21st ANNUAL SENIOR PROJECT CONFERENCE

Boston University
Department of Biomedical Engineering

Friday, April 28th, 2006
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Presentation Schedule & Technical Advisors

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Center for BioDynamics
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Neuromuscular Research Center
Center for Advanced Genomic Technologies

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Binaural Hearing
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Biomimetics Material Engineering
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Respiratory Research
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Structural Bioinformatics
Therapeutic Microtechnologies
Visual and Circulatory Biophysics
It is my pleasure to welcome our guests, our alumni, the biomedical industry, our faculty and our students to **Boston University’s 21st Annual Biomedical Engineering Senior Project Conference**. Yes, this is the 21st year our BME Seniors will present. These wonderfully talented people will inform you of their state-of-the-art design and research activities as the complete their bachelor’s degree from the 7th ranked BME program in the nation.

Biomedical Engineering synthesizes engineering, computation, math and physics with the life sciences to advance our understanding of biology and physiology, and then exploits these understandings to develop new devices and methods to improve medical care.

Boston University is the institution that will bring the best of engineering into biology and medicine and the best of biology and medicine into engineering. Our department is devoted to the broad mission of preparing research scientists to cross any interface of medicine or biology with engineering.

Boston University’s Department of Biomedical Engineering is one of the oldest Bachelors program in the nation. Boston University has the largest Biomedical Engineering Department in the country, with 31 primary tenure-track faculty and over 70 affiliated faculty. We are one of only three departments in the country to have received a Leadership Award by the Whitaker Foundation, one of only 9 to receive a Coulter Foundation Translational Biomedical Engineering Translational Research Award, and the only program in the nation to receive both. The Whitaker Leadership Award, received in 2001, provides for a net $32 million enhancement in Biomedical Engineering over the last five years. As the Whitaker Foundation states, “Leadership awards go to institutions that have already demonstrated national leadership in biomedical engineering and have articulated a clear and exciting vision for enhancing their leadership position.” We created a center for Nano and Micro Biosystems including Class 100 and Class 1000 bio-microfabrication facilities, a Micro and Nano Imaging facility, a Biointerface Technologies Facility, and a Biomedical Engineering Simulation and Computational Facility. All of these support a comprehensive educational and research program in Cell and Subcellular Bioengineering, Cell and Tissue Engineering, Biomaterials, Systems Biology and Genomics, Integrated Physiological Systems and Bioimaging, and Multiscale Modeling from the bioemolecule to the whole organ. Our Coulter Award facilitates rapid translation of basic discovery via bioengineering to innovative technologies that impact patient care and clinical practice. The intent is to catalyze collaborative projects between BME faculty and clinicians and which engage the entire commercialization network and infrastructure of the University.

The B.S. program in Biomedical Engineering is fully accredited by ABET. The undergraduate curriculum in Biomedical Engineering is designed to provide integrated training in life, physical, and engineering sciences as preparation for a variety of careers in bioengineering, applied biotechnology, and medicine. We also offer a Biomedical Engineering Industrial Internship Program that can place students for up to a year.
Seniors majoring in Biomedical Engineering are required to complete a two-semester research project which includes elements of technical writing and technical presentations along with actual independent design and research. The level and quality of these projects is extraordinarily professional. At the end of the year, students present the results of their work in this exciting forum of the entire biomedical engineering faculty and student body, along with representatives from industries and area hospitals involved in biomedical engineering. Seniors also must engage their project via a course is called “Product Design, Development and Entrepreneurship in Biomedical Engineering” taught by our Industrial Advisory Board and the School of Management. The course teaches students concepts regulatory issues, marketing, and entrepreneurship, all in the context of their projects.

Research by faculty and students takes place in departmental and selected adjunct laboratories and in seven interdisciplinary centers, all directed or co-directed by bioengineering faculty. These centers include the Hearing Research Center, Center for BioDynamics, Biomolecular Engineering Research Center, Center for Advanced Biotechnology, Center for Advanced Genomic Technology, Center for Nanotechnology and Nanobioscience, and the NeuroMuscular Research Center. Faculty members also conduct research in Biomedical Optics for advancing photonic-based technologies to diagnose and treat cell and tissue disorders; in Cell and Subcellular Mechanics with applications in wound healing and cell and tissue engineering; in Neuronal and Visual Systems with applications in understanding Parkinson’s Disease and visual processing; and in CardioRespiratory Systems with applications in deriving more sensitive and effective methods to diagnose and treat asthma and emphysema. All these efforts resulted in over $22 million in external research for last year’s budget alone.

Finally, on a personal note as course director for the past 21 years I have grown so fond and proud of what our students and department can accomplish when we choose to work together. This has been an extraordinary experience, indeed in many ways a defining one. I thank all those involved for 21 years of stress, of mentoring, of pride, of mission, and of success. Good luck to you all.

Kenneth R. Lutchen
Chair of Biomedical Engineering
Kenneth R. Lutchen, Chairman / Professor – Dr. Lutchen is interested in using systems analysis and identification techniques to investigate respiratory and pulmonary mechanics as well as the relation of mechanics to ventilation distribution. He is particularly interested in the relation between lung structure and key lung properties that influence breathing and mechanical ventilation in asthmatics and emphysema patients. His work involves the use of parameter estimation sensitivity analysis, and optimal experiment design techniques for applying mathematical models to physiological data. Dr. Lutchen is also interested in signal processing associated with respiratory impedance data and heart rate variability.

John A. White, Associate Chairman, Undergraduate Affairs / Associate Professor – Dr. White's interests focus on the electrophysiological and pharmacological properties of ion channels and how their properties shape neuronal firing patterns and the information transmission in the mammalian brain. Electrophysiological, immunocytochemical, theoretical, and computer modeling techniques are applied. Current projects examine the molecular bases of synchronous activity associated with learning and memory, and the system-level consequences of random behavior at the molecular level.

Charles R. Cantor, Professor – Dr. Cantor’s research is focused on identifying biological problems that are resistant to conventional analytical approaches and then developing new methodologies or techniques for solving these problems. His laboratory has developed methods for separating large DNA molecules, for studying structural relationships in complex assemblies of proteins and nucleic acids and for sensitive detection of proteins and nucleic acids in a variety of settings. His current interests include the development of new methods for faster DNA sequencing, the development of new variations and analogs of the polymerase chain reaction, and the discovery of human genes associated with sensory perception. He is also interested in exploring the possible use of biological molecules for applications in nanoengineering and microbotics.

Irving J. Bigio, Associate Chairman, Graduate Studies / Professor – Dr. Bigio’s research focuses on medical applications of optics, lasers and spectroscopy, with an emphasis on minimally-invasive diagnostics and therapeutics. His current activities involve the development of fiber-optic probes to detect cancer using optical spectroscopy, a method that has developed the moniker “optical biopsy.” Related technology is being developed to measure certain drug concentrations in tissue with fiber-optic probes, or “optical pharmacokinetics,” in particular as an aid in the development of new chemotherapy agents. Other interests relate to monitoring the response of tumors to treatments and less invasive treatments for various pathologies, utilizing lasers and other optical technologies.

H. Steven Colburn, Professor – Dr. Colburn’s research involves the application of signal processing, statistical communication theory, and computational modeling to the study of hearing and hearing impairments. He is particularly interested in the measurement and modeling of binaural hearing phenomena including both psychophysical and physiological aspects. Dr. Colburn is also working in the area of simulated acoustic environments.

James J. Collins, Professor – Dr. Collins’ research is directed towards developing and implementing techniques and concepts from nonlinear dynamics and statistical physics to study and improve the function of physiological and biological systems. Specifically, his research addresses questions relating to: (1) random-walk analyses of human balance control, (2) the development of an artificial vestibular control system, (3) coupled nonlinear oscillators and locomotor central pattern generators, (4) noise-enhanced sensory function, (5) noise-shaping in networks of coupled neurons, (6) dynamical control of cardiac arrhythmias, (7) controlling cell cycle dynamics, and (8) designing and constructing genetic applets.
Edward Damiano, Associate Professor – Dr. Damiano’s research activities involve the application of biomechanics and biofluid dynamics to the study of basic physiological and pathophysiological processes at the cellular, subcellular, and extracellular-matrix levels. The focus of recent work has been on microhemofluidics in capillaries and post-capillary venules, the role of the endothelial surface layer in cardiovascular physiology, and sensory mechanotransduction in the vestibular semicircular canals. Other research activities include investigations of the interactions of leukocytes with the endothelium in capillaries and post-capillary venules, the development of a novel viscometric method to analyze non-Newtonian fluids, and the development of an automated robust control system to regulate blood glucose in Type 1 diabetes.

Charles Delisi, Professor – Dr. Delisi’s research includes the development and application of computational methods for determining the structure and function of large biological molecules genome organization, and information processing in cells. Areas of interest include the structural basis of voltage gating, and the docking and design of peptide hormones, neurotransmitters and antigenic peptides for drug and vaccine development. Other projects involve the use of large databases to develop expert systems and train neural networks for the problem of rapidly identifying regions of key importance in DNA and proteins.

Carlo J. DeLuca, Professor – Dr. DeLuca’s research interests are focused on the application of engineering principles to the understanding of motor control and the development of more objective patient treatment procedures. Specifically his research work involves: a) understanding how the brain and spinal cord control the individual fibers in a muscle, and groups of muscles, in healthy as well as dysfunctional individuals; b) methodologies for objectively measuring muscle fatigue during voluntary efforts; c) means for monitoring functional activities; and d) new technologies for detecting and interpreting EMG signals. He has developed various novel techniques and technologies for electromyography, some of which have been commercialized and are now used the world over. His work on motor unit control has brought forth physiological concepts such as the “common drive.”

Micah Dembo, Professor – Dr. Dembo's main research interest is the mechanical properties of living cells and cellular components. His work is mainly theoretical and computational but involves close collaboration with experimental efforts in several laboratories. He is currently involved in mechanical studies aimed at improving understanding of cell-substratum and cell-cell adhesion, cell division, cell locomotion, cell adhesion, and various passive cell deformations.

Solomon Eisenberg, Dead ad interim, College of Engineering / Professor – Dr. Eisenberg’s research is directed towards understanding the functional role played by electrically mediated interactions in connective tissues and membranes, as well as the effects and mechanisms of interactions of externally applied electric and magnetic fields. Specifically, his research addresses: electromechanical interactions in cartilage; electrically mediated transport in charged and neutral materials; computational modeling of electric field distributions in the human thorax and heart during electrical defibrillation; computational modeling of induced currents during transcranial magnetic stimulation.

Evan A. Evans, Professor – The general objectives of Dr. Evans’ research are to expose the underlying physical mechanisms used by nature in design of complex biological organisms and the related physics of soft organic interfaces in liquids (polymers, membranes, etc.). The goal is to derive insights for biology, condensed matter physics, and advanced technology from the study of “nature’s engineering.” Mechanical experiments at the nano and micro scales are combined with theory to examine material properties of synthetic and natural membranes, properties of biological cell structure and role of force in cell biochemical function, molecular bonding and adhesion. Material concepts extracted from these studies are applied to the design of specialized nanostructures, e.g. robust membrane capsules for chemical exchange in harsh environments and nanoconduit networks for microdevices.
Maxim Frank-Kamenetskii, Professor – Dr. Frank-Kamenetskii’s research is focused on theoretical and experimental studies of various DNA structures and their relations to DNA functioning in cell. He and his co-workers discovered a novel DNA structure, triplex H-DNA, and elaborated a comprehensive theoretical approach to treat DNA topology, i.e., knots and supercoils. His current interests include the development of new approaches to sequence-specific recognition of duplex DNA using triplex mode of binding of oligonucleotides to DNA duplex.

Timothy Gardner, Assistant Professor – Dr. Gardner’s lab is working to develop novel antibiotics, new cancer therapies, and to optimize microbes for energy production and environmental clean-up. In particular, the lab develops tools to map the genome-wide properties of gene regulatory and metabolic networks in microbes, plants and mammals. The lab applies these tools to understand the complex circuitry underlying cell physiology and mechanisms of disease. In addition, the lab uses these tools to predict the mechanism and side-effects of therapeutic drugs. Research in the Gardner lab integrates methods from diverse fields including genomics, genetics, microbiology, machine learning, bioinformatics, systems engineering and statistics.

Mark W. Grinstaff, Associate Professor – Dr. Grinstaff’s research involves the design, synthesis, and characterization of polymers for tissue engineering and drug delivery applications. His current interests include the use of novel dendritic hydrogel sealants to repair corneal lacerations and dendritic scaffolds for articular cartilage repair. Dr. Grinstaff uses an interdisciplinary research approach to understand the interactions that occur at a material-biologic interface to guide the development of designer biomaterials.

Andrew C. Jackson, Professor – Dr. Jackson's research interests involve the application of engineering principles to the understanding of the mechanical properties of the human respiratory system. Specifically, his research efforts have been focused on computer modeling of the respiratory system, development of non-invasive tests of pulmonary function including fluid mechanics and acoustic phenomena in the airways, and identification techniques to analyze respiratory impedance data.

Simon Kasif, Professor – Dr. Kasif’s current research area is Bioinformatics, Computational Genomics and Molecular Engineering. More specifically, he has worked on analysis of microbial genomes, large scale genomic comparison and SNP detection, whole genome comparison, gene regulation, gene finding systems, and a variety of other algorithms and systems for functional genomics, structural genomics and comparative genomics. He has also studied artificial intelligence, parallel complexity and algorithms, constraint systems, computational learning theory, cognitive modeling and biologically inspired computing.

Amit Meller, Associate Professor - Dr. Meller research is directed toward the development of novel experimental techniques for the study of biomolecular interactions and dynamics, at the single molecule or at the single complex level. In particular, his research is focused on: (1) employing nanopore force spectroscopy to study RNA unfolding and re-folding kinetics, (2) DNA switches and transcription initiation kinetics, (3) RNA helicases activity, (4) mapping of transcription factors interactions with DNA, (5) ultra fast DNA sequencing, (6) development of novel optical methods for single molecule detection in biomedical applications.

Jerome Mertz, Associate Professor – Dr. Mertz’s research is in the development and applications of novel optical microscopy techniques for biological imaging. Most of these techniques are based on nonlinear optics with femtosecond lasers. Specific research topics include the application of two-photon excited fluorescence (TPEF) microscopy to deep imaging in brain tissue and visualization of endogenous fluorescence for clinical applications. Other topics include the application of second-harmonic generation (SHG) microscopy to cell membrane potential imaging and the photocontrol of chromophore orientation dynamics in biological membranes. Finally, alternative contrast mechanisms are being investigated including interferometric mechanisms based on optical coherence tomography (OCT) and nonlinear detection (Auto-confocal microscopy).

David C. Mountain, Professor – Dr. Mountain’s research centers around the experimental and theoretical study of electromechanical processes in the cochlea. Dr. Mountain is also interested in bioacoustic signal processing; sensory biophysics; measurement of evoked potentials and otoacoustic emissions; biomedical electronics.
Christopher Passaglia, Assistant Professor – Dr. Passaglia's research is aimed at elucidating how visual neurons process information. His work involves quantitatively analyzing the response characteristics of neurons early along the visual pathway and incorporating experimental findings into mathematical models of visual information transmission in normal and diseased states.

Kamal Sen, Assistant Professor – Dr. Sen’s research investigates the model system of the songbird to answer questions regarding how neurons in the brain encode complex natural sounds, neural substrates of selectivity for and discrimination of different categories of natural sounds, and whether these substrates are innate or shaped by learning.

Cassandra L. Smith, Professor – Dr. Smith’s research brings novel approaches and tools from the interface of genomics, genetics and biomolecular technology to complex disease studies. Current research interests include understanding how genomic DNA instability contributes to multifactorial diseases like schizophrenia that are linked to both genetic and environmental factors. Some of these studies use monozygotic (aka identical) twins, discordant for schizophrenia to understand how the well twin avoided disease. The goal of this research is to prevent and/or minimize schizophrenia. Other research takes a combinatorial chemistry approach to isolate aptamers (DNA mimics of antibodies) for use as cancer tumor targeting reagents. The goal of this research is to develop effective targeted therapies for cancer treatment and detection while minimizing damage to bystander cells.

Temple Smith, Professor – Dr. Smith is director of Biomolecular Engineering Research Center. The center has two major research objectives: to develop statistical computer approaches to detect syntactic and semantic patterns in DNA, RNA, and protein sequences and structures; and to use computer pattern analysis of those sequence patterns to understand regulation of gene expression, protein structure, and molecular evolution.

Dimitrije Stamenović, Associate Professor – Dr. Stamenović’s research centers around theoretical and experimental studies of mechanics of living tissues. His current interests are in microstructural analysis of cells, cartilage and lungs with the goal of relating their mechanical properties to the underlying structural design and distending stresses. Dr. Stamenović is also interested in mechanical properties of gas-liquid foams and microstructural determinants of foam elasticity.

Béla Suki, Associate Professor – Dr. Suki’s research interests focus both on experimental and theoretical investigation of soft tissue biomechanics from fiber to organ level with special emphasis on the mechanical properties of the lungs. His current works involve dynamics of the stress-strain relationship of tissue strips, and statistical mechanical and micromechanical modeling of avalanche phenomena in airway opening. Other interests include nonlinear system identification and signal processing applied to biomedical systems and signals.

Joe Tien, Assistant Professor – Dr. Tien’s main interests are tissue engineering; self-assembly and self-organization; and programmable cellular microenvironments. Dr. Tien and his group focus on the fabrication of artificial tissues through control of the cellular microenvironment, including branched networks such as vasculature and the pulmonary tree, and spatially complex aggregates such as liver acini. Members of the group design substrates that direct cellular interactions at the microscale and elicit a desired behavior and develop new technologies in-house as needed, to fabricate organized cell cultures. The group also uses these tools to examine how spatial and temporal variations in microenvironment affect the behavior of cells. Current work focuses on how the location and timing of cell-cell and cell-matrix interactions coordinately regulate cell behavior.

Lucia M. Vaina, Professor – Dr. Vaina’s main areas of current interest involve: (1) models of visual motion analysis in the human brain, based on computational, psychophysical, structural, and functional-neuroanatomical methods; (2) functional plasticity-learning and neurocovery, psycho-physics, functional neuroimaging and neuronal network models; and (3) functional MRI of the human visual system.
Sandor Vajda, Professor – Dr. Vajda's research centers on scientific computing; computational chemistry; combinatorial optimization; molecular biology, protein and peptide structure determination; protein engineering; drug and vaccine design. His goal is to develop a methodology that will permit a predictive understanding of ligand recognition by protein receptors. Such understanding is the key to rational drug and vaccine design strategies, and requires the solution of several challenging problems. He is currently studying the following problems: (1) evaluation of binding free energy in protein-ligand complexes; (2) development of efficient docking algorithms that will find structures for the complex at or near the global free energy minimum; (3) predicting the ensembles of conformations adopted by short linear peptides in solution; (4) design of amino acid mutations to induce certain changes in the affinity and specificity of a binding site.

