombosis is most likely to occur. However, there is no widely accepted objective method for monitoring flap vascularity in a time frame that allows for salvage of the flap from its non-viable state. In this study, we employed our recent developed noncontact diffuse correlation spectroscopy (ncDCS) for evaluating deep tissue BF without touching the vulnerable tissues in eight free muscle flaps. Seven out of eight flaps survived successfully with one unsuccessful case. Multiple BF measurements probing at the location of the transferred free tissue were performed on postoperative days 2, 4, and 7 sequentially and results were normalized to the intraoperative BF measured ~30 minutes after the flap anastomose. The average postoperative BF changes over the seven successful flaps were 1.89 ± 0.15 , 2.26 ± 0.13 and 2.43 ± 0.13 respectively on the postoperative days 2, 4, and 7. These postoperative BF values were significantly higher than the intraoperative BF value (assigning '1'), indicating gradual improvements of flap vascularity after tissue transfer. By contrast, BF improvements observed from the unsuccessful flap were 1.14 ± 0.20 , 1.34 ± 0.10 respectively on the postoperative days 2 and 4, which are less than those found in the successful flaps. This study supports the application of the novel ncDCS to evaluate BF changes in free flaps noninvasively and continually. This information holds the potential for early predicting treatment outcomes.

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College of Engineering Biomedical Research Day

Poster Presentation Abstracts

#86 Abstract Title: **Quantification of Cerebral Blood Flow and White Matter Hyperintensity in Older Adults with Low or High Risk for Cerebrovascular Disease using MRI**

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Abstract: Cerebrovascular disease (CVD) refers to a set of conditions (e.g., thrombosis, embolism and hemorrhage) that affect blood circulation to the brain. CVD is prevalent in the older population. Early detection of CVD in asymptomatic patients is the key for prophylactic interventions that can efficiently prevent stroke. The goal of this study is to use functional MRI with arterial spin labeling (ASL) and T2 fluid attenuation inversion recovery (T2-FLAIR) sequences to quantify cerebral blood perfusion and white matter hyperintensity (WMH) volume in older subjects with high or low risk to develop CVD. Twenty-six elderly subjects (65 to 85 years old) participated in this study. A CVD risk score based on Framingham study risk estimates modified for stroke predication is determined by neurologists for each individual. Since most older people show white matter hyperintensities around the ventricles, the WMH volumes bordering the ventricle were excluded from data analysis. The WMH volume and blood perfusion in (frontal, parietal, temporal and occipital lobes) were quantified, respectively. The correlations between the cerebral blood perfusion and neighboring WMH volume in each lobe and over the whole brain are being investigated to evaluate the usefulness of these measurements for distinguishing subjects with high or low risk to develop CVD.

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College of Engineering Biomedical Research Day

Poster Presentation Abstracts

#87 Abstract Title: Noncontact Diffuse Optical Assessment of Blood Flow Distribution in Wounded Tissue: A Case Study

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Abstract: Background and Objective: Chronic wound affects millions of Americans, creating pain and emotional stress. Blood flow is one of the key factors affecting wound healing. This study is to explore using a novel noncontact diffuse correlation tomography (ncDCT) developed in our laboratory to image blood flow distribution in the wounded tissue. Methods: A female subject with a diabetic ulcer in her calf participated in this study. During the measurement the subject lay on her side. A noncontact ncDCT optical probe was driven by a motorized linear stage to scan over the region of wounded tissue. The measured boundary data were used to reconstruct the blood flow distribution across the wound. Results: Blood flow contrasts over the reconstructed tissue volume were ranging from 0 to 3.01 folds to the background. On average, the blood flow contrast within the wound was 1.11 ± 0.56 . Larger (lower or higher) blood flow contrasts mainly appeared on the tissue surface close to the wound margin. In addition, blood flow variations were relatively smaller in the surrounding tissues away from the wound. Discussion and Conclusions: The noninvasive and noncontact ncDCT system is able to noninvasively generate a 3-D flow contrast image of ulcerous tissue without introducing any disturbance to the wounded tissue. Future study will recruit more subjects and will image wounded tissues at different stages. We will correlate our imaging results with clinical diagnosis and treatment outcomes to test the usefulness of ncDCT system for evaluating wound severity and healing.

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College of Engineering Biomedical Research Day

Poster Presentation Abstracts

#88 Abstract Title: **Cardiac CEST Imaging of Diffuse Fibrosis in a Murine Ang-II Model of Increased Afterload**

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Abstract: Introduction: The presence of diffuse fibrosis in the heart significantly increases a patient's risk of heart failure, arrhythmia, and sudden cardiac death. Chemical exchange saturation transfer (CEST) uses the native magnetization transfer properties of extracellular matrix proteins to contrast healthy and fibrotic tissue without requiring exogenous contrast agents. We sought to test a cardiac-CEST protocol in an Angiotensin-II (AngII) induced fibrosis model. Methods: Animals: C57Bl/6 male mice received either constant infusion of AngII or saline via mini osmotic pump for 10 days prior to performing MRI. A third group received no treatment. Immediately following MRI, hearts were harvested for picrosirius red staining. Imaging: A cardioCEST pulse sequence was used to acquire the same short-axis slice with saturation frequency offsets of $\Delta\omega = \pm 20, 15, 10, 6, 3, 1, \text{ and } 0$ ppm. A reference image was obtained at 333ppm for signal normalization. Image Analysis: Following normalization to the reference image, regions of interest were drawn in the ventricular septum and free wall. Average signal of the ROIs was plotted against saturation frequency to produce a spectrum. Magnetization transfer ratios (MTRs) and the change in magnetization transfer (Δ MT) were calculated as follows; $MTR(\omega) = [(S_{ref} - S(\omega)) / S_{ref}] * 100$, and $\Delta MT(\omega) = [1 - MTR_T(\omega) / MTR_{Ct}(\omega)] * 100$. Results: AngII treated mice demonstrated diffuse fibrosis as confirmed by picrosirius red staining. Examination of spectra revealed reduced magnetization transfer across frequency offsets in AngII treated mice. Specifically, when radiofrequency saturation was applied at 15ppm, MTR was reduced in AngII mice (Septum=4.51±9.69%, Freewall=9.64±2.81%) compared to control (Septum=17.5±3.15%, Freewall=19.4±1.99%) and saline infused mice (Septum=11.9±2.89%, Freewall=16.4 ± 1.93%).

