Biomedical and General Engineering

IMPROVED PREDICTIVE CAPABILITY OF A COMPUTATIONAL FOOT/ANKLE MODEL USING ARTIFICIAL NEURAL NETWORKS. Ruchi D. Chande & Jennifer S. Wayne, Department of Biomedical Engineering and Department of Orthopaedic Surgery, Virginia Commonwealth University. Computational models are a valuable means of investigating the biomechanics of human joints. These models' non-invasive, cost-effective nature allows for the simulation of multiple experimental iterations with relative efficiency. Given their usefulness, it is imperative to provide these models with appropriate inputs to obtain meaningful predictions. To adequately represent the joint within a computational space, cadaveric studies are referenced to inform soft tissue properties; however, some tissues are not well-described in the literature. As a result, this work sought to apply artificial neural networks (ANNs) to optimize soft tissue properties, specifically ligament stiffness, for the greater purpose of improving the predictive ability of an existing patient-specific computational foot/ankle model of Adult Acquired Flatfoot Deformity (AAFD). Both feedforward (FFN) and radial basis function (RBFN) networks were trained with known kinematic-stiffness data prior to providing final ligament stiffness predictions. The predictions from each network were then supplied to the existing AAFD model and its resulting kinematic measures, specifically navicular and 1st cuneiform heights and talo-1st metatarsal and talo-navicular angles, were compared to the patient radiograph. While the FFN performed better than the RBFN, both networks' predictions resulted in an improvement of the computational model's performance as three of the four measures of interest moved closer to those kinematic values measured on the patient radiograph.

HYPER-ELASTIC THIN-FILM-NITINOL CHARACTERIZATION FOR NEUROVASCULAR FLOW-DIVERTERS. Y. Chen[1], C. Howe[2], Y. Lee[2], S. Cheon[3], W.-H. Yeo[2], Y. Chun[1], [1]Department of Industrial Engineering, University of Pittsburgh, Pittsburgh, PA 15261 and [2]Department of Mechanical and Nuclear Engineering, Virginia Commonwealth University, VA 23284 and [3]Division of Mechanical & Automotive Engineering, Kongju National University, Republic of Korea. A cerebral aneurysm can occur when a small section of a neurovascular blood vessel is weakened, which allows blood to flow into ballooned section, or sac. Recent advancement in aneurysm treatment includes a new device called a ‘flow-diverter’. A flow-diverter can safely reduce blood flow into the aneurysm sac. In previous study, it has been found that a flow-diverter based on thin-film-nitinol (TFN) works very effectively, however there have been no studies on the mechanical safety of the TFN flow-diverter in irregular,

curved blood vessels. Here, we study the mechanical behaviors and structural safety of a micro-structured TFN membrane. Through computational and experimental study, we establish the fundamental characteristics of the stretching and bending mechanics of the structure. The results show a good agreement between computational and experimental behavior of the TFN with negligible strain change in up to 180° in bending and 500% in radial stretching. These results show ideal characteristics for the use in highly curved neurovascular blood vessels. *In vitro* experimental test qualitatively demonstrates the mechanical flexibility of the flow-diverter with multi-modal bending. *In vivo* micro X-ray and histopathology study demonstrate that the TFN can have conformal deployment in the curved blood vessel of a swine model without any significant complications or abnormalities.