Herbert F. Voigt, Professor – Dr. Voigt is currently engaged in experimental and theoretical studies of the neuronal circuitry in the cochlear nucleus. He uses single and multi-unit recording and analysis techniques to study the responses of neurons and neural nets to acoustic stimulation. Intracellular recording and marking techniques are used to associate physiological function to anatomical structure. Computational models are used to assist our understanding of the neural circuitry.

Zhiping Weng, Assistant Professor – Dr. Weng’s research focuses on computational approaches to the determination of protein structure and function and the engineering of novel proteins with desired properties. Her research interests include genome sequence analysis, classification of protein families, homology modeling, structure alignment, sequence and structure pattern recognition, the development of target energy functions and search algorithms for receptor-ligand interaction, and the design of novel sequences for stronger and more specific binding.

Joyce Y. Wong, Associate Professor – Dr. Wong’s research focuses on the development of biomaterials to probe how structure, material properties and composition of the cell-biomaterial interface affect fundamental cellular processes. Her current research interests include tissue engineering of small diameter blood vessels for bypass and intravascular pharmacology (e.g. stents); development of targeted nano- and micro-particle contrast agents for multi-modal (magnetic resonance, ultrasound, and optical) detection of atherosclerotic and vulnerable plaque; and engineering biomimetic systems to study restenosis and breast cancer.

Thomas Einhorn, Professor – Professor Einhorn’s interests include research on the repair and regeneration of bone and cartilage, reconstructive surgery of the hip and knee, and the treatment of metabolic bone disease.

Bennet Goldberg, Professor - Dr. Goldberg’s research focus includes low and room-temperature near-field scanning optical microscopy and spectroscopy in semiconductors and biological systems. Ultra-high spatial resolution combined with time-resolved spectroscopy provide new ways of examining mesoscopic systems. Magneto-optics and magneto-transport of two and one-dimensional electron systems are used to examine spin-textures in interacting electrons.

Shayamsunder Erramilli, Professor - Dr. Erramilli’s research interests include: Development of Infrared and Raman microscopy for imaging biological samples, using intrinsic contract mechanisms; Applications of Scanning Near-field Infrared Microscopy for imaging single living cells, with a view to understanding the contribution of membrane lipids to the physics of cell motion; Application of high resolution vibrational microscopy for screening pathological tissue; Specifically seeking to correlate vibrational microscopy data with synchrotron x-ray scattering data; Development of vibrational infrared pump-probe 2-D spectroscopy for the study of biomolecules; Development of novel infrared fibers (silver halide) and Quantum Cascade Laser sources for biomedical applications. [Collaboration with Prof Irving Bigio]; Development of Quantum Raman Microscopy using entangles photons.
Stephen Grossberg, Professor – Dr. Grossberg’s work concerns modeling how the brain controls behavior, and how to develop new technologies that more closely emulate properties of biological intelligence, especially how individuals can successfully adapt in real time to changing environmental conditions. Recent research projects include work on neural models of vision; audition; variable-rate speech perception; learning; memory; categorization and recognition; recall; reward and punishment; adaptive sensory-motor control; cortical development; and neural substrates in areas such as visual cortex, parietal cortex, inferotemporal cortex, prefrontal cortex, basal ganglia, cerebellum, reticular formation, spinal cord, and superior colliculus. Technological applications to machine vision, adaptive pattern recognition, and robotic systems are also being made.

James A. Hamilton, Professor - Dr. Hamilton is a Professor of Biophysics and Physiology and Director of the Cardiovascular Magnetic Resonance Spectroscopy and Imaging Laboratory at the Boston University School of Medicine. Dr. Hamilton’s research program has two main components: fatty acid transport (structural and cell biology) and MR imaging of atherosclerosis and ectopic fat. His programs are interdisciplinary with strong translational components in obesity, diabetes, cardiovascular disease, and inherited lipid disorder.

Allyn Hubbard, Associate Professor – Dr. Hubbard’s research is comprised of two major areas that partially overlap each other. The first is auditory science, which includes both experiments and models involving the mammalian, peripheral auditory system. The second research area involves building integrated circuit chips that are targeted at biomedical applications. One chip currently under development is to implement the traveling-wave amplifier model of the cochlea. Another chip creates a micro-electrophoresis chamber, which has embedded sensors that can detect DNA or other large molecules. A major focus is currently the fabrication of neural-net chips that mimic the biological vision system.

W. Clement Karl, Associate Professor – Dr. Karl's research is concerned with the development and use of statistically-based techniques for the extraction of information from images and multidimensional fields. One aspect of his work concerns the development of multiresolution methods for the processing and estimation of signals and images. For example, multiresolution approaches are being developed and used for tomographic image formation and MRI segmentation. Another aspect of his research concerns the estimation of fundamentally geometric quantities or, more generally, the role that geometry or shape may play in estimation problems. An example of this work is the estimation of cardiac vessel shape in angiograms. He is in charge of the Multi-Dimensional Signal Processing Laboratory.

Catherine Klapperich – Assistant Professor - Dr. Klapperich’s research centers on the molecular interactions that take place at the cell-biomaterial interface. She is specifically interested in the integration of cells or cell components into synthetic device environments in microscale and nanoscale systems. Her experiments focus on the integration of molecular level data from genomic and proteomic analyses into iterative materials design. Applications include microfluidic device design and polymer based tissue engineering.

Elise F. Morgan, Assistant Professor – Dr. Morgan’s research focuses on relationships between structure and mechanical function of musculoskeletal tissues at multiple length scales. She uses both experimental and computational methods to explore how the deformation and failure behaviors of tissues, primarily bone and cartilage, depend on the tissue microstructure; and conversely, how the differentiation and adaptation of tissues and cells are modulated by their local mechanical environment. Dr. Morgan is also interested in the mechanics of general multi-scale media and damage mechanics.

Matthew A. Nugent, Professor - Dr. Nugent is a Professor of Biochemistry and Ophthalmology at the Boston University School of Medicine. Dr. Nugent’s research program combines traditional biological and biochemical approaches with those of biomedical engineering. In this regard, a considerable amount of the research in his lab involves the development and use of quantitative mathematical models of dynamic cellular processes, as well as concepts related to tissue engineering and controlled drug delivery technology.
Daniel Segré, Assistant Professor - Dr. Segré is interested in the evolutionary dynamics of biological networks, in particular in the interplay between response to genetic and environmental perturbations, genomic-level functional organization, and optimal adaptation. His lab’s goals include developing models to study the regulatory and evolutionary dynamics of metabolic networks across different organisms, cell types, and interacting cell populations.

Barbara Shinn-Cunningham, Associate Professor – Dr. Shinn-Cunningham’s research interests include psychoacoustics, localization of sound sources and binaural hearing. She works with models of auditory perception, auditory plasticity and learning.

Martin Steffen, Assistant Professor – Dr. Steffen’s research focuses on developing the tools of systems biology for mammalian cells. Currently we are emphasizing the technique of mass spectrometry. Using mass spec, one can currently identify a few thousand proteins in a single experiment, as well as many important post-translational modifications.

Malvin C. Teich, Professor – Dr. Teich’s research interests center on the statistical behavior and signal processing of biological signals. He is studying how acoustical and optical stimuli are encoded into fractal sequences of action potentials at various locations in the auditory and visual systems, and how the fractal nature of the electrocardiogram can be used to distinguish normal and diseased patients. He is investigating the neurobiological origins of such behavior. He is also studying a new class of neural-based psychophysical models that consider the ascending pathways of sensory systems as amplifying neural networks. He is also developing a quantum-optical microscope that should be useful for high-resolution fluorescence studies in the neurosciences.

Joe Z. Tsien, Professor – Dr. Tsien’s research is aimed at understanding the organization principles underlying the neural network encoding and processing of learning and memory. The lab’s strategy is to take an integrated approach that combines molecular genetics, physiology, computational mathematics, and behavioral techniques. With the latest capacity to measure simultaneously ensemble activities of over 200 hundreds of individual neurons in the brain of freely behaving mice, researchers in the lab are studying the molecular and network mechanisms of learning behaviors. Current projects include: 1) The molecular and ensemble analysis of short-term memory; 2) The molecular and ensemble analysis of consolidation and storage of long-term memory; 3) The molecular and neural analysis of memory retrieval; 4) Methods for enhancing or erasing memories; 5) Monitoring and decoding neural networks; 6) Computational analysis of neural population dynamics and memory codes; 7) Brain-Machine-Interface conversions.

M. Selim Ünlü, Professor – Dr. Ünlü has broad research interests including applications of nano-optics, optoelectronic devices and spectroscopic techniques to various biological and biomedical problems. One of the recent activities involves development of biosensors based on optical waveguides and resonators. The evanescent field of a planar waveguide can be used to probe small changes in the index of refraction of objects in a well on the surface of the waveguide. Resonant optical systems enable high fidelity operation for exquisite sensitivity, as well as high density arrays for massively parallel operation. Such platforms can be ultimately used for pathogen detection and biomolecular analysis. Our research group has developed a new interferometric technique in fluorescent imaging called spectral self-interference fluorescence microscopy which yields nm-scale axial height determination. The goal of this research effort is to study sub-cellular processes as well as nanoscale biological structures such as trans-membrane proteins and surface bound nucleotides.
Mark W. Bitensky, Research Professor – Dr. Bitensky's research involves rod photoreceptors: he studies the purified gene products of the vertebrate retinal rod, particularly those protein ensembles and processes which can help understand the visual excitation and adaptation processes as observed in the intact photoreceptor cell. The rod is a specialized neuron which deploys a photosensitive organelle called the rod outer segment (ROS). His other major research area is the study of red cells, specifically refrigeration-induced ‘storage lesion’ and its molecular mechanisms, and developing new and more effective ways to store red cells for longer time periods with less deterioration.

Natalia Broude, Research Associate Professor – Dr. Broude’s research has been focused on chemistry of nucleic acids, isolation, sequencing and expression studies of a family of human genes coding for Na, K-ATPase. Her current interests include the development of new approaches to genome-wide comparative assays: multiplex PCR, targeted genomic differential display, genomic methylation profiling.

Marc Herant, Research Assistant Professor – Dr. Herant's main research interests are in developing a better understanding of cell shape and motion through the construction of theoretical models. Areas of current effort include the mechanics of phagocytosis and the dynamics of the lamellipodium.

Thomas L. Szabo, Research Professor – Professor Szabo's research goals are overcoming present limitations in imaging the body using ultrasound and other imaging modalities and finding new ways of extracting diagnostically useful information about tissue structure, health and function noninvasively. His work involves the following: multi-modal and 3D digital imaging and beam forming, signal processing, ultrasound-induced bioeffects, simulation and measurement of mechanical tissue properties, and scanning acoustic microscopy.
SCHEDULE
and
TECHNICAL
ADVISORS
DEPARTMENT OF BIOMEDICAL ENGINEERING

21st Annual Senior Project Conference
— Friday, April 28, 2006 —

7:45 - 8:10 AM  Continental Breakfast

8:10 AM  Opening Remarks:  Dr. Kenneth R. Lutchen

8:15 - 10:30 AM  SESSION I
PHO 206  Patient Monitoring, Bioinstrumentation and Medical Devices

Strengthening Balance while Balancing Strength:  A Postural Balance and Strength Training Study in a Microgravity Environment
Amanda Dwyer

Evaluation of an Adjustable Narrowband Filter Banks for Use in Alternative Hearing Aids
Ryan J. O’Shea

Designing a Device for the Continuous and Telemetric Measurement of Intraocular Pressure in Rats with Induced Glaucoma
Katherine Harihar / Justin Levy / Stephen Rocha

Design Application of a System to Track Coupling between Airways and Lung Tissue
Heather Rasich

Designing and Building a Switching System for the Headstage of a Rat
M. Asif Khan

Optimization of Coating and Surface Characterization of Novel Polymers and Proteins for Use on a Medical Device
Michelle Chan

Isolation of Nucleic Acids Using Electroosmotic Flow in a Thermoplastic Device
M. Dominika Kulinski

Development of Vibrating Sandals to Enhance Sensorimotor Function
Alexandra Duritza

The Brain Machine Interface: Using Neural Code to Control an External Device
Matthew Kersus

Mind Classifier: An Automatic Classifying Algorithm for Functional MRI Activation Map
Dongwoo Hahn

Breaking Boundaries: Analogue Brain-Computer Interface Using fMRI
Paul Bower

10:30 - 10:50 AM  BREAK
10:55 - 12:40 PM  SESSION IIA  
PHO 205  Computational Modeling in Bioengineering

**Session Chair:** Doug Cotter

Models of Dolphin Hearing  
Garth Mashmann

Modeling of Spectro-Temporal Receptive Fields and Simulation of the Population Response in Zebra Finch Field L  
Graham Voysey

Design and Implementation of a Gerbil Song Playback System  
Paul Joseph S. DeGuzman

Computational Modeling for Electrically Stimulating the Auditory Nerve  
Mitesh Amin

Modeling Synaptic Plasticity  
Patrick Duplessis

Dynamic Behavior of a Single Polymer Chain as a Model of Rheological Behavior of Living Cells  
James Wai

Pharmacokinetic Modeling and the Effects of Ototoxic Drugs  
Ajan Patel

Application of Personalized Airway Trees in Multiscale Lung to Probe Structure-Function Relations in Asthmatics  
Aladin Milutinovic

Quantitative Image Functional Modeling of the Lung with Hyperpolarized 3He MRI  
Lisa Campana

10:55 - 12:40 PM  SESSION IIB  
PHO 206  Biomedical Imaging

**Session Chair:** Irving Bigio

MRI Phantom for Quantitative MRI: A Study of Materials with Adjustable Diffusion Coefficients  
Ryan Irving

Multimodal Data – Analysis Software Package for Diffusion Weighted MRI  
Sahil Jain

Adaptation of a Two-Photon Microscope for Targeted Excitation and Photobleaching  
Jason Taclas

Real-Time Automated Segmentation of High Resolution CT Images Using Dual-Space Clustering Algorithm  
Dhruv Dhanraj Bahl

Time Course Measurements and Characterization of Various Brain Tumor Cell Lines in Mice Models Using MRI  
Eric Aronowitz / Tejash Patel

Brain Tissue Characterization Using T2 Biexponential Decay in Glioblastoma Multiforme Tumor Mouse Model  
Eo-Jin Hwang

Establishing a Quantitative Reference for the Volumetric Distribution of the Diffusion Coefficient in the Liver and the Spleen  
Rodrigo Diaz Garbizu

Quantitative MRI of Human Parotid Glands Using Dual-space Clustering Segmentation: intra-glandular analysis of T1 and T2  
John Fedele / Andrew Konowicz

A Study on Brain Tissue Using Quantitative MRI Techniques  
Christopher Gange

12:45 - 1:25 PM  LUNCH BREAK
**SESSION II A**

**Systems Biology and Genomics Engineering**

**Session Chair:** Zhiping Weng

A Bioinformatics Based Search for Novel Motifs Influencing Gene Expression of Cardiac Sarcomere Promoters

Sunil Bhat

Development of a Low-Affinity Avidin-Like Molecule for Use in Binding Assay Experimentation

Jonathan Foley

Transcription Start Sites and Gene Regulation in Drosophila

Laura Bacigalupi

Targeting Breast Cancer Cells Using Aptamers

William Seo

Constraining the Folding Process of Ribosomal RNA

Sherwin Ting

Proteomic Profiles of Peripheral Leukocytes for Biomarker Discovery in Lung Cancer

Greg Boulet / Michael Hoskins

Nanoscale Surface Forces Between Human Serum Albumin, Alkanethiol Self-Assembling Monolayers, and Oligo (ethylene oxide) Monolayers

Hailemariam Negussie

Power Output Optimization of a Shewanella Oneidensis Catalyzed Microbial Fuel Cell Through High-Throughput Screening of Mutants

Frank Juhn

**SESSION II B**

**Neurosensory Bioengineering**

**Session Chair:** John White

Development of a Perceptually Transparent Hybrid Auditory Display in a Reverberant Room Setting

Aaron Wolfson

A Physiological and Efficient Representation of Spectral Cues in Sound Localization

Krenar Tasimi

Confusion Analysis of the Coordinate-Response-Measure (CRM) Speech Corpus for Intelligibility Studies

John Patrick Gonzales

Influence of Spatial Location Cues on Auditory Object Formation

Sarah Chaudhari

Transfer of Learning Between Sound Source Stimulus Dimensions Important for Localization

Reginald Villacorta

Effects of Reverberation on Spatial Auditory Attention

Priyanka Zutshi

Statistical Modeling and Assessment of Efferent Spike Trains in the Limulus Visual System

Amy M. Tran

Microgravity Induced Changes in the Control of Motor Units

Gavin Hayes

Analysis of Correlated Firing Behavior of Motor Units During Fatiguing Muscle Contractions

Ashley Morgan

Plasticity in the Human Visual System

Sharon Hyzy / Anthony Tanella

**3:15 - 3:35 PM**

**BREAK**
Effects of Mechanical Stretch on Pulmonary Fibroblast Function
Anne Zavadil

Effects of Stretching on the Mechanical Properties of Extracellular Matrix Sheets During Elastase Treatment
Rajiv Jesudason

Assessment of Nanoindetation as a Technique for Characterizing the Mechanical Properties of Soft Tissues
Jared Bancroft

Development of Finite Element and Composite Plus Curved Beam Structural Rigidity Analysis Models for Rat Tibia with Simulated Lytic Defects
Alan Tseng / James Kimbaris

Effects of Tissue Fixation on Bone Mechanical Properties
Bryan Hermannsson

Study of Cross-Linking in Polyvinyl Alcohol Contour SE Microspheres
Sameer Grover

Synthesis of Branched Collagen Channel Mimicing Microvasculature
Lin Lin Gao

Vascular Tissue Engineering
Edward Lee

A System for Studying the Role of Substrate Mechanics in the Organization of Dynamically Cultured Vascular Smooth Muscle Cells and Extracellular Matrix
Christopher Sip

Local Incorporation of Anti-neoplastic Agents into Surgical Resection Margins for the Treatment of Mesothelioma
Sarah Lucier