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Poster Presentation Abstracts

#89 Abstract Title: **Imaging Stereocilia of Live Auditory Sensory Cells with High-Speed Hopping Probe Ion Conductance Microscopy**

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Abstract: Vertically protruding stereocilia on the apical surface of the inner ear sensory cells represent the ultimate challenge for scanning probe imaging. We previously imaged these structures (mostly unresolvable by optical microscopy) using hopping probe scanning ion conductance microscopy (HPSICM) in glutaraldehyde-fixed mammalian auditory sensory cells (Novak et al. Nat Methods, 2009). However, it required a considerable amount of time (~44 min per bundle of ~8x8 μm). To study live cells, we needed to significantly increase the speed of imaging. For Z-movement we have now used a faster piezo assembly with a resonant frequency of ~18kHz. Despite having a less sensitive strain gauge sensor, the vertical resolution of the system remained the same (~5nm). After adjusting the proportional-integral-derivative controller of the Z-scanner (~50 μs delay) and increasing the speed of approach (~5-8 times), we obtained high-resolution images of live auditory sensory bundles at a frame rate of <12 min/bundle. With our improved HPSICM system we showed, for the first time in live cells, the presence of characteristic rat inner ear stereocilia features at an X-Y resolution of ~11nm. We also imaged sensory bundles from animal models of human deafness (Shaker2 and Whirler mice) that have short stereocilia with abundant links. We confirmed the reproducibility of stereocilia links (typically ~5nm in diameter and ~100-300nm in length) in continuous time-lapse scanning and also their absence after chemical disruption with BAPTA-buffered Ca²⁺-free medium. Our improved HPSICM technique successfully visualizes the extremely convoluted surface of stereocilia in live auditory sensory cells at high resolution and faster speed.

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Poster Presentation Abstracts

#90 Abstract Title: Structured Light Illumination for Inter-Oral Dental Scanning

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Abstract: Structured light illumination or SLI is a process of 3D imaging that involves projecting a series of striped patterns such that a digital camera can derive a target surface's shape based on the warping of the stripes around the target. Although this method of 3D requires the target surface to remain still during scanning, SLI scanners can record depth with micron level accuracy using commodity hardware; furthermore, high-speed cameras and projectors are readily available that minimize the impact that target motion can have on the reconstructions. And at high speeds, repeated 3D measurements may be made to record 3D video of moving subjects. In the case of dentistry, SLI scanners represent the preferred means of making 3D dental models, absent the patient discomfort of dental impressions created from elastomers and other materials; however, dentistry offers significant challenges to structured light given the constrained space available inside the mouth. With this in mind, the University of Kentucky has been collaborating with Seikowave Inc. to develop what promises to be the world's smallest and fastest inter-oral, 3D scanner. In the associated presentation, we will review specific challenges that are being addresses include (1) the optical challenges of developing the small wand-like scanner; (2) the mathematical challenges of developing an optimized set of structured patterns that maximize accuracy while reducing the number of patterns, thereby, minimizing the impact of motion; and (3) the computational challenges of acquiring, processing, and display 3D scans at high frames rates.

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Poster Presentation Abstracts

#91 Abstract Title: Determination of Vigilance State in Mice Using a Noninvasive Motion Sensor

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Abstract: Mice play an important role in investigating the neuroscience of sleep, but the need for invasive electrophysiological (EEG/EMG) measurements for determining vigilance state limits the scope of experimentation. In this study, performed with prior IACUC approval, we tested the ability of a noninvasive measurement system that is sensitive to motion and respiratory effort in mice to perform finer discrimination of stages of sleep. Respiration pattern is known to vary considerably during sleep, and is relatively irregular in rapid eye movement (REM) sleep compared to non-REM sleep. A piezoelectric (piezo) sensor on the floor of the mouse cage generates an electrical voltage in response to applied pressure; this signal can be used to categorize the animal's behavior. The piezo signal tracks motion and discriminates sleep from wakefulness with high accuracy. It also captures thoracic movements when the animal is relatively quiet, and can therefore track breathing. Here we extract piezo signal features representing breathing regularity and levels of activity and then partition this feature space into distinct states using an unsupervised hidden Markov model. Then we investigate the correlation between the model states and conventional vigilance states (Wake, non-REM, and REM) as determined by visual scoring of simultaneous video-EEG recordings. An analysis performed on 24-hour recordings in 20 mice concluded that breathing regularity and motion estimated from piezo signals can reasonably discriminate between REM and non-REM sleep in continuous recordings. Further work is under way to refine this method for use as a convenient screening tool in sleep and behavioral research.

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Poster Presentation Abstracts

#92 Abstract Title: A Probabilistic Model to Resolve Uncertainty in Clinical Sleep Scoring

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Abstract: Scoring sleep in polysomnographic recordings is a tedious and subjective task. Uncertainty and variability between assessments of expert raters are the major obstacles. Hence, algorithms for automated sleep segmentation are in great demand. These algorithms either use inherent patterns in the data to differentiate between vigilance states (unsupervised classification) or mimic a human rater's behavior by modeling labeled samples to predict vigilance state in unlabeled data (supervised classification). Here we propose a novel technique to address three problems related to human sleep scoring: 1. The rater is confident of scoring only some of the states; 2. The rater scores all states but is uncertain of some epochs; and 3. Two raters score all states and epochs but with some disagreement. To address these problems EEG, EMG, and EOG features were extracted in 30s epochs from human-scored polysomnograms from 42 healthy human subjects in an anonymized database. A framework for quasi-supervised classification was devised in which unsupervised probabilistic models (viz. hidden Markov models) are estimated from unlabeled training data, but the training samples are tagged with variables whose values depend on available scores. Variations on this theme are used to address each of the scoring scenarios and classifier performance assessed using Cohen's kappa statistic. The quasi-supervised classifier performed significantly better than an unsupervised model and sometimes as well as a completely supervised model despite limited access to scores. This addresses the need for classifiers that mimic human scoring patterns while compensating for human uncertainty.

