20th Annual Senior Project Conference

Department of Biomedical Engineering
Boston University
Thursday, May 5, 2005
Program Overview & Faculty Profiles

Presentation Schedule & Technical Advisors

Visiting Companies & Laboratory Information

Project Abstracts

Student Resumés
Welcome to the 20th Annual Senior Project Conference. Yes, that’s right...20 years. For 20 years we have been presenting our undergraduate Seniors to the Biomedical Engineering community at large. These wonderfully talented people will inform you of the state-of-the-art design and research activities in biomedical engineering, particularly as advanced by our top-ranked Department of Biomedical Engineering.

These BME seniors represent a remarkable legacy. Today, for the 20th time, BME seniors will earn the right to join the BME Senior Project Family. What does that mean? It means that each one of these students took on an open-ended, highly challenging project synthesizing engineering and quantitative principals with biological or biomedical challenging questions and goals. Each one learned how to identify the essence of the challenge, evaluated multiple solutions, proposed and defended specific solutions, performed the necessary design and research to evaluate their solution, and evaluated their results. Each one was “severely” challenged during this process with uniquely blunt “feedback”. Each one had to defend their final product in a venue every bit as challenging and stressful as today’s. Of course, some 20 years ago, there was no PowerPoint or even readily accessible word processing and personal computers. Nevertheless, the BME seniors 20 years ago submitted superb final reports and learned how to prepare highly effective overhead transparency dependent presentations. They all defended their work in front of an audience like today’s and they did so with talent and gusto. Today, our BME seniors are challenged to prepare spectacular visual and scientific PowerPoint talks and defend them in front of over 80 biomedical companies, over 100 BME alumni, and all the BME faculty. Same stress as felt by students in Year 1. They are as ready. Make no mistake about it. Today...Boston University presents to you the best damn BME seniors in the nation. Outside guests and alumni....hold on to your hat...the ride will be astonishing.

I want to express a warm and proud welcome to the over 100 alumni spanning the 20 years of this program who are coming back to visit and attend. It is fantastic to retain your engagement in our program and to see you all again.

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’s Department of Biomedical Engineering was established in the College of Engineering in 1966, making it 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. This remarkable award, received in 2001, provides for a net $32 million enhancement in Biomedical Engineering over the next five years. Moreover, the Leadership Award validates Boston University as a true leader in this discipline. 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.” Among other things, through this award we will add 12 new faculty and enhance bench-to-bedside motivated research via coupling to the Boston University School of Medicine. We have already created a center for Nano and Micro Biosystems for applications in cell and tissue engineering, biosensors, and genomics. This month the new Life Science and Engineering Building opens, part of which was funded with the Whitaker Leadership Award. The combined new building and renovations in existing BME space will result this summer in a new Micro & Nano Imaging Facility, a new Biointerface Technologies Facility, new Class 100 and Class 1000 Bioengineering Clean Room Facilities, and a new Biomedical Engineering Simulation and Computation...
Facility. All these facilities will contribute to comprehensive educational and research programs in Cell and Subcellular Bioengineering, Protein and Genomic Engineering, and Integrated Physiological Systems.

The B.S. program in Biomedical Engineering is fully accredited by ABET. The undergraduate curriculum in Biomedical Engineering is designed to provide a foundation in the life sciences, physical sciences, 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. We competitively recruit students and faculty from all over the world to form an intellectual community whose interests and talents overlap in synergistic ways. This blending of common interests and unique skills in interdisciplinary scientific research has become the cornerstone of our department.

Seniors majoring in Biomedical Engineering are required to complete a two-semester major project which includes elements of technical writing and technical presentations along with actual independent design and research. Seniors also must participate in a complementary course taught by our Industrial Advisory Board and the School of Management. The course is called “Product Design, Development and Entrepreneurship in Biomedical Engineering” and taught students concepts of design, intellectual property, patents, regulatory issues, quality control, marketing, and entrepreneurship, all in the context of their projects.

Research by faculty and students takes place in seven interdisciplinary centers, all directed by biomedical faculty, as well as departmental laboratories. The Hearing Research Center combines theoretical and experimental studies of auditory processing to understand hearing in normal and impaired auditory systems. The Center for BioDynamics synthesizes dynamic systems theory with biophysics to advance new technologies that can improve biological and physiological function. The NeuroMuscular Research Center advances technologies for understanding and treating various neuromuscular disorders from lower-back pain to paralysis. The Center for Advanced Biotechnology brings robotics, computation, and nanotechnology to bear on unraveling genomic organization and structure and eventually treat genetic disorders. The Center for Biomolecular Engineering Research is aimed at computer-aided design of new molecular architectures (for drugs and vaccines), and at providing the computation infrastructure for the nation’s biotechnology effort. The Center for Advanced Genomic Technologies derives novel, high-throughput approaches for identifying protein function and gene, protein, and cellular regulatory systems. The Center for Nanotechnology and Nanobiosciences advances micro and nano systems for probing biology at the molecular scale and to develop drug delivery and biosensor systems. 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, cell and tissue engineering, and microfluidic phenomena in microcirculation; 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 $19 million in new external research for last year’s budget alone.

Boston University is the institution that will synthesize the best in engineering and biology with the best of interdisciplinary biomedical research.

Kenneth Lutchen, Chair
Department 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.

Tejal Desai, Associate Chairwoman, Graduate Affairs / Associate Professor - Dr. Desai's research involves the use of micro and nano-fabrication technologies to create implantable biohybrid devices for cell encapsulation, templates for cell and tissue regeneration, targeted drug delivery platforms, and novel protocols for the surface modification of biomaterials. Dr. Desai uses a multidisciplinary approach to better understand biological systems and develop micro and nanoscale therapeutic modalities for a variety of pathologies.

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.

Irving J. Bigio, 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 tumor angiogenesis and the development of optical techniques for imaging neuronal activation patterns in brain tissues.

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 mass spectrometry methods for faster DNA sequencing, the development of new variations and analogs of the polymerase chain reaction, and development of methods to detect, locate, and quantify RNA molecules in living cells. He is also interested in exploring the possible use of biological molecules for applications in nanoeengineering and microbotics. With Prof. James Collins, Dr. Cantor collaborates externally on a series of synthetic biology projects.

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. De Luca, Professor - Dr. De Luca'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 work involves: a) understanding how the brain and spinal cord control the individual fibers in a muscle, and groups of muscles, in healthy and dysfunctional individuals; including astronauts exposed to microgravity; b) means for monitoring functional activities; and c) 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.

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, Associate Dean, 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 nanoeonduit networks for microdevices.

Maxim Frank-Kamenetski, Professor - Dr. Frank-Kamenetski’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.
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.

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.

David Mountain, **Professor** - Dr. Mountain's research focuses on experimental and theoretical auditory neuroscience and on neuroinformatics. His areas of study include the study of electromechanical processes in the cochlea, the biomechanics of hearing in whales and dolphins, and on distributed computing techniques. Dr. Mountain is also interested in bioacoustic signal processing; sensory biophysics; measurement of evoked potentials and otoacoustic emissions; biomedical electronics, and biomimetic systems.

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).

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.

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 includes 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 Stamenovic, Associate Professor - Dr. Stamenovic’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. Stamenovic is also interested in mechanical properties of gas liquid foams and microstructural determinants of foam elasticity.