TRANSDERMAL MICRONEEDLE PATCH DRUG DELIVERY. Dong Sup Lee & Hong Yeo, Dept. of Mechnical & Nuclear Engineering., Virginia Commonwealth Univ., Richmond VA 23220. Transdermal drug delivery (TDD) is known for enhanced delivery effectiveness of drug compared to the oral intake, which has limitation of diminished drug concentration in the body. TDD system with penetration enhancers allow efficient transport of drug through the skin(stratum corneum) into the blood vessels. However, pain is involved with the use of penetration enhancers. Therefore, major concern was to minimize the pain involved while piercing through the skin. Recently developed methods using silicon microneedles introduced effective tissue penetration with minimal pain. Different microfabrication techniques has developed to manufacture various shapes of microneedle to optimize its design; a hollow-type needle with pen and pyramidal/concave shapes are preferable to other designs because of its capability of controlling drug amount and rate. Silicon material, however, has potential toxicity in the clinical use due to its fragility and harmful effects once it gets into the bloodstream. To resolve detrimental effects on human body, we developed a soft, conformal, skin patch with polymer microneedles in an array fashion that is biocompatible and has potential to deliver drug with pain-less injection. Microneedle will be incorporated with a thin elastomeric membrane to ensure conformal contact to the skin for continuous long-term drug delivery application. Our microfabrication method involves molding technique, which can recycle mold for multiple production of microneedle at a relatively low cost. Ultimately, the microneedle will be integrated with biological sensors and microchips in order to diagnose and release drug with automated system.

WIRELESS, STRETCHABLE INTRAORAL ELECTRONIC SYSTEM FOR PH MONITORING. Yongkuk Lee & Woon-Hong Yeo, Dept. of Mechanical & Nuclear Engineering, Virginia Commonwealth

University, Richmond, VA 23284. The development of thin, soft, stretchable wireless electronics is highly desired due to their potentials in healthcare applications. Even though many types of diminutive wireless and wearable devices have been developed, most of them still use rigid and planar platforms that limit the direct integration with soft tissues and often cause discomfort in use. Here, we introduce a wireless, stretchable intraoral electronic system for pH monitoring, which has the capability of stable, long-range Bluetooth telemetry within a low-profile, soft circuit platform. The key concept involves assemblies of hard chip-scale components and stretchable meander interconnects, together in a thin, elastomeric enclosure, to provide pH sensing via Bluetooth wireless telemetry. Experimental and computational studies establish the fundamental aspects of the bending and stretching mechanics of the intraoral electronic system. In order to enable the Bluetooth communication, antenna design is carefully optimized to maximize the range of Bluetooth signals. The system maintains Bluetooth signals even in deformation along curved surfaces. The whole system of the intraoral electronics is encapsulated with a silicone elastomer which is known to be tissue-compatible and nontoxic. For detecting pH levels of oral fluid intake, the system is laminated on a dental retainer that has curved, contoured surfaces. The functionality of the wireless intraoral electronics is demonstrated with various pH calibration solutions via wireless data recording.

DEVELOPMENT AND CHARACTERIZATION OF PROTEIN NANOPARTICLES DERIVED FROM PORCINE LUNG EXTRACELLULAR MATRIX. P. A. Link, R. A. Pouliot, M. Valentine, & R. L. Heise, Department of Biomedical Engineering, Virginia Commonwealth University, Richmond, VA 23284-2006. The objective of this work was to develop and characterize a naturally derived drug delivery vehicle for pulmonary applications. Using chemical detergents, we decellularized en bloc porcine lung tissue. We then lyophilized and cryomilled remaining scaffold into powder. Acetic Acid proved to be a good solvent to retain the digested powder in solution. The resulting solution maintained a charge and was then electrosprayed onto aluminum foil. Sterile particulate was formed through washing the particles with ethanol. The particles were suspended in sterile water and lyophilized again. Using dynamic light scattering the average diameter measured 334 nm. The zeta potential was -11.9 mV. Preliminary data shows increased cellular proliferation a in lung epithelial cell line, A549, when using 2 mg of nanoparticles per ml of media. We also found that the formed particles do not activate macrophages. Future work will examine stabilizing the nanoparticles for commercial drug delivery. This work was funded by NSF CMMI 1351162.