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Poster Presentation Abstracts

#93 Abstract Title: Feasibility of Selective Deep Sleep Restriction in Rats Using Mild Somatosensory Stimulation

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Abstract: Deep sleep plays a vital role in various physiological functions. Loss of deep sleep, which accompanies aging, could promote the cognitive decline associated with normal aging as well as neurodegenerative disorders. In order to isolate the consequences of deep sleep loss in this milieu, we propose to selectively reduce sleep depth without increasing wakefulness in young adult rats, and compare their performance on behavioral assays with that of aging rats and sham-stimulated controls. We have devised a system for controlled somatosensory stimulation for this purpose. With IACUC approval, rats are surgically implanted with a wireless EEG/EMG preamplifier. Then, a foam mat embedded with vibrating micromotors is placed under the animal's home cage in a room with controlled light/dark cycle. EEG and EMG signals are monitored continuously and signal features indicative of slow, large amplitude delta EEG oscillations and suppressed EMG tone, the hallmarks of deep sleep, are continuously compared against thresholds determined from scored training data to activate the vibration pad, thus stimulating the animal. Intensity is adjusted so as to interrupt deep sleep without rousing the animal. A trial comparison of EEG and EMG feature trends time-locked to the onset of stimulation in one animal, for 12 hours of stimulation in the light phase against a corresponding baseline period from the previous day, suggested that an intensity-dependent interruption of deep sleep occurred at its onset. This was confirmed by independent human scoring of recorded data. Trials in a larger sample are needed to refine and validate this technique.

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Poster Presentation Abstracts

#94 Abstract Title: **A System for EEG-Triggered Peripheral Nerve Stimulation to Improve Hand Function in Patients with Motor Incomplete Spinal Cord Injury**

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Abstract: Impaired hand grasp is common in patients with incomplete SCI. Open-loop electrical stimulation of peripheral afferent nerves is known to improve hand function. We hypothesize that afferent feedback in the form of peripheral nerve stimulation (PNS), applied only in response to attempted movement, will further promote beneficial corticospinal plasticity through positive reinforcement. EEG features are increasingly used as the basis for brain-machine interfaces (BMIs) to drive assistive devices by classifying imagined or attempted user movements. We have developed an EEG BMI to detect attempted hand grasp movements in patients with incomplete SCI and deliver responsive PNS. With IRB approval and informed consent, study candidates participated in an initial EEG screening session in which the ability to detect their resting sensorimotor or "mu" EEG rhythm and modulation of the rhythm by attempted movement were investigated. A custom algorithm was then used to trigger PNS in response to detected movement intent. To date 4 of 6 participants screened manifested discernable mu modulation. Of these attempted movement was detected with a mean sensitivity of approximately 60%. Here, a true detection is one that occurs after cue onset and before peak force is exerted; all other detections are considered false. An interventional study involving 12 sessions of closed-loop PNS has been initiated on one subject. The long term goal is to test whether closed-loop PNS will improve hand function more than open loop PNS in terms of standardized clinical metrics.

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College of Engineering Biomedical Research Day

Poster Presentation Abstracts

#95 Abstract Title: Effect of Ambient Temperature on Sleep in Mice

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Abstract: Changes in ambient temperature elicit thermoregulatory responses that also influence the sleep-wake cycle. Here we assess the effect of an elevation in temperature on different vigilance states in mice with the long-term objective of using it to modulate sleep. Wild type mice (C57BL/6J; n = 4) were instrumented for tethered EEG/EMG recording with IACUC approval. Each mouse was housed independently with free access to food and water and monitored using video and EEG. A custom-built thermostatic control system maintained the cage temperature at one of four values (24, 27, 30, and 33 Celsius) in the thermoneutral zone on each of four consecutive days during the light period (day) when mice are most somnolent. Vigilance state was scored visually from the recordings in consecutive 4s epochs as Wake, REM (rapid eye movement sleep), or NREM (non-REM) sleep. The effect of temperature on conventional sleep metrics was studied. Besides confirming previous knowledge, that both REM and NREM sleep increase with temperature, we found that while mean NREM bout duration increases with temperature but not the mean number of NREM bouts, the mean number of REM bouts increases but not mean REM bout duration. NREM sleep is therefore less likely to be interrupted by brief arousals: i.e., less fragmented. The implications of the converse relationship with REM sleep are less obvious. Manipulation of temperature may offer a minimally obtrusive way to titrate sleep and study the consequences in health and disease. We propose to test these working hypotheses in a broader study.