Béla Suki, Associate Professor - Dr. Suki’s primary research interest focuses both on experimental and theoretical investigation of soft tissue biomechanics from molecular to organ level with special emphasis on the mechanical properties of the normal and diseased lungs. His current research includes 1) imaging the extracellular matrix components while measuring the stress strain relationship of native and engineered tissues, 2) statistical mechanical modeling of avalanche phenomena in airway opening, 3) Surfactant release by epithelial cells during noise-induced stretching and its implication to mechanical ventilation, and 4) Stochastic modeling of complex biological phenomena such as network breakdown or the long-term fluctuations and predictability of asthma attacks.

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 coordinate 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 neurorecovery, 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; combinational 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) predicing 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.
Baltazar Aguda, Associate Professor - Dr. Aguda's research focuses on the control of the mammalian cell cycle and associated regulatory networks. In particular, cell cycle checkpoints have been shown to be associated with certain intrinsic network instabilities that are targets of signaling pathways to slow down or block cell cycle progression. One important checkpoint concerns the initiation of DNA replication; how this replication is coupled with the cell's death program (apoptosis) is another primary interest. Methods employed involve qualitative network analysis, nonlinear dynamics, computer simulations, and bioinformatics. These methods are currently being applied to the analysis of intracellular pathways relevant to chronic myeloid leukemia.

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.

Bennett 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.

Joyce Y. Wong, Clare Boothe Luce Assistant Professor - Dr. Wong's main research interest is in the development of new biomaterials which interact with living cells in novel ways. She is interested in questions relating to control of cellular behavior at the cell-material interface for drug delivery and tissue engineering applications. Her approach includes direct measurement of physicochemical interactions between biological molecules at the molecular and subcellular level. Other areas of interest include biosensors and model biomembrane systems. Dr. Wong's research uses a combination of approaches from materials science and engineering, physical chemistry, polymer science and polymer physics, surface science, and biophysics.

Secondary Faculty

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.

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.

S. Hamid Nawab, Associate Professor - Dr. Nawab's research involves advanced DSP techniques, approximate and incremental-refinement DSP structures, and partially symbolic and search-based DSP methods. Application contexts for this research include auditory scene analysis, biomedical sensing and imaging, portable multimedia devices, and communication systems.

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 constraint-based 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.

**Research Faculty**

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 photo-sensitive 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 Assistant 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.

Volkmar Heinrich, *Research Assistant Professor* - Professor Heinrich's research aims for deeper understanding of the physics that underly biological structure and function on a molecular and sub-cellular level. Experimental techniques developed explore the energy landscapes of fundamental processes such as single-molecule interactions, or membrane pore formation and rupture.

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 beamforming, signal processing, ultrasound-induced bioeffects, simulation and measurement of mechanical tissue properties, and scanning acoustic microscopy.
# 20th Annual Senior Project Conference

— Thursday, May 5, 2005 —

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<td>7:50 - 9:30 AM</td>
<td><strong>SESSION I</strong></td>
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|                    | A Novel Microfabricated Platform for Controlled, Sustained Drug Delivery to the Eye  
**Joy Tamiko Matsui** | Constructing 3D Airway Tree Models Using Hyperpolarized Noble Gas MRI  
**Niral Shah** |
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**Rebekah Gensure** | Image-Functional Modeling of the Lung: Asthma  
**Jennifer Kenyon** |
|                    | The Development of Nanoscale Electrical and Mechanical Biosensing Devices  
**Agnes Kalinowski** | Organ and Lesion Volumetry Using Dual Space Clustering and Morphological Erosion for CT Dataset  
**Kristen Kerikos** |
|                    | Development of an Array-based SPR Biosensor for the Detection of DNA-Protein Interactions  
**Dominic Fullenkamp** | Improved Coronary Artery Imaging with MRI: Suppression of the Pericardial Fluid  
**Hanan Al-Awadhi** |
|                    | Corrosion Casting for Characterization of Three-Dimensional Microstructures of Gels  
**Merrill B. Lamont III** | Light-Induced Fluorescence Imaging for Cancer Diagnosis  
**Makio Tazawa / Kin Tse** |
|                    | Characterizing and Designing Microcarriers for Peak In Vivo Performance  
**Annika Hedin** | Measuring Drug Concentration Profile in Layered Tissue  
**Colleen Hufford** |
|                    | Characterization and Analysis of Biomolecule-Bound Quantum Dots on PC12 Cells  
**Leora Nusblat** | The Use of Fluctuation Correlation Spectroscopy in Measuring Dynamic of Particles  
**Son Hoang** |
|                    | Insulin Release through Nanoporous Alumina Biocapsules  
**Priya Janardhana** | fMRI Brain-Computer-Interface: The Upgrade  
**Ugochukwu Amadi** |
|                    | Nanoporous Alumina Films for Bone Biotemplating Applications  
**Vivek Mukhatyar** |                                                |

9:35 – 9:55 AM **BREAK**

10:00 - 11:30 AM **SESSION II**

11:35 - 12:15 PM **LUNCH**
**SESSION IIIA**

**Integrated Biomechanics and Biomaterials**

**Room 206**

12:20 - 2:40 PM

**Session Chair:**

**Doug Cotter**

Dendritic Hydrogels for Use as an Ophthalmic Sealant  
*Melissa Dubowski*

Biomechanical Assessment of Engineered Cartilaginous Tissues  
*Akihiro Hidaka*

Design and Testing of an Artificial Intervertebral Disc  
*Neil Patel*

Micro-Patterned Substrata to Control Vascular Smooth Muscle Cells  
*Juliana Jackel*

Proteomic Analysis of Smooth Muscle Cells in Vitro for Uncovering Molecular Determinants of the Contractile Phenotype  
*Adiba M. Ali / Shipra Sharma*

Development of an Integrated Microfluidic System for Label-free Characterization of Microarray Binding Affinities  
*Jessica Louie*

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**EIGHT MINUTE STRETCH BREAK**

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A Design and Validation of an MRI Compatible Dynamic Spinal Testing Device  
*Ashley Chassar*

Effects of Cell Stretching on Cell Rheological Properties  
*Atalia Aron*

Effect of Cyclic Loading on the Expression of TIMP3 in Cells on Collagen-GAG Meshes  
*Rebecca Wu*

Modeling the Role of Lung Hysteresis in Response to a Deep Inspiration by a Bronchoconstricted Asthmatic  
*Nichole Faulkner*

Understanding the Breakdown Properties of Lung Tissue with Applications to Emphysema  
*Jesse Nandhavan*

Impact of Parenchymal Tethering and Smooth Muscle Constriction on In Situ Airway Pressure-Area Relationships during Deep Inspirations  
*Michael Hamilton*

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**SESSION IIIB**

**Neuroengineering and Auditory & Visual Systems**

**Room 205**

12:20 - 2:40 PM

**Session Chair:**

**John White**

The Effects of Informational Masking on Spatial Channels  
*Wei Li Fan*

Improving the Multi-electrode Chronic Recording Technique in the Hippocampus  
*Aubrey Cheung*

Monaural Intensity Discrimination: Effects of Perceptual Fusion of Target and Distractor  
*Tracy Pogal-Sussman*

Temporal Context Sensitivity of Field L Neurons in Zebra Finches  
*Jessica Gereige*

Characterization of EMG Signals from a Surface Array Electrode  
*Linda Uko*

A Pilot Study: Improving Mediolateral Balance Using a Ninety Degree Tilted Room  
*Matthew Christensen / Theresa DiPaolo*

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**EIGHT MINUTE STRETCH BREAK**

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Quantitative MRI at 1.5T vs. 3.0T: Phantoms and the Human Brain  
*Olga Nikolayeva*

Improved Techniques for Design and Construction of Implantable Multi-electrode Microdrive Arrays  
*Jonathan Sip*