IN VITRO VALIDATION OF A COMPUTATIONAL MODEL OF FIBRONECTIN ASSEMBLY. Devin B Mair, Thomas Petet, Lewis E. Scott, Seth H. Weinberg & Christopher A. Lemmon, Department of Biomedical Engineering, Virginia Commonwealth University. Richmond, VA. **Introduction:** The extracellular matrix is an assembly of proteins that surround cells and serves as the cell substrate *in vivo*. A primary component of newly synthesized ECM is fibronectin (FN), which is critical for embryonic development and wound healing. Despite years of research, the mechanism of FN assembly is still not completely understood. We hypothesize that FN assembly occurs through the revelation of buried FN-FN binding sites within *any* of the 15 Type III FN domains, and that these binding sites are exposed in a stretch-dependent manner, facilitating FN molecule binding via a beta-strand addition mechanism. **Methods:** *In-vitro*: Cells were plated on coverslips and allowed to assemble fibrils for a set amount of time. Custom MATLAB code was developed to analyze the properties of the individual fibrils assembled. *In-silico*: We developed a computational model of cell-FN-substrate biomechanical-chemical interactions to test our FN assembly hypothesis. In the model, FN-III domains are represented by Hookean springs with distinct stiffnesses, such that a FN dimer is represented by 30 springs in series. Integrin binding/unbinding is represented by a stochastic first-order reversible chemical, with force-dependent off-rate. FN-FN binding is represented by a stochastic irreversible reaction, in which binding site exposure depends on FN-III domain stretch. Model results are validated using the *in vitro* results. **Results:** Experiments and simulations both illustrate that FN fibril stretched and relaxed length and thickness approach steady state values after approximately 24 hours. Simulations predict that the ratio of stretched-to-relaxed length is maximally four, consistent with experimental results. *In-silico* predictions of substrate force reach steady state levels after approximately 24 hours. The fraction of attached integrin fibril-cell surface connections is roughly constant throughout simulations. **Conclusion:** Experimental FN fibril and the computational model predictions all illustrate three unique features: 1) FN fibrils are highly elastic, but have a maximal 4-fold elongation of their resting length; 2) FN fibril length and force are not strongly correlated. 3) FN fibrils exhibit discrete stable lengths, suggesting local minima of force balance within growing fibrils. This fibril stability has not previously been identified.

EXPLORING THE APPLICATION OF BIO-MIMICRY FOR SUSTAINABLE DESIGN. Katie S. McCullar[1], Preston C. Rhodes[2], Austin Underhill[2] & J. Nagel[2], [1]JMU Biology, [3]JMU Integrated Science and Technology, [2]JMU Engineering, Harrisonburg VA, 22801. Bio-inspired design, or biomimicry, is an approach to innovation that takes nature's time tested patterns, forms, functions, processes, and materials

and uses them to develop engineering solutions. As design challenges increase in complexity, the resulting solutions are also increasing in complexity. This translates to an exponential increase in system components, data, and the time for verification and validation. Biological systems are equally complex, however, they have evolved into elegant systems that have multi-use components, perform "up front" processing to reduce data streams, and are optimized for particular environments. Adopting inspiring features, characteristics, or strategies of biological systems can significantly impact additive manufacturing as well as improve their adaptability. We propose to investigate biological system complexity and integration at multiple levels of abstraction and then translate the insight gained to address manufacturing system sustainability. Currently many products contain multiple materials to provide different functions within the product. These multi-material products are often difficult if not impossible for consumers to recycle without immense amounts of added work. Using additive manufacturing to implement complex, bio inspired designs allows the product to provide multiple functions using a single material that can be easily recycled. Key contributions of this research include approaches for additive manufacturing strategies such as material utilization that align with a product's life cycle, thus increasing the recyclability of the product.

REAL-TIME CLASSIFICATION OF ELECTROOCULOGRAPHY SIGNALS. Saswat Mishra & W-H Yeo, Dept. of Mechanical and Nuclear Engineering, Virginia Commonwealth University, Richmond VA, 23284-2006. Electrooculography(EOG) signals are used in important applications such as, driver fatigue recognition, activity recognition, and interfacing with disabled users. The impact of these signals is powerful in assisting disabled users. The classification algorithm presented is able to detect and classify an EOG signal with more than 90% accuracy. A graphical user interface is demonstrated with a real-time classification algorithm. The classification methodology incorporates centering the signals using a peak detection method which is then transferred over to the machine learning algorithm. The machine learning algorithm identifies the motion of the signal from a database of stored signals. The database is created by the user of the program and added on to an array of previously stored values, referred to as the trained dataset. The trained dataset consists of five features, Wavelet Energy, Definite Integral, Amplitude, Amplitude Velocity, and Average Signal. The testing dataset consists of the same five features which are assessed real-time. The compilation of the peak detection algorithm, machine learning interface, and the features allows this classification program to be highly accurate.