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College of Engineering Biomedical Research Day

Poster Presentation Abstracts

#96 Abstract Title: Human intraocular thermal field in action with different boundary conditions considering aqueous humor and vitreous humor fluid flow

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Abstract: In this study, a validated 3D finite volume model of human eye is used to study the thermal field inside human eye at steady state conditions using Fluent software for analysis. The model is assumed to be axisymmetric. For this purpose, discretized bio-heat transfer equation coupled with Boussinesq equation is analyzed for different anatomical, environmental, and physiological conditions. Moreover, for a more realistic analysis natural heat convection phenomenon taking place in aqueous humour and vitreous humour of human has also been considered. Blood running over the outer part of the eye is assumed to be the heat-source. Meanwhile, the cornea is assumed to transfer the heat to environment. It is demonstrated that due to the presence of the fluid bodies inside human eye, and heat convection associated with it, the thermal field of human eye is not symmetric. Furthermore, it is shown that posterior region of the human eye is less affected by the ambient condition while the anterior segment is generally influenced by the ambient conditions. Finally, it is demonstrated that the direction of the fluid circulation is dependent on the direction vector of the gravity. As a conclusion, a modified thermal field of the human eye is presented. Keywords: eye; bio-heat; Boussinesq; conduction; convection; segment

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College of Engineering Biomedical Research Day

Poster Presentation Abstracts

#97 Abstract Title: **Improvement of hypovolemic men's and women's orthostatic tolerance by a short exposure to artificial gravity**

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Abstract: Background: Upon return to earth, ~30% of short term (<14 days) and 80% of long term (>14 days) astronauts exhibit orthostatic intolerance and successful countermeasures have not been developed. Our previous studies indicated improvement in orthostatic tolerance following 3 weeks of daily (<1 hr) Artificial Gravity (AG) training. Our current study looks for effects of a single, 90 minute bout of AG exposure compared to 90 min HDBR on cardiovascularly deconditioned men's and women's orthostatic tolerance limit (OTL). Methods We used a combination of head up tilt and lower body negative pressure to test the orthostatic tolerance limit (OTL) of nine men and eight women: following 90 min exposure to AG and following 90 min of HDBR. In both cases (21 days apart), subjects followed a protocol designed to simulate effects of space flight on the cardiovascular system. Heart rate (from ECG), continuous blood pressure, stroke volume, cardiac output, peripheral resistance (Finometer), and middle cerebral artery blood velocity (MCAv, transcranial Doppler) were measured during supine control, during OTL to presyncope and recovery. Results and Conclusions: Plasma volume loss was similar to two weeks of space flight. Orthostatic tolerance on AG day was significantly greater than on the HDBR day ($p < 0.03$). Men and women demonstrated different mechanisms of cardiovascular regulation on the two days: After AG, men's blood pressure and peripheral resistance were lower and cardiac output was higher than on the HDBR day. Women demonstrated higher cardiac output and cerebral flow following AG exposure but maintained the same blood pressure on both days. In both men and women at the time of presyncope, stroke volume was the same on each day. We conclude that AG exposure prolonged the onset of presyncope by increasing output of the heart. Our second conclusion is that men and women respond differently to AG, both at rest and during orthostatic stress. Our final conclusion is that the trigger for presyncope appeared to come from the heart.

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College of Engineering Biomedical Research Day

Poster Presentation Abstracts

#98 Abstract Title: **Computational Modeling of Passive Myocardium: Estimating Unloaded Geometry of Heart from Early-Diastolic MR images**

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Abstract: Having a stress-free geometry of the heart is a key factor in Finite Element (FE) simulation of beating hearts. Such a reference state never exists during a normal cardiac cycle; consequently Magnetic Resonance Images of the heart which are being used to construct FE models only represent the heart in its loaded states. On the other hand, FE modeling of ventricular myocardium is strongly coupled to the material characteristics of the ventricular myocardium. The quantification of these properties is affected by the FE model used in the parameter estimation process. In this study, an iterative inverse method is implemented to estimate the unloaded state of the heart along with passive material parameters of the left ventricle from MR images at early diastole. Material parameters of the constitutive law, which is incorporated in the FE solver, are updated after each new estimation of the unloaded geometry and then used in the next estimation of the unloading problem. A transversely isotropic constitutive law is used to describe myocardium material behavior. In-vivo strains were measured from MR imaging of porcine hearts, along with synchronous catheterization pressure data, and used for parameter identification of the constitutive model. Optimization was performed by minimizing the difference between MRI measured and FE predicted strains and cavity volumes using Genetic Algorithm. Optimization results indicate that using unloaded geometry as the reference state of the FE model will result in better agreement of FE predicted with in-vivo measured strains.

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Poster Presentation Abstracts

#99 Abstract Title: Computational investigation of transmural differences in left ventricular contractility

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Abstract: Myocardial contractility in the left ventricle plays an essential role in generating force and maintaining normal pump function. In previous numerical studies, people have considered myocardial contractility to be the same everywhere in the left ventricular (LV) wall. However, recent experimental studies on multi-cellular preparations of myocytes have shown that healthy human hearts exhibit transmural heterogeneity in contractile properties (Haynes et al., 2014), with myocardial contractility being higher in the mid-myocardium than in the epicardium and endocardium. In the current study, we tested whether we could predict transmural heterogeneity in-vivo using an animal model, MRI, and computational modeling. In order to determine the myocardial contractility in different transmural regions, finite element (FE) models of the LV were generated. The animal-specific FE models were generated by using the contour points from experimental MRI data of the left ventricle in healthy pigs. Optimization was used to find the transmural distribution of contractility that minimized the difference between the FE model strain and the in-vivo strain calculated with MRI. The results of the current study show good agreement with the experimental results from Haynes et al., i.e., that the mid-myocardium contracts most. Another finding was that by using different initial sarcomere lengths in each transmural region, the agreement between the model and MRI data increased. The overall conclusion from this study is that transmural differences in contractility can be detected in-vivo using MRI and modeling. This could eventually be used as a clinical tool to assess myocardium in patients with heart disease.