Mathematical Modeling of the Horseshoe Crab Eye  
*Eileen Leung*

Improving Balance through Noise-Enhanced Sensorimotor Function  
*Lee Fisher*

Linear Model Approximation of Amacrine, Bipolar, and Ganglion Cell Interactions in Salamander Retina  
*Kian Setayesh*

Effect of an Object on Heading Perception  
*Megan Lopes*

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**2:40 - 2:55 PM**

**BREAK**
3:00 - 4:20 PM  SESSION IV  
Patient Monitoring and Bioinstrumentation

Quantitative MRI: Humans vs. Other Species  
**Vivian Luh**

Design of a Novel Inhalation Device for Large Volume Liquid Aerosol Delivery  
**Diana Manzanedo**

Development, Design, and Evaluation of a Human Diagnostic for the Measurement of Exhaled Particles  
**Matthew Brande / Karim Kokash**

In Vitro Characterization of Pulmonary Technologies for the Control of Respiratory Infection  
**Amber Fotinos-Hoyer**

Development of an Isolated Airway System for In Vitro Studies of Airway Wall Properties  
**Adam LaPrad**

Optimization of Current Generation from the Breakdown of Glucose by *R. ferrireducens* in a Microbial Fuel Cell  
**Jeff McAulay**

Relative Influence of Autonomic Stimulation on Sinoatrial and Atrioventricular Nodes of Normal, Healthy Human Subjects  
**Laura Ladrigan**

4:20 - 4:40 PM  BREAK

4:45 - 6:15 PM  SESSION V  
Tissue Engineering, Biomaterials and Systems Biology

Development and Characterization of a Porous, Patterned, Microtextured Scaffold for Vascular Tissue Engineering  
**George Lee**

Tissue Engineering the Medial Layer of Small Diameter Arteries  
**Joshua Schnall**

Novel Modeling of Nature’s Design in Genomic Regulatory Networks  
**Thanh Duy Le / Tricia Sarvia**

Stringent Response vs. Stationary Phase: Expression Analysis of *Escherichia coli* through Proteome Identification  
**Alex Tamburino**

Proteomic Profiling and Analysis of Lymphocytes Related to Chronic Obstructive Pulmonary Disease  
**Morgan Thompson**

Identifying the Proteins Involved in the Cell Cycle and the Cellular Response to DNA Damage  
**Joe Canavan / Mike Lamprecht**

6:15 PM  Closing Remarks
6:20 PM  Final Conference Comments:  **Dr. Kenneth R. Lutchten**

**RECEPTION IN THE ATRIUM, 2ND FLOOR, PHOTONICS CENTER**

**FOLLOWED BY STUDENT AND ALUMNI RECEPTION IN THE COLLOQUIUM ROOM, 9TH FLOOR, PHOTONICS CENTER**
<table>
<thead>
<tr>
<th>Session</th>
<th>Name</th>
<th>Technical Advisor</th>
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<td>Joy Tamiko Matsui</td>
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<td>Katie Mulholland</td>
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A Novel Microfabricated Platform for Controlled, Sustained Drug Delivery to the Eye

Joy Tamiko Matsui

Drug administration to the posterior segment of the eye is essential in treating eye diseases that plague the vitreous body and retina. However, due to the long diffusional distance from the point of application to the affected site, effective drug delivery to these areas remains a challenge. Moreover, conventional techniques are uncomfortable, and side-effects are prevalent due to high and frequent dosages required to maintain therapeutic concentrations. The objective of this project was to design a microfabricated ocular drug delivery device that will enhance drug absorption by providing controlled, sustained release of drug to treat eye disease at a localized site in the eye. The device is intended to be comfortably worn on the conjunctival surface of the eye for at least two months and relies on unidirectional passive drug diffusion through the sclera to permeate the vitreous body. The first step in this project was using photolithography to microfabricate a silicon/epoxy wafer with individual raised features corresponding to the desired drug reservoir dimensions. Soft lithography was then employed to generate a rigid polydimethylsiloxane elastomer inverted mold of the silicon/epoxy master features. From this mold, a prototype comprised of individual biodegradable drug reservoirs encased in a biocompatible non-degradable polymer backing was developed. Mitochondrial activity and dye exclusion assays were performed on an epithelial cell line to examine both cell viability and toxicity after extended exposure to the prototype. Using a large protein molecule as a model drug, release profiles were established from the biodegradable material used to fill the reservoirs. The release of the model drug was varied by changing the density of crosslinks in the loaded biodegradable polymer. The model drug used in this project represents the many drugs specific to the treatment of the posterior segment of the eye currently in clinical research. However, an ideal method of delivery for these novel drugs has yet to be designed. Therefore, the prototype developed in this project will provide a novel method of delivering old and new ocular drugs with minimal risk of overdose while targeting delivery to the affected area.
Designing a Microfluidic Platform to Enable Rapid Testing of Multiple Infectious Diseases

Rebekah Gensure

Laboratory for Biomedical Materials Research

Current methods for diagnosis of sexually transmitted infections are often expensive, can be painful for the subject, and can take several days to produce results. The number of cases of STIs per year continues to increase, making it critical to generate a rapid testing method that is easy and efficient for both patients and doctors. The purpose of this project was to design a microfluidic apparatus that would be capable of rapidly detecting multiple sexually transmitted infections in parallel. The device was designed to incorporate two main components - a series of microfluidic mixing channels to mix the biotinylated secondary antibodies and fluorescently tagged streptavidin proteins, and a reaction channel wherein target antibodies are adsorbed to the surface and are bound by the fluorescently linked antibody complex. This binding induces a fluorescent color change to indicate the results. Preliminary proof-of-principle testing of the device was performed by adsorbing mouse IgG antibodies to the binding reaction channel as the target antibodies. For these binding reactions, biotinylated goat anti-mouse IgG (immunoglobulin) antibodies were passed through the microfluidic mixing channels and bound to streptavidin conjugated with the fluorophore AMCA to form the fluorescently tagged secondary antibody complex. Results of the diagnostic tests were indicated by a noticeable fluorescent color change (positive result). Observation of no fluorescent color change was recorded as a negative test result. The results of these binding reactions indicated that we were able to successfully adsorb our target antibodies in various concentrations onto the cyclic polyolefin substrate, a standard inexpensive medical grade polymer used to make the microfluidic device. These results also indicated that the fluorescently tagged secondary antibody complex only bound to the target antigens and not to the substrate itself, as was confirmed by control experiments with no mouse antibody. Furthermore, we found a strong correlation between the numbers of fluorescent peaks in the fluorescent profile of each channel and the relative concentration of the target antibodies, which suggests that the device may have applications for determining antibody concentration. Specificity and sensitivity of the fluorescent immunoassay was determined using a standard diagnostic test performance study, and the device was found to exhibit 100% specificity and sensitivity based on the preliminary binding reactions performed. The overall impact of the project was an improved technology for STI testing by integrating microfabrication techniques with immunochemistry. Although further testing is required for full analysis of this new testing system, preliminary testing has shown that our testing system is highly sensitive, rapid, low-cost, and easy-to-interpret.
The Development of Nanoscale Electrical and Mechanical Biosensing Devices

Agnieszka Kalinowski

The need for more efficient, label-free methods of protein detection has created another outlet for semiconductor technology. Nanofabricated semiconductor devices offer the potential for highly sensitive detection of biomolecules. For instance, detection of certain biomarkers (e.g. proteins) linked with breast cancer can facilitate early detection and improve patient treatment. The overall goal of this project is to investigate the utility of two mechanisms of silicon-based biosensing. The first is a surface-modified semiconductor nanowire whose conductance is sensitive to changes in its environment by a field-effect mechanism. The second is a surface-modified nanocantilever beam whose mechanical properties (such as deflection and resonant frequency) are altered when a biological molecule binds to it.