RECEPTION IN THE ATRIUM, 2nd FLOOR, PHOTONICS CENTER
# 2006 Senior Project Technical Advisors

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<td>Amanda Dwyer</td>
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<td>Ryan J. O’Shea</td>
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<td>Katherine Harihar / Justin Levy / Stephen Rocha</td>
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<td>Michelle Chan</td>
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<td>M. Dominika Kulinski</td>
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<td><strong>Session IIA</strong></td>
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<td>Garth Mashman</td>
<td>David C. Mountain</td>
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<td>Graham Voysey</td>
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VISITING COMPANIES and LABORATORIES
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Shaw-Fang Yet
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<tr>
<th>Company/Laboratory Representatives and Visitors Directory</th>
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<tr>
<td><strong>Center for Integration of Medicine &amp; Innovative Technology (CIMIT)</strong></td>
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| Colleen Kigin  
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Wyle Labs
Erin Taschner, Class of 2004
BME Flight Controller, International Space Station

David Rubin
BME Flight Controller
1290 Hercules Blvd.
Houston, TX 77058
SESSION I:
Patient Monitoring
Bioinstrumentation
and
Medical Devices
Strengthening Balance while Balancing Strength: Postural Balance and Strength Training Study in a Microgravity Environment

Amanda E. Dwyer
NeuroMuscular Research Center, Boston University

Quite possibly the most overt change affecting astronauts is the immediate response of the neurovestibular system to changes in gravity. Combined with coordination, muscle strength and bone loss these problems can influence safety of the flight mission during orbit. Additionally the microgravity induced neurovestibular adaptations result in post-flight balance problems during normal activities such as standing, turning corners and walking. Currently there are no in-flight countermeasures against neurovestibular adaptations and the balance related problems which they cause. The goals of this study were 1) examine whether strength and balance function could be improved simultaneously via training in an altered gravity environment and 2) to examine the role of visual input in specific balance tasks pre and post-training. A training study consisting of three groups: balance and strength training, strength training, and balance training with visual input were completed via use of a 90° room. The training room used simulates micro gravity by effectively eliminating vestibular input to postural balance control. The room is also furnished such that it induces strong visual reorientation illusions resulting in the subject perceiving themselves to be upright while in a supine position. Subjects wore a backpack frame equipped with three friction free air bearings on the back allowing frictionless frontal plane movement during training. Each group of subjects was pre and post-tested to evaluate their strength and balance function. To quantify strength function maximal isokinetic squat measurements were collected using a Computerized Ariel Exercise System (CAES), Ariel Dynamics, CA at variable velocities of 10 deg/s and 35 deg/s. From each squat set peak and average force and power measures were calculated. To quantify balance function center or pressure (COP) measurements for upright stance were taken at 100Hz using a moveable balance platform with a force plate mounted in the center. Subjects performed stationary bi-pedal stance, stationary uni-pedal stance, and continuous horizontal perturbation for both eyes open and eyes closed conditions for 10 trials of 30 seconds. Traditional balance parameters were extracted from the COP measurements as well as stabilogram-diffusion analysis was completed. Training spanned five weeks for a total of 16 training sessions. Sessions for the strength training group consisted of performing weighted squats for 6 sets of 10 repetitions beginning at 50% of each individuals’ one repetition max (ORM) weight and gradually increased to 75% ORM. Training for the balance and strength group consisted of the same protocol but with weighted squats performed on a balance board capable of only mediolateral movement. Training for the isolated balance group consisted of sessions of various challenging balance tasks: uni-pedal balancing on center and off center of balance board, bi-pedal balancing with feet in center and on outer edges of balance board. The study found that 1) significant squat strength improvement took place in those individuals who trained strength whether coupled with balance training or not 2) subjects in the strength and balance training group had improved balance post-training and 3) the dependency on visual input in balance control for those individuals trained in strength and balance was decreased post-training.
Evaluation of an Adjustable Narrowband Filter Bank for Use in Alternative Hearing Aids

Ryan O'Shea

Auditory Neurophysiology Laboratory

Hearing loss is a chronic, often irreversible, health issue that is most often treated with hearing aids. Current hearing aid designs amplify the sound entering the ear to compensate for the loss, but have not had consistent success correcting the loss of frequency selectivity that occurs when the outer hair cells (OHCs) are damaged. The goal of this research is to create an alternative method of hearing aid amplification which uses narrowband notches in the frequency domain to restore the correct frequency range to the auditory nerve fibers (ANFs). A bank of notch filters was developed by calculating the bandwidth of frequencies that reach OHCs in normal hearing individuals at characteristic frequencies (CFs) using the dual resonance nonlinear (DRNL) filter model of basilar membrane function. A MATLAB program was written which measures the bandwidth and CF parameters of the DRNL filter model and the gain in a subject’s audiogram to develop several notch filters of variable gain into a frequency domain filter. Clinical testing of the filterbank involves filtering 10 sentences through each filter and playing them to subjects though an attenuator and headphones. The trials consist of 5 sessions with normal hearing subjects and 3 with hearing impaired subjects and involve one or both ears. The filters are judged by percent correct sentence identification by the subjects. The correlation between the percent correct result and the total energy reaching the hearing threshold of hearing impaired listeners points to failure of the filter model to accomplish its goal of improved frequency selectivity. In conclusion, the filterbank developed in this project would benefit from an accurate model relating best frequency shift in the cochlea to total loss in hearing threshold due to OHC damage.
Designing a Device for the Continuous and Telemetric Measurement of Intraocular Pressure in Rats with Induced Glaucoma

Katherine Harihar, Justin Levy, Stephen Rocha

Glaucoma is the second leading cause of blindness in the world. The associated cost is $1.5 billion annually in the United States alone. Even in developed countries, half of those individuals with glaucoma remain undiagnosed. Upon diagnosis usually half of the individual's field of view has already been lost. Currently, glaucoma is detected by an elevated intraocular pressure (IOP), but the relationship with the retinal cell death is unknown. To better understand the role of intraocular pressure in glaucoma precise and continuous measurements must be taken and analyzed. Most experimentation is done in rats where an accurate model of the disease has been developed. However, when measuring pressure in rats devices designed for human measurement are used resulting in inaccurate, non-continuous data. The overall objective of this project is to aid glaucoma research by designing a device that can accurately and telemetrically measure intraocular pressure in rats that will not interfere with their daily activity. This device must record IOP throughout the rat's daily activities as well as over an entire month long period. Among considered devices, three sensors were chosen to accomplish this objective: a direct tube sensor, a strain gage sensor, and a capacitive sensor. The direct tube sensor consists of a micro tube inserted into the eye and attached to a small pressure sensor. This design was tested on enucleated lamb eyes by inputting pressure into the eye in 10mmHg increments and measuring the output of the sensor. Through testing, the device was calibrated and the pressure in the eye was then successfully related to the output of the designed sensor. The strain gage sensor is composed a micro strain gage placed on the surface of the eye with a small apparatus to apply pressure over the area. The surface properties of the eye were visualized to test the feasibility of this surface based sensor. The expansion of the eye is within the range measurable by the strain gage. The strain gage design was also tested in a wheatstone bridge configuration with the gage applied to an elastic surface. The racquetball used was pressurized in 10mmHg increments and resulting circuit output was amplified, filtered, and recorded. The data collected from this experiment was linear but cannot be properly analyzed until noise and drift can be eliminated during data acquisition. The capacitive sensor design consists of an implantable circuit with a pressure sensitive capacitor. This implanted circuit inductively coupled to an external circuit providing current. The capacitance is pressure dependent and will change the characteristic resonant frequency of the circuit. The resonant frequency can be correlated to the pressure measured by the variable capacitor in the eye. The circuit and resonance was modeled in Matlab. Two variable capacitors were constructed and tested in enucleated lamb eyes. Resonance peaks were observed for fixed capacitors but further experimentation must occur to categorize phase shift data in variable capacitors. Each device has progressed towards a working prototype. The future work has been outlined for each device to continue towards a functioning implantable sensor.
Design and Application of a System to Track Coupling Between Airways and Lung Tissue

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Airway constriction in asthmatics is much greater than in healthy subjects when exposed to lower doses of a smooth muscle contracting agent. After administration of a stimulating agent, healthy individuals can easily resolve the constriction with a deep inspiration (DI). In contrast, asthmatics cannot dilate their airways much with a DI. An emerging theory is that ASM in asthmatics becomes hyperreactive because of extended periods of reduced stretch. Previous studies have shown that preconditioning isolated ASM through tidal-like length oscillations causes it to be less stiff. The impact of pre-conditioning the lung and its effects on reactivity *in situ* has not yet been probed. The overall goal of this project was to design a system to track, in excised calf lungs, the airway response to airway constriction *in situ* and show how this response is modulated by dynamic stretching of ASM either before or after methacholine (Mch) was administered. A system was constructed to provide controlled ventilation with 8 Hz oscillations superimposed. Previously created voltage waveforms, which incorporated both 8 Hz oscillations and dynamic breathing, were sent to the pneumonic system where the desired pressure waveform was outputted to the lung. A Celesco transducer system measured the flow and pressure at three different locations. Airway resistance ($R_{aw}$) for 3 different protocols was tracked before and after administration of Mch. Since at 8 Hz the resistance of the lung is due purely to the airways a 4 Hz Butterworth high-pass filter was applied to extract the $R_{aw}$. Each protocol was tested on 4 excised calf lungs and during the protocol the Mch was administered using a nebulizer for 2 minutes during tidal breathing. The first protocol was used look at the impact of Mch without tidal breathing on $R_{aw}$ at 7cmH$_2$O and during a DI. The second protocol investigated the impact of tidal breathing on Mch response and on the response to a DI. The last protocol determined the impact of DIs directly before a Mch challenge on airway reactivity. We found that the average percent increase due to Mch in protocol 1 was 305.18% ± 333.84. Protocol 2 had an average of 230.12% ± 54.04 while protocol 3 had an average increase of 427.57% ± 142.42 in the resistance prior to a DI after stimulation. Protocol 2 and 3 were not significantly different when compared to protocol 1, indicating that neither the tidal breathing nor the DIs had an effect on the initial response to Mch. With regard to the minimum resistance seen with a DI, the values were the same before challenge and actually higher after Mch indicating that dynamic breathing and DIs further reduced the ability to bronchodilate. All of these results go against the predictions based on dynamic length oscillations. There are several possible explanations that deal with how the excised lung system differs from isolated ASM strips and isolated airways. The most likely focus has to do with the amplified impact of airway closures associated with the lack of surfactant *in situ*. The smaller level of surfactant causes there to be more surface tension within the lung. Therefore, with tidal breathing a larger amount of the lung is being ventilated with Mch causing more closures with the smaller airways. Subsequent DIs are then unable to open these closed airways in the same way they can dilate unclosed airways. In summary we have shown that the excised lung preparation significantly altered biological states that are not comparable to *in-vivo*.
Designing and building a switching system for the headstage of a rat

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Current studies of rat brains involving stimulating and measuring electrical signals from the hippocampus use separate implanted electrodes for each task. In order to minimize the number of implanted electrodes, the use of common electrodes for both stimulating and recording electrical signals is required. These electrodes are wired out of the brain to a headstage that has been mounted on top of the rat’s head. The headstage can be connected either to a recorder or a stimulator. A switching circuit is required to switch between recording and stimulating modes. Previous attempts at implementing switching circuits have been unable to prevent electrical noise from interfering with the recordings. The overall objective of this project was to design and construct a switching circuit that will eliminate electrical noise in recordings from the hippocampus. In order to eliminate electrical noise from the recordings, the wiring that connects the stimulator to the switch has been minimized to decrease the potential for noise entering the system through the wiring. A miniaturized printed circuit board (PCB) of the switching circuitry was designed and constructed in order to minimize the chances of electrical noise seeping into the system. The miniaturized PCB ensured that the circuitry was lightweight and capable of directly fitting on the headstage. The main implication of this research is that electrical signals can be stimulated into a rat’s brain and recorded using common electrodes, without the presence of electrical noise in the recordings.
Optimization of Coating and Surface Characterization of Novel Polymers and Proteins for Use on a Medical Device

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Despite the success of current angioplasty technology as a treatment for coronary artery disease, stents can fail to function due to thrombosis, an adverse reaction caused by the body’s inability to incorporate the foreign object. It is hypothesized that the use of biomaterials on the stent surface can promote endothelialization, thereby incorporating the stent in the coronary vessel with minimal foreign body response. While cellular assays are essential in evaluating the bioactive properties of various biomaterials, it is important to investigate the surface coating properties of these proteins and polymers in order to gain a better understanding of the materials as a whole. The investigation of coating properties involved the development of a protein coating procedure and the evaluation and selection of a proper protein assay for assessing the ability of various proteins to adsorb to stainless steel. Contact angle analysis was used to analyze trends in the hydrophobicity or wettability of protein and polymer surfaces. The main outcomes of this project included:

1) the development and establishment of an incubation coating method for the immobilization of protein biomaterials on stainless steel stents and disks, 2) the selection and development of a biotin assay for the assessment of surface bound proteins based on the trial and error evaluation of four protein assays, including the BCA and Bradford assays, and 3) observations of various proteins (confidential Proteins B, C, and D) using the Biotin Assay and of Polymers A and B and proteins using contact angle analysis. It was determined that Protein C has a greater affinity to stainless steel than Protein B. It was also determined by a biotin assay that a new coat method (confidential Coat Method P) may be more feasible and less wasteful for coating materials than incubation coating. Further studies need to be conducted to investigate this procedure. In summary, the development of methods for protein coating and biomaterial characterization will aid in the understanding and optimization of the coating properties and processes of several biomaterials. Additionally, this information will aid in assessing endothelial cell and platelet interactions with the biomaterial surfaces to help determine the materials best suited for improving the overall performance of various medical devices.
Isolation of Nucleic Acids using Electroosmotic Flow in a Thermoplastic Device

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Current techniques for DNA sample preparation are tedious and time-consuming requiring several pieces of laboratory equipment. The purpose of this study was to design a microfluidic platform capable of isolating nucleic acids using electroosmotic flow (EOF) to streamline DNA sample preparation techniques. This plastic chip can function as a disposable point-of-care sample preparation device for biological and diagnostic applications. The study was aimed at using EOF as the main mechanism to control the migration of a DNA sample through microfluidic channels. The use of EOF allows for a simple set-up to facilitate fluid flow in microchannels by applying an electric potential difference across the channels. The polymer used to fabricate the device was a medical grade cyclic olefin polymer, Zeonex 690R. The device channels were fabricated by wire-imprinting. The EOF of Zeonex 690R channels was characterized using the current-monitoring method. The native Zeonex substrate exhibited a mean electroosmotic flow mobility of $3.19 \times 10^{-4} \text{ cm}^2 \text{V}^{-1} \text{s}^{-1}$. Solid-phase extraction was utilized to isolate the DNA. The solid-phase consisted of a porous monolithic column embedded with silica particles formed by in situ UV photopolymerization. The channel walls were first photografted with a benzophenone initiated polymerization process which allowed for covalent attachment of the monolith to the channel walls. DNA binding to the silica particles facilitated the extraction of DNA from a chaotropic solution. Successful DNA extraction and purification was achieved using EOF. The purified DNA obtained from this process will be used in downstream applications on-chip, such as amplification by polymerase chain reaction (PCR) and DNA fingerprinting. It is demonstrated that this method produces PCR amplifiable DNA and the cyclic olefin device offers the benefits of low-cost sample preparation, disposability, and low volume consumption of samples and reagents.
Development of Vibrating Sandals to Enhance Sensorimotor Function
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Center for BioDynamics

Balance control depends, in part, on somatosensory feedback, using mechanoreceptors to detect changes in pressure on the soles of the feet. Recently, it has been shown that applying a subsensory level of mechanical noise to the soles of the feet can reduce postural sway and improve balance control during quiet standing. Here, we applied input noise during a dynamic balance activity, namely walking. We hypothesized that subsensory mechanical noise applied to the soles of the feet, via vibrating sandals, could reduce stride-to-stride variability in the gait cycle in healthy young and elderly subjects during walking. Five subjects (aged 19-21) were asked to wear a pair of custom-fit vibrating sandals and to complete a four-minute walk down a 200ft hallway. The 90% sensory threshold to a vibrotactile noise signal was determined for each foot during two-legged standing, one-legged standing and sitting for each subject. These noise amplitudes were then applied to the two-legged stance, one-legged stance and swing phases of the gait cycle respectively. Footswitches on the surface of each sandal provided feedback of the phases of the gait cycle. Four trials were performed, each containing two randomized stimulus conditions (a two-minute control (no noise) or noise interval followed by a two-minute noise or no noise interval, respectively). The mean of each stimulus condition was compared using the standard deviation and coefficient of variation of the stride-to-stride interval (heel strike to heel strike) of the gait cycle. When stimulation was applied to the soles of the feet, stride-to-stride variability decreased in each subject. Applying random mechanical vibration to the soles of the feet may improve balance control during daily activities, like walking.
The Brain Machine Interface: Using the Neural Code to Control an External Device
By: Matthew G Kersus.