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Poster Presentation Abstracts

#100 Abstract Title: Alterations in Lower Back Stiffness with Age

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Abstract: Aging is an important risk factor for low back pain (LBP). Given the role of lower back biomechanics in the development of LBP, it is important to characterize age-related changes in active and passive aspects of lower back biomechanics. Here, 60 participants in five age groups between 20 and 70 years completed two data collection sessions involving several experiments related to lower back biomechanics. Age-related differences in intrinsic trunk stiffness were investigated using a systems identification approach involving a sudden perturbation paradigm along with a lumped-parameter model of the lower back. Sudden perturbation tests included a pseudo-random sequence of anterior-posterior position perturbations (± 5 mm) that were completed with two levels of active extension pre-load (i.e., 20% and 30% of maximum voluntary extension effort-MVE). The driving force throughout the perturbations was measured using a load cell and resulting kinematics were measured using two laser displacement sensors. Preliminary analyses revealed no differences in intrinsic trunk stiffness of individuals between 20% and 30% MVE pre-loads. Hence, mean stiffness across both effort levels was used for subsequent analyses. Intrinsic stiffness generally increased with age and was larger among males vs. females. An exception to this general trend was the intrinsic stiffness of females > 62 years old, and that was lower than among females 42 - 58 years old. An increase in trunk intrinsic stiffness with age suggests that the higher incidence of LBP among older individuals may not be largely related to spinal instability.

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Poster Presentation Abstracts

#101 Abstract Title: How Aging Affects Lower Back Loading During Lifting Tasks

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Abstract: Aging is becoming an increasingly important risk factors for low back pain (LBP) due largely to the growing population of older workers. The objective of this study was to investigate the differences in lower back loading when persons of different age complete the same manual material handling (MMH) task. Sixty gender-balanced participants, aged 20 - 70 years, completed two MMH tasks involving lowering a 5 kg load from upright standing posture to both their knee height (Task-1) and a fixed height of 50 cm (Task-2), and then lifting back to the upright posture. Kinematics and kinetics data were respectively collected using accelerometers and a force platform. Mechanical demands of the MMH task on the lower back (i.e., net external moment and reaction forces) were estimated using measured kinematics and kinetics along with an inverse dynamic procedure involving a rigid multi-segment model of the lower extremities and pelvis. The maximum net external moment and reaction forces along (axial) and perpendicular (shear) to the spine, as well as corresponding flexion angles of the thorax and pelvis, are summarized in Tables 1 and 2. Older individuals completed Task-1/Task-2 with similar/lower net moments, lower/lower axial forces, and higher/higher shearing forces imposed on the lower back. Increased lumbar shear forces were likely due to larger flexion of pelvis and lower flexion of the lumbar spine older participants and may result in a higher risk of LBP.

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Poster Presentation Abstracts

#102 Abstract Title: The Effect of Joint Capsule Stiffness on Knee Contact Forces

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Abstract: Greater joint stiffness and decreased range of motion following knee joint injury or surgery may partially result from pathological joint capsular stiffness. A parametric modeling study was conducted to investigate the effects of changes in stiffness of the anterior knee joint capsule on the contact forces between the medial and lateral compartments of the knee joint. An existing detailed model of the knee joint, developed in OpenSim, was upgraded to include the joint capsule. This was done by modeling the joint capsule using two parallel elements running from the distal femoral metaphysis to the proximal tibial metaphysis, along with two crossing elements connecting the insertions of the parallel elements to each other. Two simulations involving passive flexion of the knee joint from an extended position to 45 degrees of flexion were performed for two cases: 1) normal condition and 2) stiff condition wherein a 20% increase in stiffness was achieved by changing the mechanical property of capsular elements. The magnitude and direction of the forces in all muscles, ligaments, and elements representing the joint capsule, along with their resultant were calculated. The maximum contact force increased from 2130 N to 2534 N with increased stiffness of the joint capsule. The direction of the contact force also changed with an increase in joint capsule stiffness; cosine direction of maximum resultant force were (-0.74864, 0.6579, -0.0812), and (-0.7464, 0.6562, -0.11) for normal and stiff conditions respectively. Quantitative and qualitative knowledge regarding post-injury and post-surgical alterations in joint contact forces may aid in the prevention of secondary joint disorders.

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Poster Presentation Abstracts

#103 Abstract Title: **Mechanical Changes in the Lower Back Following Six Sessions of Spinal Manipulation - Preliminary Results**

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Abstract: The use of spinal manipulation as a treatment option, in replacement or in conjunction with traditional medical care, continues to increase in popularity for those suffering from low back pain (LBP). Given the complexity and multifactorial nature of LBP, it is critical to develop diagnostic tools capable of identifying responder patients to spinal manipulation, hence enhancing its success rate. This study investigates whether alterations in the lower back mechanical environment following spinal manipulation, specifically the High-Velocity Low Amplitude (HVLA) technique, are associated with relief of LBP. Both asymptomatic participants and patients currently suffering from subacute non-specific LBP are recruited. Instability of the spine is an important measure of lower back mechanical environment. Previous studies have shown that kinematic variability and nonlinear analysis obtained from participants completing balancing tasks on an unstable seat apparatus are reliable estimates of spinal stability. Therefore, besides tests quantifying changes in active and passive mechanical properties of lower back tissues (e.g., range of motion tasks and stress relaxation), the data collection sessions also involve balancing tasks on the unstable seat apparatus. Electromyography system and accelerometers are other measurement tools used throughout the data collection sessions. All participants complete an initial data collection session. The participants will then receive six HVLA treatments over a three week period. After this three week period, participants will complete a second data collection session. The data obtained during the second data collection session will be compared to the initial data collection session. Preliminary results will be present during the conference.