In this project, finite-element simulation is used to determine the dynamics of the biofunctionalized nanomechanical sensor, immersed in a viscous fluid. In particular, resonant frequency shift is calculated as a function of the beam geometry and fluid flow parameters in the Stokes regime. The results of the finite element simulations indicate the technology has not yet been developed to deal with nanoscale systems with very low Reynolds numbers. However, the theoretical modeling proves that beam deflection due to fluid parameters will be negligible, but viscosity causes a significant change in the resonant frequency of the beam.

In the second part of the project, nanoelectronic biosensors are fabricated by electron-beam lithography and nanomachining. These sensors are bio-functionalized by chemical modification with an amino-silane (APTES) for pH sensing, biotinylated for detecting streptavidin and experimentally measured for its sensitivity. Conductance measurements with the nanoelectrical biosensors demonstrate repeatable sensitivity of 0.25 pH/nS to pH changes (for pH sensors) and 16.7nM sensitivity of streptavidin concentration binding to biotin on the surface. Although these nanoelectrical silicon biosensors have state-of-the-art sensitivity, further technological development is necessary for their clinical use.
Development of an Array-based SPR Biosensor
for the Detection of DNA-Protein Interactions
Dominic Fullenkamp

Biosensing is increasingly becoming an important tool in defense, drug discovery, and biology. A biosensor is a device that detects the presence of a specific target molecule. A surface biosensor measures the binding of solution-phase target molecules to surface-immobilized probe molecules. Surface plasmon resonance (SPR) spectroscopy, a general sensing method, has been employed to measure events such as DNA-DNA, DNA-drug, and DNA-protein binding. SPR detects molecular interactions by monitoring changes in refractive index at the surface. SPR has the advantage of not requiring fluorescent labels for the detection of biomolecular interactions and can be employed to measure kinetics in real time. Similar interactions, such as perfectly-matched and mismatched DNA hybridizations, have been shown to have different kinetic behaviors, which can be discriminated by SPR.

The main focus of this project has been to develop and characterize an array-based SPR imaging instrument. SPR imaging allows for 2-dimensional resolution of surfaces, unlike traditional angle-scanning SPR. An incoherent collimated white-light source is directed toward a prism on which a gold-coated slide has been placed. The light first passes through a 633 nm bandpass filter, polarizer, and nematic liquid crystal. The nematic liquid crystal changes the polarization state of the light based on an applied potential, allowing for normalization of spatial light intensity distribution. The angle of incidence of the light is set by a goniometer and the reflected intensity is spatially detected with a CCD camera. We have developed custom written MATLAB software to interface with the instrument. DNA can be covalently attached to the gold-coated surface, and binding events can be spatially resolved by monitoring changes in reflected light intensity. The instrument has been characterized for air and solution-based SPR imaging, using standard monolayer and patterned test surfaces.

In addition, we have worked to develop a surface chemistry that allows for DNA attachment, while preventing non-specific protein interactions. We have optimized DNA immobilization conditions on an inexpensive test surface composed of mercaptoundecanoic acid (MUA). The carboxylic acid functionality of MUA allows for standard NHS/EDC chemistry to be used to immobilize amine-terminated DNA. We have confirmed this chemistry through hybridizations of the complementary, mismatched, and control sequences to the DNA surface using our SPR imaging instrument. We observe differences in hybridization kinetics and equilibrium surface concentration for each sequence, consistent with previous work using angle-scanning SPR. We are currently working to extend the attachment chemistry developed for the MUA surface to a carboxylic acid-terminated PEG (HS-C_{11}-EG_{5}-OCH_{2}-COOH) surface.

We tested the polyethylene glycol (PEG)-based surface with a carboxylic acid terminus for non-specific protein interaction after it was capped with ethanolamine. For a model protein (thrombin), we saw good resistance to non-specific interaction. In future work, we plan to use the SPR imaging instrument to investigate thrombin interaction with selected surface immobilized DNA sequences (aptamers). Based on our current work, we believe that our instrument is sensitive enough to resolve these DNA-protein interactions.
Corrosion Casting for Characterization of Three-Dimensional Microstructures of Gels

Merrill B. Lamont III

The microvasculature provides oxygen and nutrients to tissues and plays a major role in a wide variety of diseases, e.g., in inflammation and diabetes. Corrosion casting has been used to create replicas of microvasculature beds as they would exist \textit{in vivo}. Such casts assist the investigation of disease-induced morphological changes. The overall objective of this proposal is to design a corrosion casting process to characterize the geometry of three-dimensional (3D) structures of tissue analogs \textit{in vitro}. The long-term goal is to use this process to evaluate fabricated products for tissue engineering, and to understand the remodeling of these tissue analogs after cell incorporation. Corrosion casting involves infusing low viscosity resins into the vasculature, allowing resin polymerization, and corroding away the surrounding tissue (maceration). Because agarose and collagen are the most widely used gels when fabricating microvasculature, emphasis was placed on creating a corrosion casting process for agarose, the less fragile of the two. One challenge concerns a lower density of proteins in engineered gels than in \textit{in vivo} tissues (3 mg / ml vs. 200 mg / ml). However, gel transparency allows casting compounds to be UV-cured, permitting greater control of casting conditions over the current use of self-curing resins. In designing a corrosion casting compound, an organic-based compound was investigated, since it is hypothesized that a water-based one may permeate into the gel pores and not result in a proper cast. Lastly, a weaker form of maceration was determined to address gel fragility. A model system was established to test the resolution and durability of casts, and a flow system then added the physiologically similar component of flowing the compound through the microstructure. Beyond cast development, its features were compared with those of the microstructure via microscope. In summary, this new corrosion casting process will become a key method of determining successes and quality of successes in microfabricating 3D structures of tissue analogs, and of displaying the extent of confluence upon cell ceding.
Characterizing and Designing Microcarriers for Peak in Vivo Performance

Annika Hedin
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A major goal in the targeted delivery of therapeutic agents via microcarriers (MCs) is to achieve an appropriate balance between non-specific and specific binding. Incorporation of a biocompatible methoxy poly(ethylene glycol) (PEG) blocks interactions with proteins that lead to rapid clearance from the bloodstream by components of the immune system, while homing ligands promote specific binding to a targeted site. There are several choices for core polymers available, however biodegradable poly(lactic acid) molecules have been shown to be stable and degrade slowly. The main objective of this project was to determine the structure-property relationships of PLA coated with PEG chains of varying tether lengths in the context of PEG surface density and protein adsorption in vitro with the intent of enhancing in vivo performance. A secondary aim of this project was to examine whether protein interactions inhibited specific binding between MCs liganded with Biotin-mPEG3300 and its corresponding streptavidin receptor. Particles coated with mPEG2000-DSPE and mPEG5000-DSPE had mean diameters of roughly 1.2 μm. From these diameter values and PEG concentration measurements obtained from nuclear magnetic resonance (NMR) we calculated the surface density of mPEG2000-DSPE and mPEG5000-DSPE to be 0.65 and 1.0 (chains/nm²), respectively. Exposure of liganded MCs to plasma decreased the binding between the ligands and soluble receptors under static conditions. In summary, a system was developed for quantifying the surface characteristics of PEG-lipid PLA MCs and determining the extent of protein adsorption and its effects on specific binding.
CHARACTERIZATION AND ANALYSIS OF BIOMOLECULE-BOUND QUANTUM DOTS ON PC12 CELLS