Research in the field of neuroscience has enabled scientists to map the firing patterns of neurons in regions of mice brains that are affected by a specific stimulus. These changes can then be used to control an external device, such as a door opening. However, the current testing methods do not solely apply the desired stimulus, causing errors in the acquired signal. The current device used to expose the mouse to a dropping sensation also rotates and shakes the subject, stimulating neurons aside from those specifically linked to the drop. By eliminating or reducing these stimuli, the signal will contain less noise and be easier to analyze. An elevator was constructed which prevented the cage from rotating about the vertical axis, moving in the horizontal plane, and ending in a hard landing. The new elevator implemented a breaking mechanism if the proper change in firing rate is found. Angle aluminum supports constrain the movements of the cage as it falls, while casters will provide smooth movement up and down the metal. Using Plexon’s Neural Explorer program, the firing rate pattern was tracked during the drop. The mice were exposed to the dropping stimulus in both the original and the new elevator, and the neural responses were compared using Plexon’s Neural Explorer. The braking mechanism designed for the experiment did not provided sufficient force to stop the cage before it landed. The elevator itself provided a reduced time of exposure to the shake stimulus. This illustrates that the methods of constraint adequately prevented the elevator cage from shaking. Also, the difference in a select few neural channels supports the evidence that the memory formed in the hippocampus is formed by both the event and the context.
Mind Classifier: An automatic classifying algorithm for functional MRI activation maps

Dongwoo Hahn

Brain-computer interface (BCI) is a method that allows a person to control computers or electromechanical hardware without using the brain's normal output pathway of peripheral nerves and muscles. Most popular modality for BCI is electroencephalography (EEG) because EEG system is low-cost and portable. However, because of its superior spatial resolution and reasonable temporal resolution, functional magnetic resonance imaging (fMRI) based BCI systems may have many possible applications. In this project, fMRI was used for a brain signal acquisition modality. fMRI generates color-coded activation maps which reports regional brain activations. fMRI based BCI system classifies fMRI activation maps corresponding to different mental tasks and determines the user intent involved with the mental tasks. The previously developed fMRI BCI system required the manual intervention made by operators. It also had a limited number of available commands because different functional tasks produce highly similar activation maps. The goal of this project was to improve fMRI based BCI system by removing such limitations. Three healthy volunteers (21-35 years in age) were tested on 1.5- and 3-Tesla scanners with a T2* weighted gradient echo sequence with an in plane resolution of 3.75mm*3.75mm. Twelve 6mm axial slices and thirteen 5mm axial slices were taken from 1.5T and 3T scanner respectively. Six mental tasks: right hand motor imagery, left hand motor imagery, right foot motor imagery, mental calculation, internal word generation, and visual imagery, were selected based on the preliminary experiments. To increase the classification performance, Support Vector Machine (SVM) was utilized as a classifier. The region of interest was defined based on the activated regions which have overlapped above a pre-determined threshold in several runs of the same mental task. Such automated ROI definition algorithm removed the need of manual intervention. For tuned parameters, the system successfully recognized the performed mental task with above 90% accuracy for two subjects. The results exhibited satisfying accuracy even when the last 10 and 20 seconds data was removed, suggesting the command time can be further reduced. Using the same parameters, temporal encoding and decoding approach was tested to increase the number of commands. The system determined the temporal location of command generation by using Independent Component Analysis (ICA) and cross-correlation calculation between the extracted independent components and the hemodynamic response functions (HRFs). The system successfully predicted the temporal location of a given task with above 80% accuracy when 3 seconds inter-task-interval was given between six command generation periods. We expect that the developed design from this project can be successfully applied for the actual fMRI based BCI system, providing a control and communication solution for patients with severe neuromuscular disorder.
Analogue Brain Computer Interface Using fMRI
Paul Bower
Harvard Medical School and Brigham and Women’s Hospital

The long-term goal of this project is to assist people with motor impairments in the course of everyday life via a brain computer interface (BCI) that allows for the manipulation of a computer cursor, using only thoughts as commands to the computer. Previous research on BCIs has largely used the electroencephalogram (EEG), and these BCIs have been proven robust in terms of word or letter selection, or in allowing for 1-dimensional cursor control. However, past BCI methods have not been able to achieve 2-D cursor control, and 1-D control calls for the manipulation of electrical brain brain waves by the user, an abstract phenomenon to most, and not the execution of thought commands, where a person is asked to think about executing a specific task. The specific purpose of this research was the development a BCI that uses real time functional magnetic resonance imaging (fMRI) as a mediator between the brain and the computer. This method allows for 2-D cursor control using thought tasks as directional commands, as fMRI techniques have been shown to discern thoughts from spatial and temporal analysis of the hemodynamic response in the brain. The BCI was quickly calibrated to the brain of the user via two 2.5 minute calibration runs where a user executes two thought tasks, respectively, that were used as commands to the BCI. Regions of interest (ROIs) were chosen using a novel tool allowing for an automated search of best ROIs and quickly acquired statistical and temporal analysis of brain activation from the calibration runs. During the use of the BCI, the subject executed the thought commands, T2* weighted MR image data, used to detect hemodynamic response in the brain resulting from neural activation, was transferred to a processing station where the MR activity from the two chosen ROIs was measured. The activation from the two regions generated the two directional components of a position vector assigned to a cursor visible to the subject on a 2-D plane via scaling of the input MR signal from the ROIs, and the user was able to manipulate the position of the cursor by executing none, one, or both thought commands at a time. The cursor position was updated at a rate of 0.5 Hz using developed real time fMRI techniques to transfer the MR data used to generate the cursor position. Thus, a BCI has been developed allowing for a user to move along the corners of a square with a cursor through the execution of one or two command tasks corresponding to the desired direction of movement, with the cursor position output providing feedback to the user as a near analogue, real time signal. Such a system provides a proof of principle that thought tasks can be used as commands to a cursor that is manipulated by a user. Future work with this principle might include the incorporation of EEG or NIRS technologies as a substitute for fMRI as the mediator between brain and computer during the use of this BCI, and the use such portable and cheap technologies would allow for such a BCI to be commercialized for use by those with motor limitations and others.
SESSION IIA:
Computational Modeling in Bioengineering
Models of Dolphin Hearing

Garth Mashmann

Sonar and shipping noise are two examples of manmade sounds which may adversely affect marine mammals. This effect may range from a temporary loss of hearing, or echolocation abilities, to death. Masking, when a wanted sound goes undetected because of the presence of an unwanted sound may contribute to this effect. The goal of this project was to determine what signal to noise ratio, if any, masks the echolocation signals of marine mammals. Both shipping noise and sonar SNRs were investigated. The effects of shipping noise, 3 kHz and 10 kHz signals on bottlenose dolphin and harbor porpoise echolocation signals was analyzed using EarLab, a software program developed at the Hearing Research Center at Boston University. EarLab is a software environment designed for the study of auditory pathways. A model of the human auditory system was adapted for the study of the crustacean auditory system. Sample echolocation signals for both the bottlenose dolphin and the harbor porpoise were created using MATLAB. An echolocation signal consists of two echolocation clicks. These clicks are short tone bursts. These echolocation signals are a model of a sound emitted by a dolphin which returns at a later date as the reflection from a target. Sonar signals were created as sinusoids with frequencies of 3 kHz and 10 kHz. Shipping noise was modeled as white noise. The echolocation signal was written to WAVE files. Then the signals were summed with sonar and shipping noise at different signal-to-noise ratios (SNRs) and written to WAVE files. These WAVE files were then processed using the EarLab software. The EarLab software provided four different graphical results. Each of these corresponds to a different point in the auditory pathway: the Basilar Membrane, the Inner Hair Cell, the Auditory Nerve (AN) and the Inferior Colliculus (IC). Echo detection was determined by examining the output from the IC. The masking threshold level was determined by comparing the output from simulations with noise to those without. This project showed that the masking threshold SNR was lower for a 3 kHz sinusoid than it was for a 10 kHz sinusoid. It also showed that the masking threshold SNR for a random noise signal was greater than either of the sinusoid masking threshold SNRs. Additionally the masking threshold SNR increases slightly as the time delay between the two echolocation clicks increases. In conclusion, sinusoidal maskers have lower masking threshold SNRs than a random noise signal and lower frequency sinusoids have lower masking threshold SNRs than higher frequency sinusoids.
The zebra finch is a good model species for the study of complex sound learning and perception. Zebra finch song is spectrotemporally complex, feature-rich, and has similar acoustic properties to human speech. Field L, the avian analogue of auditory cortex, is the area of the brain in which songs are analyzed and processed. Previous studies have quantified the responses of single auditory neurons to sound using Spectro-Temporal Receptive Fields (STRFs). Though a collection of these STRFs exist, they have not been systematically modeled and characterized to show the variety of feature encoding that field L possesses. Knowledge of the diversity of field L could impact studies into neural coding, speech learning, and speech perception. Therefore, this project created models of STRFs, validated these models, used these models to generate firing-rate responses to songs, and characterized these responses visually into the so-called population response.

Modeling was accomplished by a least-squares curve fitting of experimentally characterized STRFs to Gabor Functions. These have been previously shown to model neural data well. Firing rate generation was accomplished by the convolution of model responses to a series of bird songs. EarLab, a software suite specializing in modeling and visualization of the auditory system, was used to visualize the population response.

The visualizations of the population response revealed the representation of spectrotemporally complex sound by neural population in field L.
Design and Implementation of a Gerbil Song Playback System

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Auditory Neurophysiology Laboratory

Understanding how communication patterns in the brain are processed involves direct measurement of neural responses using penetrating electrodes. Humans, therefore cannot be used as subjects and animal models are needed to describe these neural mechanisms. Since Mongolian gerbils are known to have excellent low frequency hearing and communicate using ultrasonic vocalizations, they are an ideal animal model. Previous research involving gerbil vocalizations have been predominantly qualitative behavioral studies. There is a lack of quantitative data needed for more precise characterizations of neural processing of ultrasonic vocalizations. A new approach to studying the gerbil auditory system is to use species-specific vocalizations. The first step toward this new quantitative approach was taken by characterizing recorded vocalizations in the context of communication. Thermal stress calls, which were induced by isolating gerbil pups in room temperature, were characterized by periodic frequency modulated (FM) sweeps (3/sec). Tactile stress calls are much more spectrally complex, containing features such as harmonics and noise bursts. Previously recorded gerbil vocalizations were analyzed for spectral and temporal patterns. A gerbil song playback system of these calls was created to be used in future behavioral and electrophysiological experiments. A graphical user interface (GUI) was created to make playback more efficient and user friendly. The playback system was interfaced with a system capable of ultrasonic playback of acoustic stimuli to live gerbils, which invokes neural responses that can be recorded using electrodes. An interface was also created with the auditory nerve (AN) filter bank module, which simulates spike trains to be inputted into the computational model of the dorsal cochlear nucleus (DCN). The DCN model predicts behavior of real neurons in response to acoustic stimuli. Using species-specific inputs to the auditory system will help to provide a more accurate view of neural processing of communication sounds in the gerbil, which leads to a better understanding of how the human brain processes speech.
Electrical stimulation of the auditory nerve with a cochlear implant has been successful at restoring hearing to a functional level for many deaf patients. However, there is great variability in the effectiveness of cochlear implants amongst patients. Clinical experiments that aim to improve cochlear implants are difficult and time consuming to perform, and will involve system parameters that cannot be varied easily. For example, the effects of changing the encoding strategy of a speech processor may not be observed immediately because the physiological system has an adaptation period. The purpose of this project was to use a modular modeling platform that will aid in innovating current electrical stimulation strategies used in cochlear implants. Specifically this project used Earlab, a computational model of the auditory system. In Earlab one can easily manipulate the parameters that effect neural coding on the auditory nerve caused by electrical stimulation. One stimulation strategy is the continuous interleaved sampling (CIS). In the CIS strategy, pulse trains are modulated with extracted envelopes of band-passed filtered signals of the input waveform to generate electrode inputs for each envelope. The pulses on different electrodes are applied in an interleaving pattern such that no two electrodes are stimulated simultaneously. Our modeling explored the benefit of modifying the CIS strategy with a desynchronizing pulse train (DPT) that might improve the overall quality of the sound processor. A DPT is a high frequency, constant amplitude pulse stimulus that causes the population of auditory nerve fibers to fire spontaneously in a desynchronizing fashion. Therefore, the population of auditory nerve neurons will respond more like a healthy ear with spontaneous activity. In Earlab we manipulated the pulse rate and modulation depth of the CIS-DPT signal to observe the effects neural coding on the auditory nerve and compare our data with physiological data in order to confirm our model. We observed greater adaptation and desynchronization on the auditory nerve when we increase the pulse rate from 1200pps to 4800pps. We varied the modulation depth from 0-10% for a 200Hz and 400Hz sinusoid modulated with a 1200pps and 4800pps pulse train. As the modulation depth increases we expect the responses to become more precisely phase locked to the sinusoid. Finally, we tested our CIS-DPT sound processor with acoustic click trains with click rates of 50 and 800cps. As the click rate increases, the interaction of each preceding click causes an interference with each click in the electrical stimulus and hence a non-linear trend of the Root Mean Square amplitude of each electrode is observed. In summary, we will be able to identify the effectiveness of the DPT stimulus and confirm the Earlab model with physiological data comparisons. Indeed, computational modeling is the most efficient method for testing new stimulation strategies.
Modeling Synaptic Plasticity

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Synaptic plasticity is the process by which the brain adapts to patterned activity among synaptically connected neurons. The adaptation is performed by modifying the weights of the neuron connectivity. Synaptic plasticity is critically important in cognitive functions such as learning and memory. Models have been created to understand the underlying mechanisms responsible for spike timing-dependant plasticity (STDP), a recently discovered form of long-term plasticity. A mechanistic model by Acker accounts for experimental STDP data well, though we were interested in determining whether its performance can be improved. The overall objective of this project was to improve Acker’s computational model of STDP in order to better understand the underlying cellular mechanisms. Such improvement was first done by optimizing the parameters of the Acker model to minimize the root mean squared error (RMSE) between the computational and experimental data. Only those parameters that we were not fully confident in, or that did not have established values in literature, were optimized. Specifically, an algorithm was developed, incorporating the fminsearch MATLAB simplex minimization function, to optimize six parameters. A new parameter was integrated into the computational model so that it no longer requires that all synaptic receptors in the model exist in equal quantities. A competitor to Acker’s model, the Dual-Suppression Pathway (DSP) model, was also developed in MATLAB and compared to the optimized Acker model. Existing literature suggested that the cellular pathways implemented by the Acker model are superior those of the DSP model, so we have tested this conjecture. With verification of the Acker models’ superiority, and improved performance via parameter optimization and modification of existing cellular pathway computations, the focus then shifted to developing an interactive software tool to execute the model. We now possess an improved mechanistic model that can be used to reproduce experimental synaptic plasticity data with high accuracy, enabling us to further our understanding of synaptic plasticity and the cognitive functions that rely upon it.
James Wai

A dynamic polymer chain model used to study the rheological behavior of living cells

Abstract

Experiments have shown that the rheological behavior of adherent cells follow a power-law behavior, whereby the power-law exponent decreases with increasing prestress (pre-existing stress in the cytoskeleton matrix). However, the mechanism governing this relationship remains largely unknown. While this power-law behavior has been associated with network properties of actin gels or glass transition (1), there is no physical basis to these theories and no explanation for the dependence on prestress. A two dimensional polymer chain model of an actin biopolymer, used by Stamenovic et al(2), demonstrated that the rheological properties of the CSK, and it’s dependence on prestress, may originate from the effects of prestress on the dynamics of polymer chains within the CSK. Preliminary results of the model shows creep that bears striking resemblance to experimental observations- creep of model follows a power law behavior with decreasing power-law exponent and increasing prestress. However, the model is not physiologically accurate. Its creep behavior is dependent on nonlinear bond deformation. Actin biopolymers are rigid and do not deform. The aim of this project will be to expand on the model by considering more physiologically realistic parameters, by moving nonlinearity from bonds to the joints, by changing model constraints such as tube diameter, and to investigate the creep behavior of individual chain segments and its contribution to the overall creep behavior. The results of this project suggest that nonlinear elasticity is critical for the existence of creep behavior and alpha dependence. More importantly, this model suggests, that the creep behavior of the entire CSK can be understood by the dynamics of a single polymer chain.
PHARMACOKINETIC MODELING AND THE OTOTOXIC EFFECTS OF AMINOGLYCOSIDE ANTIBIOTICS

Ajan Patel

Aminoglycosides are currently the world’s most commonly used antibiotics. They are highly effective and they have low production costs. However, they also cause ototoxic effects, which can result in apoptosis of hair cells and can even cause hearing loss. Hearing loss currently affects more than 24 million Americans with the leading cause of hearing loss being cochlear hair cell damage. Since gentamicin (and other aminoglycosides) have destructive effects on hair cells, the ability to predict the extent of damage done to hair cells and the severity of hearing loss one can expect can be very beneficial. The overall objective of this project is to develop a computational model to predict the effects of certain aminoglycoside antibiotics (primarily gentamicin) in the context of how they may impair hearing. A pharmacokinetic model accounts for the method of drug delivery, drug clearance to the systemic compartments, and drug distribution throughout the cochlear compartments. The drug administration aspect of this model uses dosage type, dosage amount, duration of use, and the absorption, elimination, and diffusion coefficients to account for an intravenous infusion (and bolus) application, an intramuscular bolus application, and a round window treatment. The model also predicts the amount of drug that reaches the inner-ear (from the systemic compartment) as well as the amount that permeates throughout the cochlear compartments. Another aspect of this project structurally models the cochlea using important anatomical and physiological parameters, such as the cochlear length, surface area, volume and cross-sectional area for each subdivision, and the rate of gentamicin transfer among compartments. The current model aims to generate an output that would allow the drug concentration in different cochlear compartments to be easily compared. By ensuring that the cochlea kept its spiral structure (the cochlea was essentially divided such that each compartment had an equal number of subsections), it is possible to quickly compare gentamicin concentrations at any location and time for any compartment within the cochlea. In conclusion, the developed model is able to predict the concentration of gentamicin throughout the cochlear compartments for multiple drug administration methods, which could eventually be used to find a combination of drugs that could prevent, reduce, or eliminate the loss of hearing caused by these ototoxic effects.
Application of Personalized Airway Trees in Multi Scale Lung Models to Probe Structure-Function Relations in Asthmatics

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The human lungs are a complex system of bifurcating airways. Diseases affecting the airways result in the loss of lung function. Previous computational modeling work by Tgavalekos et al invoked a concept called Image-Function Modeling (IFM). The IFM approach uses a generic three-dimensional lung model and ventilation images (MRI or PET) to predict which airways in the model contribute to the degradation of lung function. The IFM method would be more robust if the 3D lung model was personalized for each subject for which it predicts airway closures. The overall goal of this project is to design and apply software that generates patient specific airway tree models. To obtain patient specific models, Hyperpolarized Helium MRI Imaging (Hyp. 3He MRI) of the lungs was used (about 13 coronal images that are 256 by 256 pixels) to extract data boundaries of a 3D lung for an individual subject. However, divisions between individual lung lobes (fissures) are not visible. Image registration of cryosection images of a frozen cadaver (Visible Human Data (VHD), US National Library of Medicine) was performed to map the fissure locations. The lung fissure locations are visible on the high resolution cryosection images (2048 by 1216 pixels).