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College of Engineering Biomedical Research Day

Poster Presentation Abstracts

#104 Abstract Title: **An Investigation to Resolve the Dependence of Endothelial Sprouting Rates on Hydrostatic Pressure Levels in the Cellular Microenvironment**

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Abstract: The inability of current tissue engineering strategies to generate microvasculature is a serious problem that needs to be overcome. Recently, we reported pressure may be a stimulus for microvascularizing tissues by showing that endothelial sprouting rates are selectively upregulated by 20, but not 40, mmHg. But this study only examined sprout formation after 3 days of exposure to only 2 pressures, which is insufficient to assess how pressure-sensitive EC sprouting is. Moreover, the study in question had used a 3-D microbead model that may be a challenge to translate to tissue engineering applications. The present investigation sought to adapt the use of endothelial spheroid cultures into our studies, which is likely more suitable for microvascular tissue engineering. Simultaneously, we aimed to identify the operating pressures and exposure times for controlling endothelial sprouting rates. For this purpose, we used a custom system and 3-D bovine aortic endothelial cells (BAEC) spheroid models to [i] identify the minimum durations required for accelerating endothelial sprouting under 20 mmHg and [ii] characterize the pressure dependence of BAEC sprouting by exposing cultures to 0, 5, 10, 20, 30, and 40 mmHg. Presently, our data suggests that exposure to 20 mmHg for <2 days is inadequate to enhance sprouting. Moreover, a 5 mmHg stimulus appears to be inhibitory. Based on these data together with our prior reported results, BAEC sprouting appears to display a complex pressure dependence that one can exploit to control microvessel formation rates in tissues. But more work is needed to support this possibility.

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College of Engineering Biomedical Research Day

Poster Presentation Abstracts

#105 Abstract Title: **An Ongoing Investigation to Link Cathepsin B-Mediated Cleavage of Mac-1 Integrins to the Shear-Induced Regulation of Neutrophil Adhesivity**

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Abstract: Over the past decade, our laboratory has provided substantial evidence that fluid flow mechanotransduction by neutrophils is part of an anti-inflammatory mechanism that restricts their activation under physiological (non-inflamed) conditions. We did so by showing that shear stress (SS) promotes pseudopod retraction and CD18 cleavage. Recently, we discovered Mac1 (CD11b/CD18) to be the CD18 integrin heterodimer cleaved by lysosomal cathepsin B (catB) protease. These findings suggest that [1] catB influences neutrophil-substrate interactions and [2] its release under SS restricts neutrophil adhesion. But such connections have not been supported to date. We sought to do this by determining if catB modulates adhesion/migration by neutrophils either maintained under no-flow conditions or exposed to SS. We first monitored the dependence of neutrophil migration on exogenous catB under no-flow conditions to see if this protease influences pseudopod activity during lamellipod extension and uropod retraction. We also used microfluidics chambers to examine the role of catB-related Mac1 cleavage on neutrophil adhesivity under flow. As our culture model, we assessed the ability of SS to promote neutrophil “de-adhesion” from substrates coated with platelets that express Mac1 ligands or human umbilical vein endothelial monolayers that mimic the vascular wall. Based on these experiments, catB appears to enhance neutrophil migration rates under no-flow conditions; conceivably, due to its proteolytic actions on Mac1 accelerating pseudopod detachment during uropod retraction. We also observed SS to promote neutrophil detachment from platelet- and endothelial- coated substrates in the absence, but not presence, of catB inhibitors. Taken together, our results support flow-induced catB release as a key aspect of the anti-inflammatory control of neutrophils by shear stress.

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Poster Presentation Abstracts

#106 Abstract Title: A Novel Microfluidic Platform for 3D Cell Culture and Study of Cancer Cell Metastasis

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Abstract: In this study, we develop a microfluidic platform to provide a biomimetic environment to observe and analyze cell proliferation, cell response to chemical agents and cell migration within a three-dimensional structure. This model not only presents more physiological relevance to the in vivo microenvironment of cells, but also provides the capability for dynamic high-resolution study of cell survival, biochemistry and morphology. The PDMS-based microfluidic device consists of controllable fluid flow path that enables the delivery of cell culture medium and soluble chemical signals. In addition, it is compatible with 3D cell culture in hydrogel materials that mechanically resemble the extracellular matrix. It also contains microchannels within the flow path adjacent to hydrogel to mimic in vivo vasculature, and a removable lid that allows access the hydrogel chamber for removal of the cells for further biochemical processing. In this work, we present the design, fabrication and testing of this microfluidic device, as well as a study of the viability and proliferation of MDA-231 cells in collagen within the device.

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Poster Presentation Abstracts

#107 Abstract Title: Development of CREKA-conjugated iron oxide nanoparticles for hyperthermia treatment of cancer

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Abstract: Hyperthermia, the heating of tissue between 42 and 45°C, has been shown to enhance the effects of radiation and chemotherapeutics, but current methods of hyperthermia often result in severe side effects due to lack of localization and overheating of tissue. Magnetically mediated hyperthermia provides the opportunity for localized heating, however, this method is currently limited by the lack of particle penetration into tumor tissue. In this research, a nanoparticle system composed of an iron oxide core with a crosslinked dextran coating functionalized with the tumor homing peptide, CREKA, has been developed to overcome this limitation by homing to and penetrating into tumor tissue. The iron oxide core allows for particle heating upon exposure to an alternating magnetic field while the dextran coating stabilizes the particles in suspension and decreases the cytotoxicity. The overall goal of this study was to optimize CREKA-conjugated iron oxide nanoparticles for enhanced tumor homing for effective hyperthermia treatment applications. The particles were characterized for size, stability, biocompatibility, and heating capabilities. The particles were stable in PBS and media over at least twelve hours, have a hydrated diameter of 50 nm, and can generate a significant amount of heat to raise solution temperatures well into the hyperthermia range. The cytotoxicity of the particles was analyzed through studies on A549 lung cancer cells for low particle concentrations with high exposure time and results determined that the particles have low cytotoxicity over both time frames and concentrations. Fibrinogen clots were used to determine the binding affinity of CREKA conjugated iron oxide nanoparticles compared to non-targeting nanoparticles. The binding and uptake of CREKA conjugated iron oxide nanoparticles into multicellular spheroids and monolayer cell cultures was also evaluated.