Leora Nusblat

Quantum dots are semiconductor nanocrystals capable of revolutionizing clinical testing for diseases such as cancer. By acting as fluorescent probes to target specific tissues, quantum dots hold promise to be used as an alternative to fluorescent organic dyes and proteins for biological labeling. In this project, the overall objective was to investigate specific receptor-mediated activity with quantum dots. First, we confirmed selective binding of biomolecules to quantum dots using atomic force microscopy (AFM) and X-ray photoelectron spectroscopy (XPS). Fluorescence microscopy showed that there was non-uniform binding of quantum dots and quantum dots with conjugated biomolecules. This characterization was performed using microfabricated wells to confine the dots to a certain region. Then, neurite growth measurements of nerve growth factor (NGF)-bound quantum dots in PC12 cells gave an indication of the effect of the quantum dots on bioactivity. Finally, PC12 cells attached to wells that were coated with quantum dot-bound immunoglobulin (IgG) better than in wells with unmodified quantum dots. The goal of this study was to understand the behavior of biomolecule-bound quantum dots in PC12 cells.
Insulin Release Through Nanoporous Alumina Biocapsules

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Diabetes mellitus (DM) is characterized by high blood glucose levels caused either by insufficient insulin production from the pancreatic β cells (type I diabetes), or target cell hyporesponsiveness to insulin known as insulin resistance (type II diabetes). The conventional treatment for type I diabetes is insulin daily injection, which is chronically invasive and does not mimic the typical physiological rapid rise and slow decline of blood insulin levels in response to ingested glucose. Hence, novel treatment methods are desirable. One current method is the use of nanoporous alumina biocapsules as an immunosolation device, which enables the passive diffusion of insulin, oxygen, and other nutrients, while blocking lymphocytes, macrophages, cytotoxic cell and antibodies from reaching the cells. The objective of this project will be to characterize the efficacy of the nanoporous alumina biocapsules by observing the effects of cell density, surface treatment, and pore size on insulin release over a five day encapsulation period. The nanoporous alumina biocapsules were used to encapsulate mouse insulinoma (MIN-6) cells within a collagen matrix consisting of rat tail Type I collagen, 10X HBSS, and 1M NaOH. All experiments were conducted after 3rd and 5th day of initial cell encapsulation, using a perifusion flow chamber system, in which the encapsulated alumina biocapsule was placed during a 150 minute time period. Samples of 100 uL were taken at predetermined time intervals. An enzyme linked immunosorbent assay (ELISA) was performed in order to analyze the amount of insulin released over time. All three goals of this project were conducted using the same experimental procedure as described, but each consisted of a different variable. For the first goal, insulinoma cell density was varied from 125,000 – 5x10⁶ cells/(mL collagen gel) in order to find the cell density which will produce the optimal insulin release. The second goal monitored insulin release through nanoporous alumina biocapsules surface modified with polyethylene glycol (PEG) encapsulated with the cell density found in the first goal. The final goal compared the affect of pore size on insulin release by using nanoporous alumina biocapsules anodized at 20 V and 60 V. Results obtained show that the optimal cell density is 1x10⁶ cells/(mL of collagen gel). In addition to this, it was found that PEG modified surfaces of the alumina biocapsules do not affect the diffusion of insulin through the nanoporous membranes. Finally, it was determined that alumina biocapsules anodized at 20 V do not significantly reduce insulin diffusion through the nanoporous membranes compared to the 60 V alumina biocapsules. By using implantable alumina biocapsules in type I diabetic patients, insulin could be released in a more natural physiological manner and the chronic invasiveness of daily insulin injections could potentially be eliminated.
Nanoporous Alumina Films for Bone Biotemplating Applications

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Bone tissue engineering deals with engineering biomaterials that can stimulate the deposition of minerals by bone cells (osteoblast). A major goal of bone tissue engineering is to replicate complex tissue architectures by designing better scaffold configurations and materials to better understand biological behavior with osteoblasts. The main goal of this project was to enhance osseointegration and matrix deposition by fabricating nanoporous alumina surfaces. "Cell chips" with localized patches of nanoporous alumina were fabricated for bone biotemplating applications using photolithography. These chips can be used for rapid prototyping studies. Cells were seeded on these chips to evaluate their performance on both nanoporous structure and alumina under similar culture conditions. Scanning Electron Microscopy and X-ray Photoelectron Spectroscopy were used to evaluate cell performance. Further, we also fabricated nanoporous alumina membranes using a two step anodization process in order to investigate the bone cell response. Osteoblasts were seeded on nanoporous alumina surfaces to investigate both short-term adhesion and proliferation and long-term functionality and matrix production. Cell adhesion and proliferation was characterized using a standard cell viability assay and cell counting. The total protein content was measured after cell lysis using the BCA (Bicinchoninic acid) assay for up to 4 week period of time. Finally matrix production was characterized in terms of surface concentrations of calcium and phosphorous, components of bone matrix, using X-ray photoelectron spectroscopy (XPS). The results from nanoporous alumina membranes were compared with those of amorphous alumina, aluminum, commercially available ANOPORE™ membranes, glass and latex. Results indicated that nanoporous alumina surfaces showed enhanced cell adhesion, proliferation and increased matrix production after 4 weeks of study. This research will enable us to develop better biomechanical interfaces of prosthetic devices for long term use in vivo.
Constructing 3D Airway Tree Models Using Hyperpolarized Noble Gas MRI

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Respiratory airways become constricted in people with asthma, and visualization of the airway tree can allow physicians to qualitatively assess which airways are being affected. This visualization of the airway anatomy can allow for diagnoses and evaluation of treatment efficacy. Currently, the best method for 3D rendering of airway trees is through CT scans, which also has the undesired effect of exposing the subject to ionizing radiation. Hyperpolarized Helium-3 (HypH) MRI is a novel imaging modality that can be used to image gas spaces, such as the pulmonary airways. Previous 3D renderings of the airway trees from HypH MRI dynamic multislice imaging suffer from the high aspect ratio of the scan’s voxels. The overall objective of this study is to determine whether programming projection reconstruction into a HypH MRI pulse sequence would provide an alternative and superior lung imaging method for rendering 3D airway trees. Simulations of projection reconstruction were performed on 2D virtual objects, representing axial slices of lung airways, to determine an optimal backprojection filter as well as to examine the quality of reconstruction. The effects of lung motion on image quality due to inhalation were also assessed by quantifying the errors in reconstruction of expanding 2D virtual objects. The results of the 2D simulations showed feasibility of implementing a projection reconstruction pulse sequence in HypH MRI of the airways. The airways of a human subject was imaged using 18 projections during inhalation of HypH gas. The projection images were processed to reconstruct each axial slice of the airway tree. These slices were then stacked to create a 3D rendering of the subject’s airway tree. The preliminary product demonstrates that this 3D rendering approach is feasible, and is superior in resolution to previous 3D airway tree models produced by HypH MRI dynamic multislice protocols. With this promising result, scan parameters will be further adjusted to improve the 3D rendering outcome.
Image Functional Modeling of the Lung: Asthma