Collaborative efforts with Betke et al in the Computer Science department at Boston University have implemented the registration procedures necessary for mapping fissure locations from the VHD images into the MRI images. The algorithm generates an airway tree into the personalized lung space. With these trees, various constriction patterns (means and standard deviations ranging from 0 to 60 percent with 20 percent increments) were imposed, and we predicted lung resistance and elastance versus frequency. Prediction of resistance and elastance from our personalized airway trees show that trees are consistent with but clearly distinct from the original Tawhai model. The distribution of airways in the model was skewed. Sensitivity tests revealed that the skewed result cannot be avoided when airway termination parameters are varied. These findings suggest that personalized models may prove critical improvements to pattern matching simulations with real oscillatory mechanics and imaging. Future studies need to establish if predicting ventilation and mechanics for an individual will be distinct from the personalized approach.
Asthma is a lung disease in which airway constriction is hyper-responsive to a stimulus. However, it remains unknown as to which airways constrict the most in a given individual. Advances in imaging and modeling of the lung allow us to probe the structure-function mechanisms that contribute to ventilation and mechanical dysfunction during asthma. The goal of this project was to interface an anatomically consistent 3D model of an airway tree with Hyperpolarized (Hyp) $^3$He magnetic resonance images (MRI) via a new paradigm called Image Functional Modeling (IFM) so as to identify the airway conditions responsible for reduced lung function in asthma on a personalized basis. Enhancements of previous approaches included incorporating a more anatomically correct upper airway and developing methods to compare real and predicted ventilation distributions in 3D. Imaging and mechanical data was acquired for 3 healthy and 3 asthmatic subjects pre and post bronchial provocation. Image processing was done to align the images at each condition, remove image artifacts, and threshold the image to eliminate noise without losing lung information. These images then showed 3D locations of ventilation which were then spatially mapped in the model. A new anatomically correct upper airway model was placed in front of the airway tree. Following bronchoprovocation the terminal airways which are responsible for major ventilation defects were identified based on the imaging data. A family of airway constriction patterns which accurately matched mechanical data was found and ventilation images were predicted for each pattern. These images were then compared to real ventilation images. Visual comparisons were done by rescaling and smoothing the predicted ventilation to make it the same scale and resolution as the real image. Statistical comparisons were done by plotting the cumulative density function (CDF) of ventilation per unit volume in 3D for both the real and predicted values. Visual comparisons revealed much more heterogeneity in real data. Specifically there is increased ventilation toward the back of the lung in real images, which also displays areas with much larger amounts of ventilation than ever predicted in the model. Statistical comparisons indicate that lowering the degree of mean constriction applied to the ventilation defects more accurately characterizes poorly ventilating units in all healthy subjects without sacrificing a mechanical fit. Results indicate there is a fairly wide set of airway conditions that can explain both sets of data simultaneously. Also, the constriction leading to the severely defected areas based on imaging data do not necessarily require closure or near closure but approximately a 70% reduction in original diameters. By using ventilation data we showed that the heterogeneity of airway constriction is likely to be slightly larger then that what we would have predicted based on mechanical data alone. In summary we have substantially advanced the capacity to take quantitative information predicted by 3D models and synthesize them with both imaging data related to ventilation distribution and mechanical data related to lung properties.
SESSION IIB:
Biomedical Imaging
MRI Phantom for Quantitative Diffusion MRI: 
A Study in Materials with Adjustable Diffusion Coefficients

Ryan Irving

Conventional spin echo diffusion imaging techniques provide poor temporal resolution and are prone to imaging artifacts. Each scan take hundreds of milliseconds to complete, in which time bulk motion of the imaging subject can greatly distort the image. A more rapid diffusion imaging pulse sequence would allow for higher quality images to be made. Furthermore, if diffusion images could be generated from any scan that provides quantitative longitudinal relaxation data, then a diffusion map could be generated without the use of a specialized scan. The goals of this project were 1) to design, construct and test a phantom for quantitative diffusion MRI with aqueous diffusion coefficients over the range of $2 \times 10^{-3}$ mm$^2$/s to $2 \times 10^{-5}$ mm$^2$/s, 2) to compare a new correlation time diffusion imaging method (BPP) to the standard pulse field gradient (PFG) diffusion measurement technique, 3) to observe the quantitative data available in MRI scans that used a reduced refocusing (RF) angle. Phantoms featured sucrose and guar gum fiber solutions along with a small collection of materials used in published MR studies. Each phantom was scanned at 1.5T with a PFG sequence (b-values of 0, 1000 and 2000) and a mix-turbo spin echo (mix-TSE) pulse sequences (RF = 110°, 130°, 150°, 180°) using a Phillips MR scanner. The BPP diffusion maps were generated from quantitative data generated from the mix-TSE scan using software developed in the MATHCAD programming environment. The BPP diffusion maps are then compared to the PFG maps. Reduced RF scans were evaluated by direct comparison of $T_1$, $T_2$ and PD maps to corresponding maps generated from RF 180° data. In sucrose solutions are made to cover a diffusion coefficient range spanning from $2.2 \times 10^{-3}$ mm$^2$/s to $1.74 \times 10^{-5}$ mm$^2$/s. In both sucrose and reference materials there is nearly 1:1 agreement between the BPP and PFG diffusion measurement methods. Fiber solutions always yield lower BPP diffusion measurements than PFG measurements. Reduced RF scans produce very similar quantitative MR data in RF 130° and RF 150° scans without large reductions in signal to noise ratio (SNR) or noticeable depreciation in image quality. RF 110° scans have much lower SNR in $T_2$ maps and provide poorer image quality than higher RF scans. Sucrose and guar gum fiber solutions with reference materials cover a wide range of MR parameters in aqueous solutions and pure materials, including longitudinal (spin-lattice, $T_1$) relaxation time and transverse (spin-spin, $T_2$) relaxation time as well as diffusion coefficients. Proton density (PD) is nearly constant in all phantom materials, however. BPP and PFG data agreement in phantom experiments suggest that BPP should be further tested in more complex systems more closely resembling tissue. RF 130° scans offer the greatest radiation exposure reduction with minimal impact on image quality, to further test the impacts of RF reduction further experiments should be conducted in more complex systems.
A Multimodal Data-Analysis Package for Diffusion Weighted MRI

Sahil Jain

Diffusion Tensor Imaging (DTI) is a fairly new Magnetic Resonance Imaging technique which models the anisotropic diffusion (i.e. random motion flux in one direction) of water molecules in tissue. High measure of anisotropic diffusion has been correlated with high probability of axonal white matter tracts and thus, DTI is extensively used in the field of Neuroscience & Medical Imaging to study nerve fiber connectivity. One of the most challenging current problems in DTI is the need for a comprehensive data analysis package for high-resolution diffusion weighted magnetic resonance (MR) data, from which DTI is calculated. Such a package must meet non-invasive fiber tracking and intensive computational needs of scientists. It should also integrate multi-parametric MR data to aid multimodal complex registration, clustering and custom-algorithm design. The overall objective of this project was to develop a comprehensive and multimodal DTI data analysis package to meet this challenge. In contrast to using traditional Math packages like Matlab which have non-compilable script based programming models, we proposed a binary Windows based platform which would support diversified data formats like Dicom, Philips PAR/REC and SPM Analyze. It was optimized to handle three and four dimensional matrix computations along with image processing and algorithm design. Our approach was to design an application kernel based on the Microsoft .NET Platform which could automatically handle issues of memory management, CPU time prioritization and thread queues. Low level image processing was also implemented to allow application of filters needed to improve and optimize data quality. The visualization routines involved parallel plotting and real-time display of multiple modalities: Anatomy, DTI, functional MRI and Perfusion. Additionally, we compiled the software abstract class libraries which made the package scalable and the code snippets reusable. The software was bundled with integrated help, documentation of libraries and compiled binaries for 32-bit and 64-bit x86 platforms. Real time processing results during testing showed an increase in productivity and quality by upto 50%. In summary, we were able to resolve computational and investigatory bottle-necks in DTI processing and create a scalable and robust platform which could serve as the first stage of pre-processing for various types of MR data.
Adaptation of a Two-Photon Fluorescence Microscope for Targeted Excitation and Photobleaching

Jason Taclas

This project involves two-photon fluorescence microscopes in the Boston University Biomicroscopy lab. A two-photon fluorescence microscope is different from other scanning laser microscopes in that fluorescent molecules that would normally require a photon of visible or ultraviolet light to fluoresce are excited by simultaneously absorbing two photons of infrared wavelength. The low probability of a two-photon absorption event restricts excitation to a small focal volume, allowing 3-D spatial resolution. If exposed to too much light, a fluorescent molecule will photobleach (lose its ability to fluoresce). Another form of excitation, uncaging, involves removing a photoreactive inhibitor group. These phenomena can be used along with the small excitation volume to perform targeted excitation techniques such as fluorescence loss in photobleaching (FLIP) and fluorescence recovery after photobleaching (FRAP), and uncaging. The goal of this project was to produce a software module capable of targeted excitation experiments. These techniques depend on modulation of the laser intensity over regions of interest (ROI) within a sample. In addition to the Biomicroscopy lab’s interest in these techniques, the Neuronal Dynamics lab group is interested in performing uncaging experiments for targeted release of glutamate in rat brain slices, and the Visual Information Processing lab is interested in performing FLIP experiments to determine connectivity of ganglion cells in rat and salamander retinas. In order to perform these experiments while producing images in real time, the microscope control computer needs to affect the laser intensity within the ROIs. In order to produce the appropriate signals a new data acquisition (DAQ) card was installed on the microscope control computer. This project developed software modules written in LabVIEW to create images using the driver for the new DAQ card, and perform targeted excitation experiments. The imaging modules developed in this project were tested first on known signals through a terminal box, and then using the microscope to generate images of fluorescence-labeled pollen samples. In order to test the targeted excitation, a fluorescent test slide was imaged. The ROIs corresponded to areas in the sample to which higher laser intensity was to be applied. The resulting images confirm that the intensity changes occurred in the selected regions of interest. Integration of the software modules produced in this project into other LabVIEW microscopy programs will enable these microscopes to perform targeted excitation techniques.
Real-Time Automated Segmentation of High-Quality CT images using Dual-Space Clustering Algorithm
Dhruv Dhanraj Bahl

With the increasing success of interventional radiology, the need for non-invasive diagnostic procedures requires the development of accurate statistical models. Current post-imaging diagnostic techniques for high resolution Computerized Tomography (CT) scans, known as the Gold Standard, are highly qualitative and provide grounds for inaccurate diagnosis. Traditional techniques for quantitative image analysis require manual contour tracing to segment CT data sets through human intervention. The proposed study intends to refine an existing image segmentation algorithm called Dual-Space Clustering (DSC) Segmentation to improve accuracy and efficiency. The secondary aim is to produce an accurate statistical model for predicting steatosis, i.e. fat infiltration in the liver, by contrasting the CT numbers of the liver and the spleen. The segmentation process is accelerated by restructuring the existing algorithm, which is scripted in MathCad Version 2001i. CT data sets are three-dimensional (3D) sets consisting of slices, where each slice is composed of a square matrix of 512 pixels. Masks were employed to (a) restrict the 3D data sets to slices containing target region; (b) remove generous segmentations by localizing target area; and (c) restricting segmentation function to target pixels only. All volume within the 3D data set and without the target area is rendered a null CT value automatically. The mean time for manual segmentation was 23.0 +/- 5 minutes. The mean time for segmentation using the DSC was 14.0 +/- 2 minutes. The masking and restructuring allowed us to reduce the mean time by a factor of 6. In conclusion, we will be able to process CT data sets to obtain quantitative CT values for various parenchyma(s). This will allow us to create accurate statistical diagnostic models that chart physiological conditions by contrasting normalized CT numbers.
Time Course Measurements and Characterization of Various Brain Tumor Cell Lines in Mice Models using MRI

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Glioblastoma multiforme (GBM) is the most common and most aggressive of the primary brain tumors, tumors which originate in the brain. Medulloblastoma (MB) is highly malignant, and one of the most common gliomas in the pediatric population. The standard treatment of both GBM and MB has remained essentially unchanged for many years. Standard treatment includes surgical resection, radiation, and chemotherapy. Clearly, this is an extremely debilitating process for the patient, which in the case of brain tumors such as GBM and MB, has not extended survival substantially. As a consequence of this lack of major progress, the development of anti-angiogenic therapeutics has come to the forefront of brain tumor research. Angiogenesis, the physiological process of blood vessel formation, has been clearly linked to tumor growth. By utilizing anti-angiogenic drugs, blood vessels which would provide sustenance to the tumor are prevented from developing, thereby precluding tumor growth. The objectives of this project are: (1) to develop a baseline growth trend for both GBM and MB using MRI, (2) to test various therapeutics on both tumor types, also using MRI, and (3) to utilize a new Diffusion MRI modality in order to examine diffusion within GBM. In order to obtain tumor data for both control and treated subjects, as well as for diffusion, human tumor cells were injected into the left frontal lobe of test mice. Following a tumor growth incubation period, MRI scanning began. Scans were taken on high resolution (every two days) until the tumor grew to approximately 80% of the total brain volume. After scanning was complete, the images were analyzed using computer software and volume measurements were computed. By comparing control subject growth trends to treated subject growth trends, drug efficacy was evaluated. Additionally, by also investigating diffusion within GBM tumors, insight into the role of angiogenesis during different stages of tumor growth was explored. Ideally, this project will further GBM and MB curative research by testing the effects of various anti-angiogenic therapeutics. In time, research such as this will hopefully lead to a less debilitating and more successful brain tumor treatment method.
Brain Tissue Characterization using T2 Biexponential Decay in
Glioblastoma Multiforme Tumor Mouse Model

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Glioblastoma Multiforme (GBM), the most common and malignant tumor
that mainly grows in the central nervous system, is difficult to treat under
conventional methods because neither the cause nor the treatment of this tumor
has been fully identified. Due to the failure of a number of treatments including
radiation, chemotherapy and surgical resection, this project targets the
quantitative analysis of the GBM tumor throughout Magnetic Resonance Imaging
(MRI) techniques. When MR signal decays over T2 relaxation time in the white
matter of the brain, two components of T2 values, fast and slow components are
considered, which results in biexponential decay of the signal intensity over the
given T2 relaxation period. The overall objective of this project is to analyze
biexponential decay behaviors of MR signal over T2 relaxation time within the
tumor regions. A total of 10 mice were injected with GBM tumor cells, and the
image of the brain with the tumor was scanned every 2 day starting from 7 days
to 23 days from the tumor injection. Meanwhile, an algorithm to measure T2
biexponential decay behavior of the tumor was designed to which the image
scans of each individual was applied. The generation of image scans into the
algorithm enabled determination of amplitudes and decay rates of the
biexponential decay equation. The change of constants with respect to
increasing days from the tumor injection was analyzed in order to investigate
periodical change of the GBM tumor. The change of constants within the core,
outer and border of the tumor regions was studied in order to investigate regional
change of the GBM tumor. For a periodical change, the variance of the constants
in the tumor tissues to those of the normal tissues enlarges as time from the
tumor injection increases. For a regional change, the variance of the constants in
the tumor tissues to those of the normal tissues increases as the region moves
from the border, outer and core of the tumor. The both results signify one
important feature about the T2 biexponential decay constants of the GBM tumor:
the more the tissue retains the characteristics of GBM tumor, the larger the
variance of the constant is yielded from that of the normal tissue. By measuring
the variance of the T2 biexponential decay constants to those of the normal
tissue, the relative extent to which the tumor is developed can be identified. The
results of this project provide with the quantitative characteristics of the GBM
tumor tissues by revealing the relationship of the T2 biexponential decay
constants.
Establishing Quantitative Reference Values for the Diffusion Coefficient in the Liver and the Spleen: A Study of 22 Healthy Subjects

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Diffusion coefficient ($D$) measurements have been used successfully as a diagnostic tool in the area of brain imaging, specifically for the diagnosis of demyelinating disorders, intracranial infections and ischaemic stroke. The use of diffusion coefficient measurements as a diagnostic tool for abdominal magnetic resonance images (MRI) has been less successful due to extreme sensitivity of the images to motion artifacts. This study proposed a quantitative technique for calculating the volumetric distribution of the diffusion coefficient in the liver and the spleen using a respiratory triggered mixed-turbo spin echo pulse sequence and adapting a mathematical algorithm to map the distribution of the diffusion coefficient in the organs of the abdomen. The study further aimed to use this quantitative technique, which relies on the measurements of proton density (PD) and spin-lattice relaxation time ($T_1$) to calculate $D$, to create a reference of diffusion values in the liver and the spleen of healthy subjects which do not rely on b-factors chosen. By using a technique that does not rely on pulsed-field gradients, the images acquired are much less vulnerable to motion artifacts due to gross patient motion, peristalsis, and respiration. The results of this study allow for the correlation of the diffusion coefficient to the intra-abdominal fat fraction of each subject and a comparison with the same diffusion coefficient measurements in subjects with known pathologies. The power of this study lies in the creation of diffusion coefficient reference values $0.364\pm0.048 \times 10^{-3} \ mm^2 / sec$ for the liver and $0.447\pm0.074 \times 10^{-3} \ mm^2 / sec$ for the spleen which can be used to compare with subjects with diffuse hepatic lesions. A quantitative technique has thus been established for the mapping of the diffusion coefficient in abdominal organs that will allow for future research to focus on quantitatively establishing diffusion coefficient reference values for known hepatic lesions (hepatocellular carcinomas (HCC), fatty liver, cirrhosis, etc). The major implication of this study is its potential use as a diagnostic tool for diffuse hepatic lesions in abdominal MRI.
Quantitative MRI of Human Parotid Glands
Using Dual-Space Clustering Segmentation:
T1 & T2 Intra-glandular Analysis of 21 Patients

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Current medical technologies allow doctors to discern healthy tissue from diseased tissue with limited accuracy; assessment can be invasive and time-prohibitive. Developments in medical imaging have significantly enhanced the way diseases are diagnosed; yet, conventional magnetic resonance imaging (MRI) techniques remain predominantly qualitative. There is no widely accepted method available that provides information as absolute quantities free from experimental conditions or subjective bias. The purpose of this research was to study quantitative MRI (Q-MRI) of the parotid gland using mixed turbo spin-echo (mixed-TSE) pulse sequence and dual-space clustering (DSC) segmentation in order to quantify parotid fat content as a function of age. This would serve as the basis for future quantification of parotid gland pathogenesis.

MRI was performed using the mixed-TSE pulse sequence (80 contiguous slices, 0.9x0.9x2.5 mm³ voxel) in 21 subjects (healthy, n = 19; HIV, n = 1, Radiation therapy, n=1). 42 parotid glands (ages: 23 to 87 years (mean, 43.2), 8 male and 13 female). Mixed-TSE directly-acquired images were used to generate self-coregistered T1, T2, and diffusion Q-MRI maps, which were input to a sequential DSC segmentation algorithm. This algorithm produced segments of the bilateral parotid glands. Then, spectra of T1, T2 and diffusion were analyzed.