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Poster Presentation Abstracts

#108 Abstract Title: Using Microfluidic Models to Determine the Effects of CD151 and TGF β -1 on Tumor Cell Adhesion and Extravasation

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Abstract: Metastasis is the cause of 90 % of all cancer related deaths. One protein that has been implicated as a player in the metastatic process is CD151, a tetraspanin that, while present on all cells, is up regulated in cancers with poor prognoses. Despite this association, there are conflicting studies regarding the role of CD151 in metastasis due to the fact that in vivo models have poor visualization and low control over variables, and until recently, many in vitro techniques have not been able to mimic the environment inside of a blood vessel. Another protein that has been linked to metastasis is TGF β -1, a member of the transforming growth factor-beta family. At early stages of cancer, this protein suppresses tumor effects, but as the cancer progresses, the signaling switches causing it to take a prometastatic function. Little research has been performed to determine how this protein affects the individual stages of metastasis. A novel way to determine the effects that these proteins have on the stages of adhesion and extravasation, microfluidics have been employed which has been possible to study this phenomenon to gain greater understanding of this process. Data suggests that TGF β -1 has a greater impact on tumor cell adhesion than CD151, which would make it a preferred target for drug delivery of anti-cancer drugs.

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Poster Presentation Abstracts

#109 Abstract Title: Evaluating Poly(trolox ester) Antioxidant Nanoparticle Therapy and the Prevention of Cancer Cell Adhesion

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Abstract: Circulating tumor cells that metastasize from a primary tumor in the body are the leading cause of cancer death in the United States. These circulating tumors can adhere to the endothelial lining of the vascular system and extravasate through the lining to form deadly secondary tumors. Ischemic environments during extensive surgery in the removal of primary tumors can be detrimental to the body causing inflammatory responses, permitting an imbalance in the consumption of ROS by natural occurring antioxidants and an upregulation of cell adhesion molecules along the endothelium. If circulating tumor cells are within the system at the time of upregulation, cancer cells may adhere to the endothelium more readily. Poly(trolox) ester (PTx) antioxidant nanoparticles can be introduced to the system to release trolox, an analogue of the antioxidant Vitamin E. PTx nanoparticles can allow for the scavenging of reactive oxygen species and suppress oxidative stress. In this study, a Hypoxanthine/Xanthine Oxidase injury model is used to mimic a hypoxic environment in the circulatory system and its effect on cancer cell adhesion. Static studies are strengthened by developing a flow system to mimic physiological responses of the stopping and starting of flow. It is hypothesized that the addition of poly(trolox) ester nanoparticles to both static and flow studies will lead the suppression of reactive oxygen species, downregulation of adhesion molecules, and prevention of invasive breast cancer cell adhesion.

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Poster Presentation Abstracts

#110 Abstract Title: Reducible Disulfide Poly(β -amino ester) Hydrogels for Antioxidant Delivery

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Abstract: The treatment and prevention of oxidative stress-based diseases are typically carried out via administration of additional antioxidant capacity to the cellular site. Ordinarily, cells maintain a reducing environment within the cytosol through regeneration of the thiol compound, glutathione (GSH)/glutathione disulfide (GSSG). However, in the case of oxidative stress based disease, or artificially introduced oxidation (e.g. radiation, chemotherapy), additional antioxidant capacity could be beneficial to healthy cells. In this work, we hypothesize that a biomimetic polymeric disulfide system could supplement the behavior of GSH/GSSG through delivery of a redox responsive material based upon poly(β -amino ester) (PBAE) chemistry. We have formulated a PBAE hydrogel that covalently contains a disulfide crosslinker, which when placed in reducing conditions produces a free thiol product. It was found that with an increasing content of disulfide crosslinker, the bulk degradation rate in PBS was increased, and that in DMSO + reducing agent there was a threshold of complete solubility at ≥ 33 mol% disulfide. Further, these disulfide hydrogel degradation products increased cellular viability based on both material concentration, and in minimization of oxidative stress on HUVEC. This disulfide polymer may be advantageous in cell therapy compared to small molecule antioxidant delivery due to its solid/liquid reversibility in a redox environment, terminal biodegradation into small molecular weight products, high loading capacity through covalent drug addition, and post-synthesis modification via reduction to terminal thiols.

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College of Engineering Biomedical Research Day

Poster Presentation Abstracts

#111 Abstract Title: **Static and dynamic properties of biodegradable poly(antioxidant β -amino ester) networks based on incorporation of curcumin diacrylate**

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Abstract: Biodegradable polymers have found use in a variety of biomedical applications including sutures, drug delivery, tissue engineering and orthopedic implants [1, 2]. Poly(antioxidant β -amino esters) (PA β AE) are a recently-developed class of biodegradable polymeric hydrogels that have shown promise in their ability to control cellular response by reducing oxidative stress and thereby improving biocompatibility [3]. PA β AE undergoes a hydrolytic degradation to give controlled antioxidant release without burst release. The degradation and resulting antioxidant properties of these biomaterials are closely related to the composition and architecture of the networks established during polymerization. Therefore, in order to efficiently design PA β AE for specific biomedical applications, it is important to understand the impact of synthesis conditions on the thermomechanical properties of the resulting polymer networks. In this work, we examine a series of hydrogel networks formed by polymerization of a commercial diacrylate, polyethylene glycol diacrylate (PEG400DA), and a primary diamine, 4,7,10-trioxa-1,13-tridecanediamine (TTD), in combination with acrylate-functionalized curcumin (i.e., curcumin diacrylate – CDA). Swelling response of these hydrogels in acetonitrile (ACN) and aqueous degradation at 37°C were evaluated as a function of composition. Network structure and thermomechanical response properties were examined using dynamic mechanical analysis and broadband dielectric spectroscopy. An increase in CDA content led to an overall increase in the glass transition temperature and corresponding degradation time. It was demonstrated that network hydrophilicity, crosslink density, and overall flexibility could all be modified directly by variations in CDA content as a basis by which to control the degradation properties of the resulting materials.