USING ORGANOPHOSPHATE HYDROLASE AND POLYANILINE FABRIC TO DETECT AND DEGRADE NERVE AGENTS. E. Newsome, C. Tang, and S.S. Fong, Dept. of Chemical & Life Science Engineering, Virginia Commonwealth University, Richmond, Virginia 23284. Chemical warfare is a reality that puts civilian and military personnel at serious risk. The goal of this project is to develop a functionalized fabric that can detect and neutralize nerve agents. The design will utilize an organophosphate hydrolase (OPH) enzyme that has been designed with a molecular tag for cloning and isolation. The OPH will be attached to polyaniline and in the presence of water, select nerve agents (e.g. sarin, tabun) can be neutralized resulting in a localized change in pH that can be detected colorimetrically. Progress to date includes design of a tagged OPH and isolation of the tagged protein. Ongoing work is focusing on immobilization on polyaniline fibers and functional characterization of the immobilized enzyme using proxy chemicals (non-toxic analogues to target nerve agents).

AN ACTIVE IMMOBILIZATION SYSTEM FOR HEAD AND NECK EXTERNAL BEAM RADIOTHERAPY USING A 6D TABLE AND RADIOFREQUENCY LOCALIZATION. M. Ostyn[1,2], S. Kim[1], W. H. Yeo[2], T. Dwyer[2], R. Cruikshank[2], M. Rosario[2], & D. Martinez[2], [1]Radiation Oncology, Medical Physics Graduate Program, School of Medicine, Virginia Commonwealth University, Richmond, VA 23298, [2]Department of Mechanical and Nuclear Engineering, School of Engineering, Virginia Commonwealth University, Richmond, VA 23284. One of the most widely used tools used for cancer treatment is external beam radiotherapy. Aside from acute exposure, the greatest risks involved in radiotherapy are incidental radiation dosage to healthy tissue and lack of adequate coverage to the target disease; patient motion and improper patient setup exacerbate both of these problems. Here we present an active immobilization system to reduce these risks in head and neck treatments. The system includes a mechanical device for actively correcting the position of a patient's head, and a radiofrequency localization system designed to track patient motion. A prototype of the mechanical device is presented. The localization system comprises of skin-wearable RF beacons and an external tracking system. We develop an analytical model to estimate the angulation accuracy of the proposed tracking system using Monte Carlo. The results indicate that such a system requires an angular resolution of about 0.04° to achieve the millimeter-level localization accuracy desired in the clinical environment. This study was funded by the Mark A. Sternheimer Award and School of Engineering, Virginia Commonwealth University.

A COMPUTATIONAL MODEL OF LUNG FIBROBLAST MIGRATION WITH IN VITRO VALIDATION. James A. Ratti[1], Angela M. Reynolds[2,3] & Rebecca L. Heise[1,3], [1]Pulmonary Mechanobiology Lab, Dept. of Biomedical Engineering and [2]Dept. of Mathematics & Applied Mathematics, VCU; [3]Johnson Center for Critical Care & Pulmonary Research, VCU Medical Center. Chronic Obstructive Pulmonary Disease (COPD) is currently the 3rd leading age-adjusted cause of death in the United States. The primary cause of this disease is known to be tobacco smoke, yet it is unclear which cellular pathways produce these symptoms. Fibroblasts are known for their roles in tissue inflammation and remodeling, and these functions have been found to be inhibited in COPD patients. To evaluate how lung fibroblast populations from COPD patients differ from healthy ones, we developed an agent-based model of lung fibroblasts during wound healing using the NetLogo platform. This model separates the healing response in terms of the migration, proliferation, death and senescence rates of these cells, and accounts for the effects of serum deprivation and cigarette smoke condensate exposure. Simulations were performed in NetLogo to select biologically suitable parameter sets for each cell type. Model results were validated using data gathered from *in vitro* experiments consisting of scratch-migration assays and MTT assays. This model is the first step in creating a computational tool that will allow us to explore the role of these fibroblast functions on the overall disease progression and evaluate responses to therapeutics for COPD.