There was no significant difference in Q-MRI spectra between the right and left parotid glands in the same subject. Identifiable spectral features for the parenchymal and fatty tissues were identified in T1 and T2 spectra and used to calculate volume of the fat and parenchyma. No significant difference was seen in the volume measurement derived from T1 and T2 spectra. Fatty tissue showed increase in volume with aging, while the parenchymal tissue decreased with aging. However, T1 and T2 measurements of the parenchymal and fatty tissues were approximately constant over the age range studied. Slightly increased diffusion was noted with aging.

QMRI of the parotid gland using mixed-TSE and DSC segmentation algorithm was performed. QMRI spectra provided volume of parenchymal and fatty tissues of the gland as well as their T1, T2 and diffusion measurements separately. Age effect was noted in the gland; fat increases with aging. T1 and T2 measurement of the parenchyma and fat were approximately constant. This technique allows quantitative analysis of the entire volume of the parotid gland and may be helpful to diagnose sub-clinical diffuse parenchymal disease of the parotid gland.
A Study on Dating the Brain with Quantitative MRI Techniques

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It would be useful in many clinical cases to be able to assess the age on any given brain independent of the actual age of the person. If these two ages differ, this difference may correspond to a developmental disability (in children) or a degenerative condition like Alzheimer's disease (in the elderly). Currently no baseline models or brain dating systems exist however. The goals of this project are to establish models of aging based on quantitative MRI (Q-MRI) parameters and to use these models to design a system that can assign a date to any scanned brain.

To create aging models, the brain was segmented into its primary tissue types, white matter (WM), grey matter (GM), and cerebral spinal fluid (CSF). The segmentation involved separating the brain from the rest of the head with the Dual Space Clustering algorithm, and separating the individual tissues with an automated ellipsoidal algorithm. The volumes of each of these segments was measured and spectra for each Q-MRI image type (PD, T1, T2) were created by plotting binned histograms of the segment's voxel intensities. These spectra were compared to a Gaussian distribution and characterized by several statistical parameters including: mean, standard deviation, peak height and location, bandwidth, skew and kurtosis. Each of the parameters were taken for each tissue segment of 24 healthy subjects (age range 23-87) and plotted with respect to the subject's age. Regressions and correlation analysis were performed on these plots to determine the aging models. The dating system combined the segmentation and statistical processes, using these models as a basis to interpolate ages of other subjects. The system was tested on 11 volunteers (age range 20 – 75).

Volumetric analysis showed that after age 40 GM volume decreases and CSF volume increases. Spectral analysis revealed that each of the spectral distributions were unimodal and positively skewed. The results for the T1 image type in particular show that the GM and WM distributions are moving towards each other, meaning that WM and GM are changing to become more similar as we age. The dating system was created using these aging models and computed ages within 5 years of the actual age on 63% of the subjects, with bigger misses on the older subjects.

Q-MRI spectral analysis was able to quantitatively model the effects of aging on the brain. These models allowed a system to accurately assign a date to several individuals.
SESSION IIIA:
Systems Biology and Genomics Engineering
A Bioinformatics Based Search for Novel Motifs Influencing Gene Expression of Cardiac Sarcomere Promoters

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The cardiac sarcomere is one of the largest and most important protein complexes present in the human body. Due to its contractile function, the component proteins are constantly under stress and strain (of a beating heart), and thus require special mechanisms to build and repair new or malfunctioning subunits. The recently completed Human Genome Project provides the ability to examine the creation of these proteins at a molecular level, and determine if common regulatory proteins play a significant role in affecting the transcription rate of these component proteins. In the study, 2kb promoter regions of seven genes coding for major sarcomere proteins were analyzed using an expectation-maximization multiple sequence alignment algorithm, and a 15base motif (GGCAGCAGGGAGGA) was isolated that appeared within proximity to the transcriptional start site in all seven promoters. This motif was then placed in the middle of a random 50b probe that contained no known regulatory binding sites, and 5’ chemically labeled with biotin to allow for experimental verification. The probe was subject to a binding reaction with neonatal rat nuclear lysate to allow for any present transcription factors to bind the probe, and the experiment was verified with an electrophoretic mobility shift assay to determine if any protein-DNA interactions had occurred. A gel-shift was observed indicating that some nuclear protein had bound the motif and possibly regulates the expression of the cardiac sarcomere genes used in this study. Further studies are necessary to fully investigate the biological significance of the motif.
Development of a Low-Affinity Avidin-Like Molecule for Use in Binding Assay Experimentation

Jonathan Foley
Protein Engineering Laboratory

Competition binding experiments are a common technique used to compare the binding rates of reactions and determine dissociation constants, a vital characteristic of biotinylated pharmaceuticals which depend on the ability to attach and detach at specific rates to be effective. However, a shortcoming exists currently in the techniques use to make these measurements if the known interaction between avidin and biotin is used to determine these coefficients. The extreme strength of these bonds creates a long equilibrium time, which for a protein whose stability is minimal at best, can significantly lower the activity through degradation and give inaccurate measurements. The overall objective of this project was to create a novel molecule which can be used for competition binding measurements with the avidin-biotin system but which will reach equilibrium quicker than the current system. This goal was intended to be achieved by developing a low-affinity avidin-like molecule. The protein chosen as a basis of experimentation is edin, a member of the avidin/streptavidin family which, unlike either of them, does not possess any affinity to biotin. Using site directed mutagenesis, wild-type edin was altered to possess a combination of three mutations; E35G, R65W, and K104W. Competent E.coli was transformed with the resulting engineered DNA plasmids, and then inoculated, grown overnight, and induced to produce the mutated proteins, referred to as muteins. The muteins were extracted from the E.coli in the form of insoluble, unfolded inclusion bodies using sonication to lyse the cells, and the inclusion bodies were refolded into active form in a specialized refolding buffer. Folded proteins were concentrated and purified and checked for proper conformance with fast protein liquid chromatography to separate out unfolded and misfolded protein. The muteins will then be measured for biotin affinity using fluorescence polarimetry which determined how much of a marker of biotin-4-fluorescein had bound to the mutein in question. No muteins were found to possess a significantly higher amount of binding to biotin-4-fluorescein than wild-type edin, which lead to the conclusion that further study is required on edin in order to be able to accurately modify edin to increase its affinity. In summary, an engineered protein with low biotin affinity whose purpose is to act as a competition binding reagent was attempted to be developed using genetic/protein engineering and measured for its affinity using fluorescence polarimetry.
Transcription Start Sites and Gene Regulation in Drosophila
Laura Bacigalupi

Studying the upstream regions of different species of Drosophila, which is commonly known as the fruit fly, should provide us with more information on the regulatory elements that affect all genes. The goal of this project was to use comparative genomics to develop a better understanding of the core promoter region and how it has evolved using a closely related set of species. The core promoter region is the region which spans from 60 bp upstream of the gene’s transcription start site (TSS) to 40 bp downstream of the gene’s TSS. The ten most significant motifs found in the core promoter region were determined. The motifs were identified using MEME, an algorithm that identifies conserved ungapped blocks from the input sequences. Then the TSS was predicted for a select group of genes from six different species of Drosophila, this was accomplished by scanning the upstream regions of genes and locating clusters of the motifs identified. Finally, the upstream regions of different genes compared between different species were analyzed. The upstream regions of genes within syntenic blocks and the upstream regions of genes on the boundaries of syntenic blocks were analyzed across six species of Drosophila. Using the information obtained from the analysis of the genes on the boundaries of syntenic blocks and genes within syntenic blocks it has been determined that the breakpoints associated with the syntenic blocks are occurring upstream of the core promoters of the genes on the boundaries of the syntenic blocks. In summary, by identifying common motifs found in the Drosophila genes’ upstream regions it was possible to make predictions of the TSS for genes in which the TSS is unknown.
Targeting carcinoembryonic antigen using aptamers

William Seo

Aptamers are small nucleic acid molecules, isolated from combinatorial libraries by a procedure called SELEX, that bind to a target molecule by forming three dimensional structures. The binding of an aptamer is a highly specific interaction, with the ability to discriminate between related proteins that share common sets of structural domains. The characteristics and properties of aptamers make them attractive reagents that can be useful in cancer diagnosis and therapy. In the present study, aptamers are used to identify cancer cells by binding to carcinoembryonic antigen (CEA), a highly glycosylated glycoprotein and the most widely used tumor marker. Four aptamers were selected to target free (CEA) protein in vitro and the binding interaction was quantified using a fluorescent polarization assay. The secondary structures of the selected aptamers were predicted using a free energy minimization algorithm to analyze the role of stem-loops in target recognition. Two aptamers bound to CEA with calculated dissociation constants ($K_d$) of 94.2nM and 3049.9nM, while the other two aptamers did not bind to CEA.
Constraining the Folding Process of Ribosomal RNA

Sherwin Ting

The ribosome is a large complex structure that is responsible for protein synthesis in both prokaryotic and eukaryotic cells. In order to perform its function, the secondary structure of the ribosome is extremely important. Despite the potential for many possible secondary structure conformations, the native sequence of the ribosomal RNA (rRNA) is able to find the correct, functional and universally conserved fold. The goal of this study is to develop a computational analysis to investigate two mechanisms that appear to aid in the folding process of the rRNA secondary structure: binding of ribosomal proteins and rRNA sequence composition.

The analysis was carried out by using rRNA-ribosomal protein interaction data for the large subunit of the archaeal specimen, *H. marismortui* and the free energy minimization software for secondary structure prediction *mfold*. For each ribosomal protein, the interaction data was inputted into the free energy minimization software, which in turn gave a predicted number of possible stable structures. Combinations of proteins were also analyzed using an assembly map which gave the order to which different proteins bind to the native rRNA sequence. The constrains of multiple proteins were combined and inputted into the prediction software *mfold*.

In order to analyze the significance of sequence composition, the rRNA sequence was mutated and inputted into the free energy minimization software. Mutation was done on to levels: In the first group of mutations, the position and the type of mutation of the base were chosen randomly; In the second group of mutations, rRNA composition was mutated by randomly replacing canonical base pairs (G-U, G-C, A-U) with alternate canonical base pairs. The mutated sequences were inputted into the prediction software *mfold*.

Results indicate that ribosomal proteins constrain the rRNA by reducing the number of possible stable folds. In addition, rRNA composition does play a significant role in the secondary structure folding process of the ribosome. In summary, this report will determine the affects of proteins and RNA composition on the folding process of the secondary structure of the large subunit of the archaeal specimen, *H. marismortui* and indicate how the ribosome attains its functional structure despite numerous stable folds.
Proteomic Profiles of Peripheral Leukocytes for Biomarker Discovery in Lung Cancer

Greg Boulet
Michael Hoskins
Boston University Medical Center

Despite many advances in imaging technology, detecting lung cancer in its earliest stages remains a significant medical problem. The location and function of the lungs prevents the routine use of invasive methods including tissue biopsy for diagnostic purposes. However, an alternative method is suggested by recent advances in mass spectrometry technology, and studies showing "immunologic awareness" of lung cancer, in which biomarkers would be comprised of proteomic patterns in immune cells for lung cancer detection. Biomarkers are proteins or molecules that can be used to indicate a disease condition, and have been employed for screening in several other diseases, most notably in prostate cancer (the prostate specific antigen, PSA test). The goal of this project was to establish that lung cancer can be detected by isolating T-lymphocytes and monocytes from the peripheral circulation and analyzing their respective proteomic profiles via mass spectrometry. Using these profiles, we hoped to find proteins that can act as biomarkers specific for lung cancer, analogous to PSA and prostate cancer. From blood samples from recently diagnosed individuals with lung cancer, we separated individual leukocyte cell types, and separated their total cellular lysate using gel electrophoresis (1D-PAGE). After tryptic digestion, peptides were separated according to their hydrophobicity using reverse-phase liquid chromatography, and injected directly into the mass spectrometer which recorded the top 10 MS2 spectra for each MS1 scan. MS2 spectra were compared to theoretical peptide spectra in the NCBI RefSeq database using SEQUEST to compute a cross-correlation score (XCorr), with high XCorr values indicating peptide identifications. The T cells and monocytes from cancer patients were compared with those from healthy smokers, and those from individuals suffering from chronic obstructed pulmonary disease (COPD), an inflammatory disease of the lung. After the profiles of lymphocytes from two lung cancer patients, five COPD patients, and five healthy smokers were obtained, they were analyzed to find specific proteins that were differentially expressed in lung cancer samples. Eight proteins were observed to be unique to T-cells in lung cancer, seven proteins unique to monocytes in lung cancer, and several proteins that were present in all five healthy smoker samples but not lung cancer samples. Several of these proteins, like the Wiskott-Aldrich-Syndrome Protein, are associated with cancer in the literature. The results from this study have provided a foundation to continue research in leukocyte proteomics in order to develop a biomarker for the early detection of lung cancer. In summary, we isolated and compared the proteomic profiles of T cells and monocytes from healthy smokers, COPD patients, and lung cancer patients. We then compared them to find proteins expressed in patients with cancer that were not expressed in the other conditions, or vice versa. These proteins may later be used as a platform for the early detection of lung cancer.
Nanoscale Surface Forces between Human Serum Albumin, Alkanethiol Self-Assembling Monolayers, and oligo (ethylene oxide) Monolayers

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Hailemariam Negussie

It is estimated that more than 3 million people in the United States have long-term biomedical implants such as vascular grafts, pacemakers, catheters and joint replacements. Challenges to medically implanted blood-contacting biomaterials arise as the implanted devices fail to resist the adsorption of plasma proteins. Once proteins are adsorbed to the surface of the biomaterials, they open the pathway for the coagulation cascade potentially leading to thrombosis and inflammation. Oligo (ethylene oxide) (OEO) functionalized surfaces have shown promise in the area of protein adsorption resistance. The overall objective of the project is to study and quantify the nanoscale interactions between the protein, human serum albumin (HSA) and OEO functionalized monolayers in vitro using the technique of chemically specific high resolution force spectroscopy. Thiol-terminated OEO was chemically end-attached to gold-coated planar substrates and the normal nanoscale intermolecular interaction force (perpendicular to the sample plane) was measured with an HSA-functionalized probe tip (end radius ~ 50 nm) at a constant displacement rate (1 μm/s) on approach (probe tip advancing toward the surface) and retract (probe tip moving away from the surface). The specific aims of this project were 1) to study the effect of molecular surface order by varying the OEO chemisorption incubation time from 5 seconds, 24 hours, and 3 days, 2) to quantify the effect of bulk salt concentration (0.01, 0.1, and 1M Tris (Hydroxymethyl) Aminomethane buffers, pH 7.8), and 3) to quantify the effect of surface chemistry by looking at a hydrophobic, CH₃-terminated alkanethiol modified probe tip, and a hydrophilic, OH-terminated alkanethiol modified probe tip. Overall, our results indicate that OEO SAM surfaces incubated at shorter periods were more resistant to protein adsorption, especially at 0.01M and 0.1M ionic concentrations. OEO SAM surfaces incubated at longer periods, however, allowed more adsorbed protein.
Identification of Enhanced Metal Reducing *Shewanella oneidensis* *MR-1* Mutants through High-Throughput Optical Screens.

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*Shewanella oneidensis* MR-1 is a facultative anaerobic bacteria recognized for its ability to reduce a wide variety of metals. These bacteria have potential applications in soil decontamination, or bioremediation, notably for the decontamination of heavy metals such as Uranium and Chromium, as well as for the production of clean alternative energy in microbial fuel cells. However, before these applications can be developed into viable solutions, more detailed understanding of the biology mediating its ability to reduce these metals must be gained. In this project insertional *Shewanella* knockout mutants capable of enhanced metal reducing abilities were be targeted through high-throughput reductive ability screens. These knockouts were be created through the process of transposon mutagenesis and were collected to form a library of 3,840 separate *Shewanella oneidensis* MR-1 mutants. These mutants will then be screened to quantify each knockout strains' metal reducing capabilities. Mutants demonstrating significantly increased reductive abilities will then be selected for validation and further testing.
SESSION IIIB: Neurosensory Bioengineering
Development of a Perceptually Transparent Hybrid Auditory Display in a Reverberant Room Setting

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In realistic listening situations, acoustic waves reflect and reverberate off of surfaces. Since most auditory research has been conducted in anechoic (reflection free) auditory spaces there is a lack of knowledge of human listening abilities in real environments. The overall goal of this project was to develop a perceptually transparent hybrid auditory display for a reverberant environment. This hybrid auditory display has been developed in three distinct stages. First, a method was developed to produce equivalent sound pressure at the eardrum when presenting stimuli in the free-field (over a loudspeaker) and virtually (over tube-phones). This method involves measuring left- and right-ear head-related-transfer-functions (HRTFs) on an anthropomorphic acoustic dummy (KEMAR). These filters describe the ratio of sound pressures between the ear drum and the sound source. Then, acoustic responses to a virtual stimulus, constructed by filtering a noise burst with the HRTFs, were recorded at the eardrums of KEMAR and compared to the free-field responses to the same stimulus waveforms. These recordings were quantitatively compared and a compensating filter was determined to equalize the differences between the two sound pressure waveforms. In the second stage of the project, miniature recording microphones were used to measure the HRTFs at the entrance of a blocked ear canal. To account for the effects of this recording device and the blocking of the ear canal, an equalizing filter was empirically determined. This equalizing filter was tested by comparing free-field and virtual stimuli on KEMAR. In the third stage, personalized virtual stimuli were constructed from equalized-blocked-ear-canal HRTF measurements made on human subjects. Free-field and virtual stimuli were then played to subjects in listening experiments to determine if they could differentiate between the two stimuli. Results from measurements on KEMAR indicate a maximum of +/- 2 dB difference in the magnitude frequency spectrum of sound pressure waveforms recorded at five median-plane loudspeaker locations (-90°, -45°, 0°, 45°, 90°). Preliminary results from the second and third stages have demonstrated proof of concept and identified probable sources of error in accurately measuring the blocked-ear-canal equalizing filter. In summary, the design of a perceptually transparent hybrid auditory display has been successful on KEMAR, and pilot experiments with human listeners indicate that the technique is appropriate for virtual acoustic displays in reverberant environments.
A Physiological and Efficient Representation of Spectral Cues in Sound Localization