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Poster Presentation Abstracts

#112 Abstract Title: Collagen Crosslinking Reagent Utilized to Stiffen Soft Palate in Equine Snoring

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Abstract: Snoring is a sleep cycle disruption affecting between 33-82% of Americans¹. Snoring can lead to obstructive sleep apnea syndrome (OSAS) affecting about 52% of the population¹. Current treatments have limited and inconsistent effectiveness. Injecting a non-toxic protein crosslinking agent into the soft palate could augment the mechanical properties and reduce mechanical degradation to decrease the incidence and severity of snoring and OSAS. A pilot in vivo study used three horses with dorsal displacement of the soft palate (DDSP) and three control horses as snoring and OSAS models. The horses were injected with a buffered genipin solution in two locations on the soft palate. Before and after the injections, breathing audio was recorded for each horse. This data was analyzed using Matlab and ImageJ with time domain, frequency domain, and spectrogram graphs. In the time domain graphs, pre injection recordings had large gaps without breathing, however, in the post injection recordings, it was steady and continuous. The frequency domain graphs had an average percent decrease of 40.5% in the area under the amplitude curve for frequencies below 500 Hz. There was also a reduction in higher frequency amplitudes for at least one horse. The spectrograms had an average percent reduction of 40.38% in the amount of high amplitude points. The reduction of low frequency amplitudes demonstrated a vibrational decrease in snoring. The decrease in high frequency amplitudes represented a reduction in palate flipping. Overall, the results validate the potential for a new treatment for snoring and OSAS pending future studies.

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College of Engineering Biomedical Research Day

Poster Presentation Abstracts

#113 Abstract Title: Development of a Local, Sustained Delivery Vehicle for Zoledronic Acid to Treat Tumor-Mediated Bone Resorption

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Abstract: Osteolysis and the related pain negatively impact the quality of life for cancer patients with skeletal metastases. Zoledronic acid (ZA) is a third-generation bisphosphonate that inhibits bone resorption. Intravenous delivery, however, is inefficient and is associated with side effects that include osteonecrosis of the jaw. The purpose of this study was to improve delivery of ZA to the local tumor environment. ZA was polymerized into poly(methyl methacrylate) (PMMA) bone cement at drug loadings of 0, 1, 2, and 5% by mass. Cylindrical samples were incubated in phosphate-buffered saline to measure drug elution for 8 weeks. ZA mass percent loadings above 5% showed statistically significant decreases measured in compressive modulus and ultimate strength of PMMA, which were considered potentially hazardous in clinical use, and therefore were not tested for drug elution. Alternatively, ZA was incorporated into poly(lactic-co-glycolic acid) (PLGA) microspheres that were consolidated into thin films for drug release studies. ZA concentrations were measured by high performance liquid chromatography. Drug elution from both materials progressed over 8 wk, but release rate was highest during the first day. For ZA release from PMMA, ANOVA showed a significant ($p < 0.05$) increase in release for increased drug loading. The PMMA samples with the highest theoretical drug loading, 15.2 mg ZA, released a total of 2.6 mg (17%). PLGA films theoretically containing 3.58 mg ZA released a total of 3.46 mg (96%) over 8 wk. Therefore, PLGA may provide a better local delivery vehicle for ZA compared to PMMA.

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Poster Presentation Abstracts

#114 Abstract Title: **Fabrication and Characterization of Application Based Functionally Graded Hybrid Polymeric Scaffolds**

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Abstract: The ultimate goal of this research is to fabricate and characterize hybrid polymeric scaffolds composed of at least two components to mimic natural tissue structure at specific defect sites. Using salt particles and degradable hydrogel particles as a porogens allows for controlled pore opening after implantation as well as the potential for drug release during degradation. The controlled pore opening also allows the scaffolds to withstand the necessary mechanical properties at the implant site while degrading at a rate consistent with tissue regeneration. The system comprised poly(lactic-co-glycolic acid) (PLGA), poly(β -amino ester) (PBAE), and salt particles. In the present study, homogenous and layered scaffolds were examined to determine the compositional relationship, mass loss, pore size and pattern of porosity development to design application-based scaffolds. This study demonstrated controlled pore opening with degradation as a function of time through different HG porogens. Spatiotemporal modulation of hybrid scaffold properties, e.g., pore opening, pore size, and mechanical and structural characteristics, can be used to design scaffolds for specific applications.

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Poster Presentation Abstracts

#115 Abstract Title: Synthesis and Characterization of a Simvastatin Polyprodrug

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Abstract: Poly(lactic-co-glycolic acid) and poly(ϵ -caprolactone) are commonly used in drug delivery due to bioinertness and tunable degradation. However, drug payload limitations can often exist. By directly polymerizing bioactive agents into the polymer backbone and changing the comonomer ratio, drug loading can be controlled. Simvastatin, which has anti-atherosclerotic, osteogenic, anti-inflammatory, and angiogenic properties, is being copolymerized into a biodegradable polymer by ring-opening polymerization of its lactone ring. Simvastatin was mixed with 550, 2000, or 5000 Da monomethyl ether poly(ethylene glycol) (mPEG) at a 100 to 1 molar ratio with 1 wt% of triazabicyclodecene (TBD) at 150°C for 24 hr. Reactions using stannous octoate and 5 kDa mPEG were run at 230°C. Small mPEG-block-poly(simvastatin) disks were incubated in saline for degradation studies. Gel permeation and high performance liquid chromatography, nuclear magnetic resonance (NMR) and ultraviolet spectroscopy, and mass spectrometry were used for analysis. The molecular weight (MW) of mPEG-block-poly(simvastatin) was 10, 15, and 18-29 kDa using 550, 2000, and 5000 mPEG, respectively. NMR measurements showed a MW of 21 kDa. After 4 weeks, 64 μ g and 100 μ g of free simvastatin were released from the copolymer made via TBD and stannous octoate, respectively. Mass spectrometry of the degraded products revealed trimers, dimers, and open and closed-ring forms of simvastatin. Successful polymerization of simvastatin was seen along with slow drug release and identified forms of the drug in the degradation products. Poly(simvastatin) may be useful in tissue regenerative applications.

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