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Asthma is a chronic respiratory disease in which airway hyper-reactivity causes increases in the lung's resistive and elastic properties, making it difficult to breathe. One way to assess lung structure is through a new imaging modality – Hyperpolarized (Hyp) $^3$He MRI. The goal of this project was to synthesize anatomically consistent airway tree models with Hyp $^3$He MRI imaging data to advance an approach called Image Functional Modeling (IFM). Using IFM, it is possible to quantify the airway structures responsible for ventilation and mechanical defects in asthmatics. Specifically, we examined the response to a deep inspiration in 3 healthy and 5 asthmatic subjects. Images were taken from healthy and asthmatic subjects, pre- and post-Methacholine (Mch) challenge and post-Deep Inspiration (DI). After bronchial challenge, all subjects showed heterogeneous distribution of ventilation defects. Also, lung resistance ($R_L$) and elastance ($E_L$) were measured as a function of frequency for each condition. These plots indicated mechanical heterogeneity of airway constriction post-challenge – specifically, an increase in the frequency dependence of $R_L$ and $E_L$. In MATLAB, image-processing algorithm was developed to align corresponding image slices within the field of view between conditions (i.e., baseline and post-Mch) and allow for the manual removal of image artifacts. Next, an optimal threshold was determined and used to convert the intensity Hyp $^3$He MRI images to binary image masks (all-or-nothing ventilation). A 3D model of terminal lung units was then morphed to the image-based masks, identifying ventilation at the terminal airways. This quantification showed a similar percent drop in ventilation post-Mch in healthy and asthmatic subjects. Post-DI, ventilation recovery was seen in all of the healthy subjects, whereas only two asthmatics recovered significantly. When comparing healthy and asthmatic subjects with the same level of constriction post-Mch, the healthy subjects were able to re-ventilate to a greater extent following a DI. The ventilation defects were then mapped into a 3D computational lung model and $R_L$ and $E_L$ were simulated at various degrees and locations of constriction. Matching the model-simulated mechanics with actual measured mechanics, we observed heterogeneous constriction throughout the airway tree, consistent to the ventilation distribution of the images. On average, asthmatics needed a greater standard deviation of constriction compared to healthy subjects both post-Mch and post-DI. This implies a greater heterogeneity of airway constriction necessary to match the mechanical increase in frequency dependence. In summary, IFM was used to show that post-Mch, asthmatic and healthy subjects constrict in a similar pattern regarding level of airway closure and heterogeneity. However, healthy subjects benefited more from a DI in terms of ventilation and mechanical recovery.
Organ and Lesion Volumetry Using Dual Space Clustering Segmentation and Morphological Erosion for CT Datasets

Kristen Keriakos

The purpose of this project was to further develop and evaluate a highly automated algorithm for the simultaneous segmentation of liver and liver lesions from contrast-enhanced, multi-detector computed tomography (MDCT) data sets. A segmentation algorithm based on dual-space clustering and morphological erosion was developed in Mathcad version 2001i. Two regions of interest (ROIs) are selected by the user, one within normal liver parenchyma and one within the lesion. The algorithm then segments both the liver and the total lesion burden contained within the liver automatically. Segmentation parameters that can be manually adjusted if needed include the cluster sizes (in Hounsfield numbers space and anatomical space) and percent acceptance. A total of 21 data sets of patients with normal and with abnormal livers containing morphologically different liver lesions were selected to test the speed and automation level of the technique. For the thirteen normal livers, an average of two segmentation trials were required to produce acceptable liver segments. For the eight abnormal livers, an average of three segmentation trials were required. In all cases the execution time associated with each trial was approximately four minutes. The total mean operator time per data set of normal livers was 9.2 ± 3 minutes, including the amount of time needed to select the ROIs and evaluate the results of each run of the segmentation algorithm. For abnormal livers, this time increased to an average of 12.5 ± 4.5 minutes. For normal livers, and those livers containing well circumscribed lesions, volumetric comparison was made to manual contour tracings. The manual contour tracings over all liver shapes required an average of 23.0 ± 5.0 minutes user time. The algorithm was shown to be considerably faster and much less user-intensive in comparison to the manual contour tracings. The correlation over all liver volumes was shown to be high, with an average error of 5.8% and an overall R² value of 0.7. The technique also has special application to those lesions characterized as highly infiltrative which are not segmentable by manual contour tracings.
Coronary artery disease (CAD) is one of the major causes of mortality and morbidity in the United States. CAD results from coronary arteries constriction due to fat and plaque accumulations, and symptoms include arrhythmias, shortness of breath, angina and death. Diagnostic cardiology uses coronary magnetic resonance angiography (coronary MRA), the application of the magnetic resonance imaging techniques to the heart, to diagnose CAD more carefully. This methodology suppresses the signals of fats and the myocardium in order to visualize the coronaries. However, the presence of the pericardial fluid (PCF) adjacent to the coronaries reduces the image resolution. The goal of this project, therefore, is to improve the current coronary MRA pulse sequence by reducing obstructive signals of PCF. To achieve this, we 1) assessed the PCF prevalence among cardiovascular patients; 2) measured the PCF relaxation times, $T_1$ and $T_2$; 3) attempted to develop an MR pulse sequence that suppresses the PCF signals using Philips programming and graphics tools. We found that about 25% of the population examined have PCF. In addition, measurements of the PCF relaxation times, $T_1$ and $T_2$ were found to be $\sim 1632$ ms and $104$ ms respectively, which are lower than expected. The modified pulse sequence was successful in suppressing the signals of PCF, however the signals from blood and the myocardium were also suppressed, which reduced image quality instead of improving it. Further investigations are required to find another approach to PCF suppression.
Light Induced Fluorescence Imaging System for Cancer Diagnosis

Makio Tazawa
Kin Tse
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Diagnosis of cancer on the surfaces of internal tissues is performed largely by random, costly, and invasive biopsy methods. Point spectroscopy methods provide a less invasive alternative; however, they are still random and time consuming. Cancerous lesions exhibit different concentrations (from normal tissues) of metabolites and structural proteins, some of which can fluoresce. Additionally, exogenous drugs can be administered to tissues and result in much higher fluorophore concentrations in lesions due to the drugs' high affinity for cancer cells. The overall objective of this project was to build a highly sensitive in vivo imaging system capable of contrasting the fluorescence in tissue due to normal activity and cancerous activity. To this end, an endoscope-based system coupled to a highly sensitive CCD (charged-coupled device) camera was chosen for the design. Using an optical fiber through the endoscope channel, gel phantoms were illuminated with 440 nm excitation light, and the emitted light was focused, filtered and detected by the camera. The gel phantoms were designed to simulate the autofluorescence background due to endogenous fluorophores of normal tissue, as well as the higher intensity, exogenous drug fluorescence of cancerous tissue. Fluorescein was used as the fluorophore simulating the autofluorescence background in the gels at a concentration of $10^{-6}$ g/mL, and 1 mm$^2$ cancerous lesions were simulated using the fluorophore rhodamine 6G for the induced fluorescence in concentrations ranging from $10^{-5}$ g/mL to $10^{-4}$ g/mL. Software was developed to control the camera, light source, and for processing of the images. A false color scheme, according to varying intensity was added to the images. A method to improve the contrast between exogenous drug fluorescence and the autofluorescence of tissue was developed using elastic scattering spectroscopy, ESS. Using ESS, correction factors for the images were obtained from measurements on the gels, to adjust the image intensity according to wavelengths of autofluorescence and induced fluorescence. Using this method, the intensity ratio between induced fluorescence and autofluorescence has been increased 22% to 150%, depending on the concentrations present. This device could serve as a guide for surgeries, biopsies and spectroscopy methods, making diagnosing and removal of cancer earlier, less expensive and time-consuming.
MEASURING DRUG CONCENTRATION PROFILE IN LAYERED TISSUE

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Drugs are used to treat many different diseases. In order to determine the effectiveness of a drug, it is important to resolve the local drug concentration and depth profile in the target tissue. Photodynamic therapy is a cancer treatment, where a photosensitive agent is light activated, causing necrosis of the surrounding cells. It is important to know the concentrations of photodynamic therapy drugs at different tissue layers in order to minimize damage to healthy cells. Optical pharmacokinetics will provide a non-invasive drug concentration profile in real time.