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Sound localization is a complex phenomenon of the auditory system that results from a combination of auditory cues, the least understood of which are spectral cues resulting from the filtering of sound by the outer ear. The location-dependent spectral shaping determined by the filtering of the pinna can be represented in spatialization filters known as Head Related Transfer Functions (HRTFs), which are used to study spectral cues in sound localization. In previous studies, the HRTF magnitude spectrum was smoothed uniformly across frequency via lowpass filtering in an attempt to determine the level of detail in spectral features necessary for localization (i.e. the overall shape without fine spectral structure). The altered spectra were used to create virtual stimuli played over headphones that were tested against real sound sources in psychophysical studies designed to determine the perceptual accuracy of the representations. Although results showed the relative unimportance of fine spectral detail, the question remains whether the perceptual quality of spectral resolution varies non-uniformly; in accordance with cochlear filtering. The goal of this study was to improve the current representations by accounting for the non-uniform resolution in frequency encoding that result from the physiological properties of the basilar membrane. A signal processing algorithm was designed to model the filtering action of the basilar membrane by smoothing the HRTF magnitude spectrum non-uniformly, using the mel scale to represent the approximately logarithmic relationship between frequency and the resolution with which the frequencies are encoded. Cochlear filter bank models were used as the basis of selecting the mel scale to represent this relationship, as the bandpass filters comprising them have center frequencies spaced approximately uniformly on the mel scale. This approach resulted in reconstructed HRTF spectra whose spectral resolution agreed with the expected resolution that results from peripheral processing in the auditory system. In the experimental phase of the study, psychophysical tests were conducted on three normal-hearing subjects using a 4-interval, 2-alternative forced-choice paradigm in which subjects were asked to discriminate stimuli filtered with measured HRTFs from stimuli filtered with reconstructed HRTFs with different levels of reconstruction. Both uniform and mel-weighted smoothing techniques were tested for comparison. Results showed a statistically significant decrease in subjects' performance abilities using the mel-weighted filters. These findings suggest that localization relies more heavily on the spectral detail of lower frequencies due to the non-uniform resolution of frequency encoding in cochlear processing. Taking advantage of the known physiology associated with cochlear function, we were able to successfully render a more efficient representation of the spectral cues necessary for sound localization by using our mel-weighted algorithm. This work has the potential to improve the processing capabilities of hearing prostheses.
Confusion Analysis of the Coordinate-Response-Measure (CRM)
Speech Corpus for Intelligibility Studies

John Patrick Gonzales

Most speech intelligibility experiments involve playing a target stimulus to subjects and asking them to indicate what they think they hear. Results of these experiments can be skewed by subjects’ response tendencies or trends that depend on the characteristics of the stimulus used, posing problems in interpreting experimental results. The CRM speech corpus (set of sentences) is a popularly used stimulus that has been shown to yield uneven patterns in subjects’ performance and responses. How these patterns or trends arise, and whether they change with parameters that specify listening conditions has not yet been determined. The overall objective of this study is to determine if and how subject response trends that arise with the use of the CRM speech corpus change with the degree of reverberation in the listening environment. Reverberation is the result of the reflection of sound waves off of walls in an enclosed space, and is a factor that has been shown to affect speech intelligibility. To determine whether or not response trends change with reverberation, confusion matrices, which are matrices that indicate how frequently subjects select particular responses when played particular targets, were obtained and analyzed. These confusion matrices were obtained from three subjects, using the CRM speech corpus, under three reverberant conditions: 1) no reverberation, 2) simulated classroom reverberation, 3) simulated bathroom reverberation. The sentences from the CRM speech corpus were played to subjects with speech-shaped noise (SSN), over headphones in a soundproof booth, with each of the three levels of reverberation. Subjects were asked to identify three key words in each sentence, over a total of 1200 trials per condition. The effects of reverberation on response trends were analyzed by comparing the following measures obtained from confusion matrices: a) the subjects’ performance in identifying each keyword, b) the amount of bias in the selection of responses c) the mutual information between targets and responses, d) the distribution of errors in the confusion matrices, and e) the correlation coefficients between the confusion matrices obtained in different levels of reverberation. The analyses performed show that the confusion matrices and response trends changed when the levels of reverberation in the environment were varied. The changes observed were subject-specific, and occurred with great variability, and appear to have been strongly influenced by the subject response biases. Studying the response trends associated with the use of the CRM speech corpus, and whether or not they change with reverberation, can lead to both a better understanding of how the CRM speech corpus can be used as an effective tool in speech intelligibility studies and to better designs of prosthetic hearing devices.
Influence of Spatial Location Cues on Auditory Object

Formation

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This project improves our understanding of auditory attention, psychophysics, perception, and object recognition by designing a system to measure how acoustic spatial cues influence the process of sound source segregation. We conducted experiments to examine how the perception of sound objects (or “streams”) “builds up” as the brain accrues information about how to separate acoustical energy into different sources. We also investigated the phenomenon of auditory illusions: cases where the perceived objects are inconsistent with the sound mixture that is actually presented to the listener. We designed two separate experiments: a “Reaction Time Experiment,” and a “Rhythm Recognition Experiment.” Both experiments required human subjects to listen to particular sound stimuli and respond to questions regarding the sound stimuli. Instructional set, tone repetition rate, and spatial location of the stimulus were the varied parameters in both experiments. The first experiment investigated how human listeners responded to sound stimulus positioned at different locations in space presented at different repetition rates. The second experiment investigated how human listeners perceived sounds when the presented stimulus was actually different than what was perceived. After performing various pair wise t-tests of significance, we found that space does in fact influence the process of sound source segregation. When subjects were asked to try to use space to segregate sounds, they did so more effectively at slow tone repetition rates. When subjects were asked to try to ignore space to group sounds together, they were unable to do so. In conclusion, we found that instruction does not override spatial separation and tone repetition rate and spatial location affect the subject’s percept of the sound. Our research indicates that spatial localization cues are important when trying to segregate sounds in the natural environment.
Human listeners can distinguish the location of sound-sources or discriminate sounds from an array of localization tasks. By delaying sound signals, the different arrival times between the ears, interaural time differences (ITDs), become a cue for locating a sound source. Sensitivity to sound level differences at the two ears, interaural level differences (ILDs), becomes another cue to determine horizontal location, or azimuth, of sound sources. These two cues are often modified to assess the issues of whether listeners can discriminate correctly sound source locations. In this project, we designed experiments to determine how humans learn to effectively use these localization cues to localize sound sources. This study provided a quantitative measure of ILD and ITD discrimination thresholds of untrained listeners to determine the presence of learning. The overall goal of this project was to address the rates of learning humans exhibit when they discriminate sound-source locations using modified ITD and ILD sound cues. The experiments involved a target stimulus that is presented to the subject where the stimulus will have either an ITD or ILD based on the reference signal. Threshold was defined as the minimum ITD or ILD difference required for 70.7% correct discrimination. Untrained subjects had two 2-hour sessions all experiments. Listeners did not show improvement in threshold within and between sessions in the first and second experiment. In the first experiment, subjects experienced ITD discrimination tasks with ITD increments ranging from 320μs to 10μs. Subjects in the second experiment experienced ILD discrimination tasks with ILD increments ranging from 8dB to 0.25dB. Each discrimination experiment consisted of playing the subject four intervals of sound with the second or third interval containing the target sound. Experiment 3 investigated any change in performance when the timing delay of the signal involves both the carrier and envelope. Experiment 3 doubts as to whether interaural envelope delays are inherently weaker cues at low frequencies. Experiment 4 investigated whether a 4I,2AFC discrimination task method provides equal or better performance than a 2I,2AFC. These results of examining the difference between the 2I,2AFC and 4I,2AFC discrimination task shows that any of these methods can be used to adequately determine discrimination thresholds with equal confidence in the data acquired. In order to accurately produce a hearing device or method of hearing-impaired therapy, the effects of learning is important in localizing sound sources. It is essential to understand how the binaural auditory system interprets modified sound cues to provide insight to the neural encoding of ILD and ITD cues. The results of the experiments will increase the understanding of how the binaural auditory system processes modified sound cues, potentially leading to improved hearing devices and hearing-impaired therapy.
Effects of Reverberation on Spatial Auditory Attention

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Spatial unmasking is the improvement in the ability to detect or understand a target sound when it is spatially separated from simultaneous masking sounds. Previous studies for speech intelligibility indicate a large amount of spatial unmasking in both anechoic (without echo) and reverberant (with echo – like an ordinary room) environments. Previous studies using Zebra finch calls as a signal demonstrate that spatial unmasking of birdsong occurs in anechoic conditions. The results suggest that spatial separation aids humans in segregating complex natural sounds via mechanisms that are not specific to speech. The current study expands on the previous work to explore spatial unmasking patterns for birdsong signals in reverberant conditions. Results show a decrease in spatial unmasking for birdsongs in reverberation. This is inconsistent with results from speech studies. Reverberation might reduce the spatial benefit seen for birdsong and not speech because 1) birdsong has more rapid temporal fluctuations than speech, 2) reverberation acts to reduce temporal fluctuations, and 3) temporal fluctuations are necessary to allow listener to hear sounds in a mixture. A new birdsong signal designed to resemble speech in its temporal structure (slower temporal fluctuations) was designed. Spatial unmasking re-appeared for this new signal in reverberation. This indicates that signals with slower temporal fluctuations are more effectively segregated in reverberation and can benefit from spatial attention. As a whole, these results suggest that the brain possesses mechanisms for segregating complex sources that are not specific to speech, although speech (and other signals resembling speech in their temporal structure) is more robust in reverberation than signals containing faster fluctuations.
Statistical Modeling and Analysis of Efferent Spike Trains
in the Limulus Visual System

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Spike trains encode and carry physiological information through neural networks and are commonly characterized by their statistical properties. For the horseshoe crab, Limulus polyphemus, efferent spike train activity in the optic nerve enhances retinal sensitivity in the lateral eyes during the night. This unique feature of its visual system can be used to investigate the statistical components of endogenous spike trains and quantitatively assess their significance. Humans also use spike trains to convey information. Hence, this study infers which statistical properties of spike occurrences is most important, mean firing rate or temporal patterning. The overall objective of this study is to statistically describe the structure of efferent spike train patterns and to evaluate the sufficiency of different ordered statistical models in driving the lateral eyes into a state of increased retinal sensitivity. The general technical approach was to record actual spike trains from a Limulus, analyze and statistically model the neural activity, and run stimulation experiments on the efferent fibers in effort to assess the adequacy of the modeling. Electroretinogram (ERG) recordings were first conducted using corneal electrodes to measure the normal retinal response of the lateral eyes during the nighttime state. Endogenous spike train data was then acquired for analysis. We then studied the organization of the recorded spike trains by using 1st and 2nd-order statistics to develop models that describe the neural firing events. A series of efferent fiber stimulation experiments were also performed, to investigate the retinal response of the Limulus lateral eye to arbitrary nerve shock paradigms. We generated three different statistical models that captured varying levels of dependency on mean rate and temporal sequencing. The simplest model was solely based on mean firing rate, while the Gamma model and composite Gamma model suggest some degree of coding significance in the temporal pattern of spike events. In summary, this study of spike trains infers how well different levels of applied statistics embody the features of neural encoding. The results suggest the type of statistical modeling required to reproduce spike trains that sufficiently carry information and thus elicit desired physiological responses.
Microgravity induced changes in the control of motor units.

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The objective of this project is to determine if exposure to microgravity results in changes in the control of concurrently active motor units (MUs). Previous research has demonstrated that exposure to microgravity or to microgravity-like environments will cause detrimental changes in the biochemical and physiological properties of skeletal muscle leading to atrophy and loss of strength. These changes stem from hypokinesia and hypodynamia. The goal of this project is to determine if degradation occurs in the neural control pathways of skeletal muscle and to use these results to better describe the loss of strength experienced after space flight. Electromyographic (EMG) data were collected from an astronaut both pre and post space flight via sensors inserted into two distinct muscles, the first dorsal interosseous and the vastus medialis. During the test sessions the subject contracted each muscle at a maximum and prescribed force levels. The EMG data were processed with the Precision Decomposition technique to obtain individual MU firing trains to extract neural control parameters. These parameters included the cross correlation among MU firing rates (common drive coefficient), the cross correlation of firing rates and the force output, the average firing rate and the recruitment threshold. The results indicate changes in both the neurological and physical control parameters of concurrently active MUs upon return from space. Some parameters, those corresponding to previously reported inverse relationship between MU firing rate and recruitment threshold, were maintained between preflight and post flight days. These changes indicate a restructuring in the neural control of skeletal muscle upon return from space, no manifest on the day of return, but rather on the subsequent days. This indicates that the neuromuscular system requires a re-adaptation to earth gravity, beyond the effects of atrophy that more accurately describes the loss of muscle function experienced after space flight.
Analysis of Correlated Firing Behavior of Motor Units during Fatiguing Muscle Contractions

Ashley Morgan

Understanding of the neural control of muscle function has made great progress. Many individual motor unit control properties have been studied and classified, however little is known about the correlated firing activity among motor unit pairs across a series of fatigue contractions. This project has gathered quantitative data relating to the correlated behavior of pairs of motor units by creating and modifying MATLAB routines that measure synchronization and cross-correlation. This research used previously collected motor unit firing-time data from a study of motor unit recruitment and firing rate during fatigue. In synchronization analysis, the firing-time files of two motor units are selected. The firings of the motor units are compared by finding the forward and backward time differences between them. The latencies are then sorted into a Cross Interval Histogram and compared to a statistically determined threshold that marks synchronization. The strength of synchronization, known as the Synch Index, is then calculated. Cross-correlation begins by using firing-time files as input to calculate the mean firing rate of each of the motor units, by passing a Hanning window of 400ms duration over the firing-time file. The calculated mean firing rate is then used as the input to calculate the cross-correlation between motor units. Synchronization and cross-correlation were calculated for four contractions in each of five subjects’ fatigue series over the interval of 20-55 seconds. Additionally, cross-correlation was calculated between motor unit pairs and motor units paired with the force output of the contractions over the last five seconds of each of the contractions studied. In general, most motor unit pairs studied, 53 out of 62, showed some degree of synchronization, yet all synchronization levels were low with synch indices averaging 2.5. Cross-correlation values over both the 20-55 second and last five seconds of contraction ranges varied much more dramatically from 0.07 to 0.68. Cross-correlation between motor units and force resulted in steadily increasing values as fatigue progressed, ranging from 0.20 to 0.80. In conclusion, synchronization levels are low and remain constant through fatiguing muscle contractions; indicating that synchronization is not affected by muscle fatigue. Cross-correlation, on the other hand, is variable through fatiguing muscle contractions, with a steady increase in force cross-correlation as the muscle becomes more fatigued. The data will be valuable in the assessment of the functional state of the muscle and can lead to better modeling of human muscle through an improved understanding of the behavior of motor units.
Neural Plasticity in the Human Visual System
Sharon Hyzy and Anthony Tanella

Plasticity studies in the brain are important because they show how the representation of objects can be moderated through learning. While much is known about plasticity at lower levels of the visual system, less is known about areas that cover larger portions of the visual field and integrate inputs from many neurons. Perceptual learning is a form of plasticity that occurs through task specific training and is characterized by improved performance in the particular task. For this project, the specific task is left/right motion direction discrimination within a visual stereo motion stimulus (SMS) imposed on a random field of dots. The SMS is set to appear at varying distances away from the plane of the computer monitor (disparity) and differ in number of dots moving in the same direction (coherence). The goal of this project is to determine whether training human subjects to discriminate motion directions in SMS will induce perceptual learning and if the learning is specific to the SMS disparity and region of the visual field in which training occurred. Subject eye positions were monitored during stimulus presentation using an Arrington Viewpoint Eyetracker. The interface between the eye tracker and the experiment allowed for real time control of the region of visual training by detecting eye position in the visual field during the experiment. Subject performance was tested pre-training with the SMS able to appear in all four quadrants, disparities, and coherence levels. Subjects were then trained once a day for a period of 11-14 days with the SMS restricted to the lower right quadrant of the visual field at a particular disparity. After the subjects had completed training, they were again tested with the SMS in all four quadrants, disparities, and coherence levels. Using a generalized linear model, we determined five of the seven subjects had a significant decreasing trend in threshold coherence ($C_T$) over the training period, indicating an increase in motion discrimination ability. Upon further analysis of subject performance, we found two subjects demonstrated a slow learning mechanism across a period of days that generalized to significant improvements in motion discrimination ability ($p<0.05$, student’s t-test, $\chi^2$) and learning in both trained and untrained quadrants and disparities. Three subjects demonstrated a fast learning mechanism where large decreases in $C_T$ occurred during the pre-training test session with small improvements in performance over the course of long term training. We have seen two mechanisms of learning: slow learning with significantly improved performance over trained and untrained parameters, and fast learning with large improvements in stereo motion discrimination ability occurring on the pre-training day. In summary, we have demonstrated perceptual learning can occur for SMS and the learning can transfer to untrained quadrants and disparities under slow learning conditions.
SESSION IV:

Biomaterials
Tissue Engineering
Drug Delivery
and
Biomechanics
Effect of Mechanical Stretching on Pulmonary Fibroblast Function

Anne Zavadić
Cell and Tissue Mechanics Laboratory

Tissue remodeling is an intrinsic response to mechanical stretching in the lung. Little is known about the effect of mechanical stimuli on pulmonary fibroblasts' ability to maintain the extracellular matrix composition. A recent study demonstrated that type I procollagen mRNA production increased in stretched fibroblasts. However, this study used a continuous cell line and the actual amount of protein found in the cells and the media was not established. The purpose of this project was to investigate the synthesis of type I and type III collagen by primary mouse pulmonary fibroblasts in response to short durations of cyclic stretch. Pulmonary fibroblasts were isolated from mouse lungs using a previously developed technique of primary cell isolation, grown to confluence in cell culture flasks, at which point they were cultured on laminin-coated, elastic membranes. Twenty-four hours after seeding, the cells were stretched at 25% increase in surface area at 3 cycles per minute for 4 or 8 hours. Twelve hours following the stretch period the cells and secreted type I collagen were imaged using two-photon second harmonic generation microscopy. The total protein concentration was calculated for each sample and Western blots were conducted for both the cells and the media to quantify the synthesis and secretion of collagen type I and type III as a function of mechanical stimulus. We found that type I collagen related second harmonics are stronger in stretched cells than in unstretched controls, indicating that more collagen is being produced in stretched cells. From the Western blots, however, we found that the production of collagen is not upregulated with stretch. The total protein concentration in the cells decreased with stretch for both 4 and 8-hour time points and the total protein concentration in the media increased with stretch for both time points. In conclusion our data appears to show that the protein secretion increases with stretch but that the concentration of type I collagen is independent of stretch while type III collagen production and secretion seems to be upregulated in response to mechanical stretch.
Effects of Stretching on the Mechanical Properties of Extracellular Matrix Sheets During Elastase Treatment