IMMUNOSUPPRESSIVE MODALITIES OF TUMOR-STROMA INTERACTIONS IN A THREE-DIMENSIONAL IN VITRO CO-CULTURE BREAST TUMOR MODEL. Lewis E Scott, Dept. of Biomed. Eng., Virginia Commonwealth Univ., Richmond, VA 23220. Tumors repurpose extrinsic and intrinsic modalities of evading immunosurveillance, both of which inhibit aberrant immune responses. The latter is exacted through expression of cell surface receptors, such as programmed death ligand 1 (PD-L1), which have inhibitory effects to cytotoxic tumor immunity. Extrinsic control mechanisms are less understood, though regulatory T cells (Treg) appear to play a dominant role in suppression of helper and cytotoxic T cells within the tumor microenvironment. Due to the role tumor associated fibroblasts (TAF) have been shown to play in tumor progression, we propose that TAF induce a Treg subpopulation via transforming growth factor beta (TGF-β) to suppress anti-tumor immunity. In this model, PD-L1 expression prevents expansion of cytotoxic T cells (CD8+) whereas TAF induction of Treg inhibits helper and cytotoxic T cell expansion, thus presenting a bimodal immunosuppressive mechanism of immune evasion. To test this, we co-cultured PD-L1-expressing malignant mammary epithelial cells with activated, naïve T lymphocytes in Matrigel. Next, we

introduced adipose stem cells (bASC) to the co-culture and measure changes in the population of Treg. In the presence of malignant epithelial cells, bASC secrete inflammatory cytokines associated with T cell recruitment as well as Treg differentiation, notably is TGF-β. In future work, we will inhibit PD-L1 and perform cell viability assays to determine the effectiveness of CD8+ T cell-induced tumor apoptosis. Additional TGF-β blocking is expected to down regulate immunosuppression, increase CD8+ activity and consequently lead to tumor suppression.

CONTROL OF A PROSTHETIC HAND WITH SKIN-LIKE ELECTRONICS. Michael J. Teller & Woon Hong Yeo, Dept. of Mech. Engineering, Virginia Commonwealth Univ., Richmond VA. 23284. Recent advances in manufacturing expand various fabrication opportunities for creating complex features such as human organs and body parts. Here we utilize the 3D printing method that fabricates a realistic prosthetic hand based on the ABS plastic. Electromechanical components including a series of servos finalize the assembly of an electronic prosthetic hand. A portable wireless system with skin-mounted electrodes allows the high-quality recording of surface electromyograms (EMG), produced by the movement of the skeletal muscles. Data acquisition software including signal filtering and classification algorithms collects raw EMG data from the forearm and convert them to digital signals for a continuous control of the prosthetic hand. The development of the prototype device and control system enable EMG from wide ranging areas of the body. The measurements have quality sufficient for advanced forms of human-machine interfaces.