The goal of this project is to explore the effects of fiber angles and fiber separation on the measurement of drug concentration at different tissue depths. A system was created that measures the tissue spectrum from multiple fibers of a probe simultaneously. Several optical fiber probes were designed and developed with specific fiber angles and separations. Spectral measurements were taken from liquid tissue phantoms with different scattering and absorption properties to determine the optimal fiber configuration which presents a photon path-length that is independent of the scattering properties of tissue. A software system was developed to control the measurement system and analyze the spectral data. The trends in the data are consistent with Monte Carlo computational simulations; which predicted the optimal fiber separation for each angle tested. The maximal depth penetration was determined by making spectral measurements of layered agarose tissue phantoms. The data shows that larger fiber angles results in measurements of superficial drug concentration. The information on the optimal fiber separation and depth penetration of light in tissue for angled fibers expands upon past research. This system is useful to map the kinetics and distribution of drugs in layered tissues, enabling the assessment of local effectiveness of drug treatments and facilitating the measurement of real-time concentrations of photodynamic drugs.
The Use of Fluctuation Correlation Spectroscopy in Measuring the Dynamic of Particles

Son Hoang

Fluctuation correlation spectroscopy (FCS) is a non-invasive optical technique of analyzing the intensity fluctuations of particles in determining the dynamic of particles in a small observation or focal volume, on the order of femtoliter. Autocorrelation analysis of the FCS intensity fluctuation can be used to measure concentration, diffusion properties and dynamic of particles. Under normal circumstance, FCS apparatus are constructed to analyze molecular dynamics of samples that undergo random diffusion in the observation volume. However, FCS lacked the ability to analyze intensity fluctuation of particles with directed motion. Traditional approach of study intensity fluctuation with directed motion with Fluorescence Cross-Correlation Spectroscopy was technically inconvenient since the technique requires two laser beams to be aligned parallel to each other. The overall object of this project is to validate a simpler alternative to cross-correlation with a single beam technique that would allow FCS to analyze the dynamic of particles in both random diffusion and directed motion. By implementing an oscillating mirror to the original FCS apparatus, we allowed the laser beam to follow, with and against, the flow of particles. As the laser beam followed the direction of flow, the particles resided longer in the focal volume, resulted in slower fluctuation signals. As the laser moved in the opposite direction of flow, the particles spent less time in the focal volume, consequently resulted in faster intensity fluctuations. The new method was demonstrated with the use of air bubbles for stronger intensity fluctuation signal that was able to undergo directed motion. The differences in duration and strength of intensity fluctuation of bubbles were studied with autocorrelation analysis. The bubbles were generated in two different mediums, distilled water and motor oil, to vary the speed of the bubble due to differences in their viscosity. The variation in velocities was to demonstrate the accuracy of the apparatus in analyzing the dynamic of particles with different parameters. By analyzing the differences in the number of particles in the observation volume due to the upward and downward oscillations of the scanning mirror, we were able to determine the velocity of particles with great accuracy. We had successfully validated a new technique with the FCS apparatus to demonstrate the ability of FCS in measuring the dynamic of particles for both random diffusion and directed motion. Furthermore, the apparatus can easily be implemented in a laser scanning microscope, thus imaging and analyzing the dynamic of molecules with directed motion such as cellular movements can be made possible. By successfully demonstrating that FCS potential in analyzing particles or molecules with directed motion, we have open up new possibilities in the field of optical imaging and biological microscopy.
fMRI Brain Computer Interface: The Upgrade

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Brain computer interfacing is the act of using brain signals as a non-muscular pathway for neuronal directive transmission to an outside-the-body port. Existing brain computer interface — BCI — systems rely on signals obtained through electroencephalography resulting in low signal spatial resolution. Upgrading a BCI using functional magnetic resonance imaging - fMRI — provided accurate signal localization and thereby precise thought interpretation through high spatial resolution. Additionally, fMRI signal acquisition takes place in a completely non-invasive manner, simplifying the experimental process. The primary goal of this project was to optimize the fMRI BCI through the compilation of six solely thought driven tasks and the creation of an accurate, efficient pattern matching algorithm to determine user intent. The following study used fMRI to determine areas of neural activity in response to one imagining moving the left hand and the right hand, mentally visualizing faces and symbols, generating rhymes in the mind, and mentally subtracting numbers. Each of the six mental tasks was completed individually within a sixty second “event based” experimental paradigm producing a unique magnetic resonance signal pattern. The acquired signal was translated into a functional brain activity image map using a program called Statistical Parametric Mapping (SPM02) operating under the MATLAB programming environment. Furthermore, a statistical pattern matching algorithm was created to identify which of the six mental tasks was completed. The fMRI BCI classified each of the six tasks to 92% accuracy where the minimum image map pixel intensity for activation significance was a p-value of 0.001. Signal to image reconstruction was completed in 20 seconds while task recognition was completed in < 1 second using a 2GHz Intel CPU. Results suggest that the six tasks were significantly statistically unique in brain activation area thereby making them suitable for use as potential BCI command controls. The upgraded fMRI BCI has been shown to have successfully increased the number of simple tasks which activate significantly different areas of the brain and also to have implemented a new accurate, efficient pattern matching algorithm enabling the use of fMRI to detect spatial pattern activation and decipher BCI user intent. The advancement of the fMRI BCI will give rise to a world of potential independence for those who suffer from physically debilitating diseases such as cerebral palsy or Lou Gehrig’s as well provide users with a much higher level of detail in regard to brain activity localization.
Dendritic Hydrogels for Use as an Ophthalmic Sealant

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The overall objective of this project was to synthesize and characterize dendritic hydrogels in order to determine whether these compounds are a viable alternative to the use of sutures for closing ophthalmic wounds. The hydrogels are composed of dendrons, which have high solubility, high surface area to volume ratio, and a large number of cysteine end groups for functionalization. Dendrons are also thought to be biocompatible because they are composed solely of cysteine and lysine, which are amino acids native to the body. These dendrons were combined with several polyethylene glycol (PEG) linkers to create hydrogels. These hydrogels are well-defined polymer networks held together by crosslinks, in this case a thiazolidine linkage. Three PEG-based compounds were used to create hydrogels in this experiment. The three PEG-based compound had three different end groups. PEG-C2-Dialdehyde, PEG-C3-Dialdehyde, PEG-C4-Dialdehyde were tested. These PEG compounds range in stability, where PEG-C4-Dialdehyde is the most stable, and the PEG-C2-Dialdehyde, is the least stable. The stability of the PEG compound used dictates the stability of the hydrogel formed. The three hydrogels formed have undergone a battery of tests to determine biocompatibility; including mechanical, adhesive, and optical experiments. Using the TA Instruments AR 1000 the phase angle and Young’s, Storage, and Loss Moduli of the hydrogels were determined. This instrument was also used to determine the properties of the natural cornea and cyanoacrylate-based adhesives. This data showed that the hydrogel made with PEG-C4-Dialdehyde was the optimal choice for a sealant, because it was the most elastic hydrogel. To evaluate the adhesive properties of the hydrogels formed with PEG-C3-Dialdehyde and PEG-C4-Dialdehyde, 4.1 mm central lacerations were sealed on human eyes, and the holding pressure was tested. Eyes were also sealed using standard nylon sutures. The data obtained showed that eyes sealed with PEG-C4-Dialdehyde hydrogels held 160 +/- 25 mmHg, which is a higher intraocular pressure than any other sealant, including sutures (55 +/- 28 mmHg). The optical properties of hydrogels made using PEG-C4-Dialdehyde were investigated using an integrating sphere apparatus. A laser with a wavelength of 633 nm was shone through the hydrogel samples, at which point the transmittance was determined. The results show that hydrogels made with chemically pure compounds and pure buffer solution, have a transmittance of 90.5% (+/-2.5%). A high transmittance is important for these hydrogels because of their ocular applications. These results strongly indicate that hydrogels formed using PEG-C4-Dialdehyde may be an alternative to the suture as an ophthalmic sealant. In order to advance this research, more testing will need to be done in terms of degradation time and cell toxicity. If these studies go well, this hydrogel has the potential for in vivo experimentation.
Biomechanical Assessment
of Engineered Cartilaginous Tissue