Rajiv Jesudason

Pulmonary Physiology and Dynamics Lab

The structural and functional characteristics of cells are related to and dependent on the organization, composition and mechanical properties of the extracellular matrix (ECM). The mechanical properties of ECM are a function of the proteins, elastin and collagen. These proteins provide flexibility, elasticity and structure to tissues and organs. Pulmonary emphysema and vessel wall aneurysm are specific disease conditions that are characterized by degradation of the elastin in the ECM due to an imbalance among proteases and protease inhibitors. This degradation greatly affects the normal function of tissue. In addition, it has been suggested that mechanical forces applied to the lung parenchyma as a result of stretching the tissue during breathing exert strenuous loads on enzymatically weakened ECM, thereby accelerating the breakdown of tissue. Previous studies have characterized the effect of elastase digestion on the mechanical properties of ECM. However, no previous study has examined the effect of stretching on the mechanical properties of the ECM during digestion by elastase. Our study used a previously developed stretching apparatus consisting of a computer controlled lever arm and force transducer. Cell culture-based ECM samples were cut into strips, attached to the stretching system, and loaded with static or cyclic stretch. Dynamic mechanical and quasi-static stress-strain measurements were taken at specific time points during digestion by elastase. Comparison of pure digestion and digestion with static stretch conditions showed that the application of stretch resulted in a greater rate of decrease in the stiffness of the ECM than digestion alone. Furthermore, the application of static stretch with digestion resulted in a greater reduction in failure stress than digestion alone, with a stress value 92% less than the control group. The application of cyclic stretching during digestion resulted in catastrophic failure after 10 minutes of digestion for the majority of tested samples. Thus, not only the presence but the dynamic nature of mechanical forces on ECM tissues can have a significant impact on the deterioration of functional properties when the tissues are exposed to enzymes. Information obtained from this project should prove useful in characterizing the roles that mechanical forces play in the progression of emphysema and vessel wall aneurysm.
Assessment of Nanoindentation as a Technique for Quantifying the Mechanical Properties of Soft Tissues

Jared Bancroft

Boston University Orthopaedic and Developmental Biomechanics Laboratory

Use of animal models in biomechanical research has been a standard for characterizing the mechanical properties of musculoskeletal tissues. With the advent of genetically modifiable mice and the development of rodent models for the study of human diseases such as osteoarthritis and osteoporosis, a shift toward using smaller animals has occurred. Conventional methods for testing tissue samples (such as uniaxial compression and indentation) often require larger volumes of tissue than can be obtained from these small animals. Nanoindentation is a cutting-edge technology for determining mechanical properties of materials when large samples of the materials cannot be obtained, though nanoindentation has not been verified for use in soft, hydrated, viscoelastic tissues found commonly in musculoskeletal research. To determine the effectiveness of nanoindentation in quantifying mechanical properties of soft, hydrated, viscoelastic materials, a direct comparison between proven classical methods (uniaxial compression) and nanoindentation was made. To provide a reliable comparison, poly-(2-hydroxyethyl methacrylate) (poly-HEMA) hydrogels were used. Poly-HEMA is a homogenous soft, hydrated, viscoelastic material which displays mechanical properties similar to tissues of interest to musculoskeletal researchers. Samples (n=6) were tested in both uniaxial confined compression and uniaxial unconfined compression using a creep protocol in a Dynamic Mechanical Analyzer (DMA) (Q800, TA Instruments, New Castle, DE). The results of these tests (aggregate modulus, $H_A$, and Young’s modulus, $E$, respectively) were then used to calculate the Poisson’s ratio ($\nu$) for poly-HEMA. The biphasic theory for creep testing was used to determine the permeability, $k$. Samples were then tested in a nanoindentation system (TriboScope, Hysitron, Minneapolis, MN) using a 50-micron conospherical tip. A Finite Element Analysis was used to curve-fit the load-displacement data of the nanoindentation test, which resulted in values for $E$, $\nu$ and $k$. The Young’s modulus was in all cases severely overestimated by nanoindentation, by at least an order of magnitude. There was also no correlation between the Finite Element Analysis load vs. displacement curves and the experimental load vs. displacement curves produced through nanoindentation. Although there was no correlation between values determined via nanoindentation and those values determined by standard testing techniques, there is much hope for the use of nanoindentation in the fields of musculoskeletal and biomechanical research. There were many unknowns that were out of the scope of this current study. In the future, more time needs to be taken to fully analyze poly-HEMA, to rule out depth dependence due to uneven crosslinking. A larger sample group must be used to more precisely quantify Young’s modulus, aggregate modulus, Poisson’s ratio, and permeability. Work also needs to be done to investigate any nonlinear nature of the solid phase of the poly-HEMA hydrogels. These studies will help to create a more accurate model of the sample/nanoindenter tip system and provide more insight into the feasibility of using nanoindentation on soft, hydrated, viscoelastic materials.
DEVELOPMENT OF FINITE ELEMENT AND COMPOSITE PLUS CURVED BEAM STRUCTURAL RIGIDITY ANALYSIS MODELS FOR RAT TIBIA WITH SIMULATED LY蒂C DEФECTS

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The skeleton is the third most common site for metastatic cancer behind the lungs and the liver, and one third to one half of all cancers metastasize to bone. Approximately 30% of this metastasis cases result in fractures or produce symptoms severe enough to warrant treatment. However, very few clinical techniques exist to accurately establish guidelines for estimating fracture risk or monitor the response of skeletal metastases to treatment. The aim of this project was to increase the viability of a computed tomography (CT) based system for estimating fracture risk by applying the principles of curved beam theory to the composite beam theory based structural rigidity analysis (SRA) and to compare these results to finite element analysis and mechanical testing. Previous SRA studies have used composite beam theory to estimate the fracture risk in bones affected by metastatic cancer alone, and by augmenting it with the curved beam theory; we hope to account for the complex geometry of various anatomic sites, such as the femur. We validated this approach by using rat tibia with its natural curvature. In order to perform this validation, stimulated metastatic lesions were created in the tibias and scanned using computed tomography. The CT images were then re-sliced along their center of curvature and the re-sliced images were used to analyze the bones. Based on its mechanical properties, the axial and bending rigidities of the bones were calculated for each slice. With the properties of each slice calculated, the bone was treated like an anisotropic beam. The fracture load was calculated using both curved + composite beam and composite beam structural rigidity analysis. Finite element models were created directly from image data by assigning nodal connectivity and bone tissue properties. Finite element analysis was performed with an assumed uniform Young’s modulus of 10 GPa and a Poisson’s ratio of 0.33. The preliminary results validate the inclusion of curved beam theory to structural rigidity analysis and suggest that it is superior to finite element analysis, which performed poorly in estimating both fracture load and displacement. Future work will include improving the methods for accounting for the curvature in a tibia. Eventually, this work will be furthered developed in the femur with the ultimate goal being the improved clinical treatment of patients.
The Effects of Fixation on Bone Mechanical Properties

Project Abstract
Bryan Hermannsson

Traditionally, bone samples are mechanically tested under fresh or fresh frozen conditions. Most studies require these specimens to meet specific species, sex, age, and pathological conditions. A much larger pool of fixed tissue samples is available to the research community. The ability to use fixed bone samples in mechanical testing experiments would increase lab resources and safety because of the sterilization properties of formalin. The overall objective of this project was to study the effects of bone tissue preparation and preservation (fresh, fresh frozen, fixed) on the mechanical properties of murine bone. 48 C47 mice were used for all specimens. Fresh specimens were tested immediately post excision and used as a control while the others will be either frozen for 2 weeks or fixed in 10% formalin for 2 weeks under standard tissue fixation protocols. Lumbar vertebrae (L3, L4, L5) were tested under axial compression and compared across preservation modes. Femurs were tested under 4-point bending and also compared across preservation modes. Two speeds of testing (cyclic and failure) were performed to examine the contribution of collagen cross-linking to bone strength. Cyclic loading was performed at a speed of 30 mm/min for 500 cycles using a triangular waveform. Applied strain never exceeded 40% of yield strain measured from the pilot study. This was to ensure testing never went beyond the linear elastic region. Failure loading was performed at a speed of 1.88mm/mm. Using Matlab modulus (E), yield stress (σy), yield strain (εy), ultimate stress (σu), and ultimate strain (εu) were calculated as the parameters for comparison. Through two-way ANOVA analysis of variance, it was found that differences in mechanical properties for all bones between all preservation groups were statistically insignificant. This proves the null hypothesis that tissue fixation does not effect bone mechanical properties. Hopefully, the results and conclusions from this study will increase the number of bone experiments performed as well as protect the safety of biomechanics researchers.

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Study of cross-linking properties in poly (vinyl alcohol) and its effects for a drug loaded device

Sameer Grover

The project’s overall objective was to study the mechanical cross-linking effects of a biocompatible polymer, poly (vinyl alcohol). Our ultimate goal was to incorporate a drug into these polymer-based microspheres for localized, accurate, and targeted delivery. This objective will be achieved by completing the following specific goals:

1. To study the affects of mechanical cross-linking methods in PVA.
2. To study the affects of imbibing drug into the microsphere post alginate removal.
3. To study the release profiles of direct loading with PVA/Alginate microspheres.

Mechanical cross-linking was studied first because a drug agent cannot be incorporated in the microspheres with the current cross-linking process. The chemicals used to cross-link the polymer would degrade the drug. We focused primarily on three methods: cyclic freeze-drying, electron-beam radiation and cyclic freeze-thawing. Cyclic freeze-drying involves creating microspheres that are comprised of PVA and sodium alginate. These microspheres are frozen in liquid nitrogen, then lyophilized for 24 hours to de-hydrate the microspheres for PVA retention studies. Electron-beam radiation involved irradiating microspheres at various doses to cross-link unsaturated organic resins into durable compounds with physical properties. These microspheres were also used in PVA retention studies. Lastly, cyclic freeze-thawing froze the microspheres at -70°C for 20 hours and thawed at 24°C for 4 hours. These microspheres underwent the same PVA retention test as the previous cross-linked microspheres. PVA retention studies involved removing the alginate from the microspheres to determine if any PVA dissolved as well. We determined if PVA dissolved with the sodium alginate then the microsphere is not completely cross-linked. All the methods of mechanical cross-linking are studied under two formulations of PVA and sodium alginate for comparison. Additionally, the experiments are run under triplicates to ensure minimal variability between data sets. Preliminary data showed that cyclic freeze-drying the microspheres achieved the most PVA retention and was thus cross-linked the most. The other two methods did not achieve an increase in cross-linking as the number of cycles or doses of radiation increased. After establishing the best approach of cross-linking the microspheres, we will ultimately be able to incorporate the drug into the microspheres.
Synthesis of Branched Collagen Channel Mimicking Microvasculature

Lin Lin Gao

In vitro models of microvasculature networks can be used to study the effects of drugs on vessels, inflammation and potentially can be clinically used for wound healing and perfusion of cells in artificial implants. Thus far, straight segments of artificially engineered microvessels resembling real in vivo microvasculature have been created using collagen. However, in order to obtain 2-dimensional and 3-dimensional networks, branched channels are needed. The goal of this experiment was 1. to mold and separate from polydimethylsiloxane (PDMS) a gelatin branching structure that is hydrated and stable at room temperature with less than 20% isotropic deviation from initial design dimensions, 2. to synthesize a patent collagen channel from a sacrificial gelatin structure, which has dimensions that closely mimic the initial design and 3. to introduce flow in order to feed and perfuse human umbilical vein endothelial cells (HUVECs) seeded within the collagen branching microvessel for several days until HUVECs reach confluence. The AutoSketch drawing of the Y-shaped channel is made into a transparency, which is then used in photolithography to create a silicon wafer with the raised branch design. Polydimethylsiloxane (PDMS) is poured onto the wafer and upon gelling, the branch structure is imprinted as negative relief onto the polymer. Using MIMIC (micromolding in capillaries), gelatin is gelled onto the PDMS mold and upon removal is in the shape of the original branch design and is encased by collagen. Once the gelatin melts and is removed, the collagen encases a patent collagen channel. After flushing out the residual gelatin and perfusing the collagen with media, HUVECs are seeded into the inlet and are allowed to adhere to the channel. Finally, a cap with tubing connecting the inlet and outlets to flow is added. Because gelatin exhibits isotropic expansion, procedural changes are made such that the expansion was limited to 12%. To ensure patency of the collagen channels, the channels were first visualized with fluorescent bead and then measured to determine degree of reproducibility. Finally, once HUVECs were seeded into the channels, they were visualized using DAPI and Hoechst staining. In conclusion, reproducible collagen channels have been made with dimensions within reasonable standard deviation from what was proposed and the HUVECs retained viability for up to 72 hours. Although this illustrates the feasibility of the synthesis method and that HUVECs are able to stay alive within the branched structure, further trials are needed to determine the long-term HUVECs behavior within the collagen confines.
Vascular Tissue Engineering: Micropatterned Substrates to control Gene Expression and Organization of Cell-Secreted Extracellular Matrix

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It has been a major challenge to engineer functional small diameter arterial replacements for coronary bypass operations. A key issue that has limited the success of small diameter synthetic arterial grafts has been a lack of arterial compliance. Current efforts towards developing small diameter artery replacements have been inadequate partly due to a lack of elastin, an extracellular matrix (ECM) protein that gives arteries their compliance. Neonatal rat smooth muscle cells (NRSMCs) have been shown to secrete large amounts of elastin in culture, but this secreted elastin lacks the structural organization found in native arteries. In the medial layer of native vessels, the extracellular matrix is a highly organized network that may influence the mechanics of the vessel. The overall objective is to develop and evaluate the composition, structural characteristics, and organization of an extracellular matrix produced by NRSMCs grown on microtextured substrates. This study is motivated by previous studies in our laboratory where a combination of microfabrication techniques and biomaterial scaffold designs were shown to align and organize ECM proteins secreted by vascular smooth muscle cells. Using this technology, we seeded cultured NRSMCs onto microfabricated scaffolds to serve as a template for elastin to form a highly organized network. The secreted elastin was visualized by immunofluorescent staining microscopy to confirm the presence and general organization of elastin. The results confirmed that elastin was covered throughout the surfaces of both flat and textured substrates. Furthermore, elastin was shown to be oriented parallel to the micropatterned grooves whereas no preferred orientation was shown on flat substrates. Quantitative analysis from real-time PCR (qRT-PCR) showed gene expression levels of elastin and other ECM proteins over three weeks of initial seeding of cells. Gene expression levels of elastin on various micropatterned substrates as well as other ECM proteins increased two-fold compared to non-patterned substrates after one week of initial cell seeding. These results support that ECM production is generally increased when organized on micropatterned substrates. These combined results of both immunofluorescence and qRT-PCR suggest that aligned elastin and ECM organization were present on micropatterned substrates, while none were shown on flat substrates. Using this approach, we can gain a better understanding of the role of micropatterned substrate on the organization and functional properties of the extracellular matrix with the ultimate goal of creating a suitable artificial replacement for small diameter arteries.
A system for studying the role of substrate mechanics in the organization of dynamically cultured vascular smooth muscle cells and extracellular matrix

Christopher Sip

Tissue-engineering of a functional medial-layer has been a major challenge for producing an effective small-diameter arterial substitute. The medial-layer of the native artery consists of a highly organized contractile smooth muscle cells (SMCs) and various proteins comprising the extracellular matrix (ECM). Our approach focuses on the critical ECM protein elastin which provides vessel compliance but is rarely produced in tissue-engineered arteries due to its developmental down-regulation. Previous systems of mechanical stimulation have shown increases in elastin production, but these studies have not examined the effects of systematically altering the substrate stiffness. This is important because recent studies have revealed the importance of substrate stiffness on modulating cell behavior especially in the context of cardiovascular disease. We aimed to develop a system for studying cell-surface interactions including the alignment of SMCs and the organization of the ECM of samples cultured under mechanical stimulus with varying substrate elastic moduli. Since neonatal rat SMCs exhibit enhanced elastin production, they will be used in our system as a means to study the development of elastin fiber networks. For studying the response of neonatal rat SMCs, we developed precisely-engineered polyacrylamide (PAAM) substrates and designed a pneumatically-driven cyclic-strain bioreactor device. A simple gel formation process was developed to produce tubular PAAM gels of varying elastic modulus for the application of cyclic-strain. The gels demonstrated negligible creep, equilibrium swelling, and maintained integrity under mechanical stimulation over a period of 1 week. Although various methods for seeding the outer surface of tubular PAAM gels were explored, only limited cell adhesion was observed and no consistent methodology was determined. A device was fabricated and tested for its capability to apply cyclic-strain to PAAM substrates. Moreover, a biomimetic system was developed for studying cell-surface interactions, but a unique cell seeding problem was discovered which requires further understanding. Overall, the system will be able to facilitate the rational design of improved biomaterial scaffolds and arterial substitutes by elucidating the complex interactions between cells and substrate under dynamic culture conditions.
Local Incorporation of Anti-neoplastic Agents into Surgical Resection Margins for the Treatment of Mesothelioma
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Malignant Pleural Mesothelioma (MPM) is a rare but aggressive cancer of mesothelial cells which compromise the lining of the chest wall and the external layer covering the pericardium, diaphragm and lungs. Thousands of people are affected each year and recently the incidence of the disease has been increasing. The overall objective of this project is to incorporate Pemetrexed into bioabsorbable microspheres to develop a convenient and safe drug delivery system. Pemetrexed is an anti-neoplastic agent (a drug that inhibits tumor cell growth) used to decrease recurrence following surgical resection for the treatment of MPM. The main focus was to show drug incorporation and prove cell growth inhibition in vitro. Bioabsorbable poly D,L lactide co glycolic (PLGA) microspheres were first loaded with 0.9% NaCl only (control) and Pemetrexed, an anticancer drug proven for the best clinical response in the treatment of MPM. Microspheres were tested in vitro using a Thiazolyl Blue Tetrazolium Bromide (MTT) proliferation assay. The absorbance was measured on an ELISA plate reader and then translated to number of cells using a number of cells versus absorbance standard titration curve function to quantify cell proliferation. The cells’ sensitivity to the Pemetrexed was measured to be between 1 - 0.1ug/ml. Because the Pemetrexed PLGA microspheres did not show any cell growth inhibition, a proprietary polymer was chosen because of its chemical structure and degradation behavior. The Pemetrexed proprietary polymer inhibited cell growth at a concentration above 500,000 microspheres per 100µl. Results using Paclitaxel, another anti-neoplastic drug less used for lung cancer proved just as effective in vitro with a dose of 0.01µl/ml and concentrations above 5 million microspheres per 100µl. This project will be significant in the development of future drug delivery systems for preventing local cancer recurrence and establishing a standard of care for Mesothelioma treatment.