AUTOMATIC CALCULATION OF FEMORAL VERSION USING PROXIMAL FEMUR LANDMARKS. Nathan J Veilleux & Jennifer S Wayne, Department of Biomed. Eng., Virginia Commonwealth Univ., Richmond VA. 23220The success of total hip replacement surgery depends on proper anteversion of the femoral stem. Femoral version is defined as the angle between the femoral neck and condyles in a horizontal plane. An excessively retroverted or anteverted femoral stem will lead to impingement and stem loosening, shortening the life of the hip implant. However, there is no accurate way for surgeons to measure femoral version, since the femoral condyles aren't visible during the surgery. This means that a new technique for estimating version that only uses the proximal femur (the region visible during surgery) needs to be developed. CT scan data for 80 entire femurs and 215 proximal femurs has been provided by the VCU Department of Radiology. Each CT scan has been converted into a 3D model in the program Mimics. The point cloud from each model has been extracted and imported into Matlab, where a program has been developed that is able to

automatically calculate femoral version using the entire femur. The program is currently being adapted to perform calculations of femoral version using only the proximal femur. The consistency of version calculations using only the proximal femur will be evaluated with respect to those made using the entire femur with the ultimate goal of creating a tool that can be used to assist orthopaedic surgeons in aligning the stem of a femur implant during total hip arthroplasty.

THE EFFECT OF MTBI ON READING PERFORMANCE BASED ON EYE MOVEMENT MEASUREMENT AND ANALYSIS. Zoe Villamar & Paul A. Wetzel, Department of Biomedical Engineering, Virginia Commonwealth University, Richmond, VA 23220. Mild traumatic brain injuries (mTBIs) can cause cognitive impairment and oculomotor dysfunction. The subjects of this study are military personnel who have sustained an mTBI from a blast or motor vehicle accident in a combat zone. While reading, a person mainly uses versional eye movements, particularly saccades. Saccades are voluntary jumps between phases of fixations. The reading task requires a certain level of cognitive ability compared to a simple tracking task and it also requires the use of the saccadic system. Using an eye movement tracking system, this study aims to objectively determine how eye movements are affected by mTBI when performing a reading task. Eye movements were measured using the Eyelink II. This headgear-supported eye tracking system collects data at 500 Hz. The data were analyzed for the number of saccades, saccade duration, saccade velocity, saccade acceleration, position accuracy, and fixation stability. The number of regressions and blinks were also assessed. It was found that those who had mTBI had difficulty with the reading task compared to the normal control group. The mTBI group had significantly more regressions while reading, demonstrating the cognitive impairment that the subjects sustained due to the mTBI. The mTBI group also showed an overall negative effect on the saccadic system compared to the control group. This work shows how eye movement tracking on a reading task can be used to determine the effects of mTBI on the oculomotor system as well as the effects on a cognitive task.

NOVEL SMALL AIRWAY MODEL USING ELECTROSPUN DECELLULARIZED LUNG EXTRACELLULAR MATRIX. B. M. Young, B. P. Allen, B. A. Blakeny, R. A. Pouliot, R. L.Heise, Department of Biomedical Engineering, Virginia Commonwealth University, VA 23284. This research included the development of an *in vitro* small airway model using electrospun decellularized pig lung for the study of smooth muscle cellular interactions with surrounding extracellular matrix (ECM). With currently no relevant or controllable *in vivo* or *in vitro* model to investigate diseases and normal interactions of small airway components, the development of a physiologically

relevant in vitro model with comparable cell attachment, signaling, and organization to natural tissue is necessary to develop new treatments for airway disease. The addition of DPLECM significantly changed the PLLA scaffold mechanically, biologically, and physically to bring it closer to the characteristics of the human lung. DPLECM scaffolds exhibited a significant decrease in the elastic modulus compared with PLLA alone. Histological staining and SDS-PAGE showed that after scaffold fabrication, essential proteins or protein fragments in natural ECM are still present after processing. Human bronchial smooth muscle cells (HBSMCs) seeded onto PLECM scaffolds formed multiple layers of cells compared to scaffolds composed solely of PLLA. Phenotype of smooth muscle is better maintained when DPLECM is incorporated into the scaffold shown by enhanced contractile protein expression and increased collagen production for normal smooth muscle remodeling of the scaffold. In summary, this research demonstrates that a PLLA/DPLECM composite electrospun mat is a promising tool to produce an *in vitro* model with the potential to uncover unknown characteristics of bronchiole smooth muscle behavior in diseased or normal states. This study was funded by NSF Career Award.