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Articular cartilage has low capacity for natural repair due to the absence of blood vessels. Without blood vessels, the chondrocyte cells that reside in articular cartilage receive inadequate nutrition, and in turn, the production of the extracellular matrix (ECM) that serves as the architectural framework is very limited. Previous studies in our laboratory and others have shown that controlled mechanical stimulation can induce cartilaginous tissue formation in a healing bone defect. For example, controlled bending stimulation of a surgically created osteotomy in the rat femur results in the formation of cartilaginous tissue rather than bone in the osteotomy gap. This newly formed cartilage displays structural and molecular characteristics of articular cartilage. The overall goal of this project was to assess the biomechanical and biochemical properties of these engineered rat cartilaginous tissues, and to compare its biological functionality to healthy and degenerated rat articular cartilage. We used a noncontacting osmotic loading method to induce swelling and calculate strain. In this method, cartilage samples were equilibrated in NaCl solutions of varying osmolarity. Swelling that resulted from changes in external bath concentration were translated into strain via displacement calculations of chondrocyte nuclei. High-resolution images were acquired for displacement calculation by fluorescently staining osmotically loaded specimens and capturing their image using a laser scanning confocal microscope. The biochemical properties of specimens were determined by measuring their glycosaminoglycan (GAG) content and water content. In this manner, their fixed charge density and water volume fraction were quantified. Our results further confirmed the presence of cartilaginous tissue within the defect gap. Biochemical analyses indicated GAG content similar to that found in healthy, native articular cartilage. Through confocal image analysis, we saw lacunae and clusters of chondrocyte nuclei indicating the presence of viable cartilaginous tissue within the defect gap. It was believed that the high volume of nuclei was a sign of continuing growth of cartilaginous tissue. Swelling in the tissue could not be obtained using the performed experimental methods. The absence of swelling was confirmed through two-dimensional strain analysis and three-dimensional displacement calculations. The overall result of this study revealed encouraging biochemical similarities between the engineered cartilaginous tissue and native articular cartilage. Our findings also indicated the need to improve experimental procedures for the noncontacting osmotic loading method.
Design and Testing of an Intervertebral Disc Replacement

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With the sharp expected increases in over-65 and obese populations, it is likely that the incidence of back pain will increase steadily in the United States during the next 50 years. One of the most common causes of back pain is the ailment known as a "slipped disc." This term refers to the condition during which the intervertebral disc herniates as the load bearing nucleus pulposus protrudes through the annulus fibrosis into the intervertebral space. Current therapies such as spinal fusion and conservative care reduce lateral mobility and only result in short term relief respectively. The inefficiencies of the mentioned therapies result in reoccurring disc herniations between other vertebrae of the spine. The goal of this project was to create a nucleus pulposus replacement that could closely mimic the native intervertebral disc specifically in terms of its swelling capability, biocompatibility, and mechanical competency. The intervertebral disc replacement was made out of a polyHEMA polymer that was modified to contain a net positive charge. This modification allowed the gel to absorb charged fluids and thus ensured that the swelling capability was maximized. Once a satisfactory gel had been created and had a quantified swelling ratio above 1, the biocompatibility objective was achieved by testing the device in the presence of native fibroblasts and noting the resulting cell death using the standard MTT assay. A standard of biocompatibility was achieved when the device that was shown to be less toxic than a sample of latex. Finally, mechanically competency was ensured by quantifying the Young’s modulus of the device using the Texas Instruments Dynamic Mechanical Analyzer Q800. In the end, the most appropriate form the device was a polyHEMA polymer device that was modified to have a net positive charge after being soaked in Chondroitin-6-Sulfate. This form of the device showed a swelling ratio of approximately 1.33, exhibited the best biocompatibility, and proved to have a substantial Young’s modulus of 8000 Pascals. The future implantation of this device will surpass current therapies for disc herniation because this device was able to simultaneously maintain mechanical competency along with biocompatibility in the spinal environment. One final benefit of the device is its potential to be implanted via a minimally invasive procedure. Because the device takes shape as it absorbs surrounding fluid, a large incision is not necessary since the device will not be at full volume prior to implantation. As a result, future patients with suffering from intervertebral disc herniation can expect to receive both a safe and effective treatment via a surgery during which the created device is implanted in replacement of the native nucleus pulposus.
Micropatterned Substrata to Control Vascular Smooth Muscle Cells
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Vascular smooth muscle cells express a contractile phenotype in vivo that is lost as cells proliferate in vitro. The manufacture of a successful tissue engineered blood vessel requires the ability of VSMCs to proliferate and populate a scaffold, then revert back to a contractile state. In vivo, VSMCs are highly elongated and previous studies from our lab have shown that cell shape influences the localization of proteins such as F-actin and calponin that have a contractile function. Further work by others found that cell constrainment reduces proliferation as well. However, all of these studies investigated cells on rigid substrates, which do not mimic the mechanical environment of the arterial wall and cannot functionally measure contractile force generation. To quantify the effects of cell shape on functional cell contractility we have developed a method to constrain cells on surfaces with physiologically relevant mechanical properties. We hypothesize that by constraining VSMCs in an elongated fashion we can recover some of their contractile function. We used soft photolithography techniques to pattern 10-micron lanes of collagen onto cell compatible polyacrylamide gels. We observed a two-fold increase in the ratio of length to width of VSMCs on patterned surfaces compared to unpatterned surfaces. To measure force generation of VSMCs at rest and during contraction, we used traction force microscopy to compute traction forces based on the displacement of fluorescent beads before and after addition of the vasoconstrictor potassium chloride (KCl). We observed no statistically significant differences in basal traction forces or traction forces after the addition of KCl generated by patterned and unpatterned cells. In conclusion, we have developed a novel means of micropatterning cells on substrates with physiologically relevant compliance ranges for further study to determine quantitatively the relationship between cell shape and contractibility.
Proteomic Analysis of Smooth Muscle Cells in vitro for Uncovering Molecular Determinants of the Contractile Phenotype

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A major challenge for vascular tissue engineering is the ability to control vascular smooth muscle cell (VSMC) behavior: proliferation is required to expand cell number while contractility is necessary for proper function of the tissue. VSMCs grown in vitro lose their native, contractile phenotype over time, adopting a synthetic, proliferative phenotype. Current assays used to distinguish between contractile and synthetic VSMCs largely rely on expression of only a few molecular markers. The main objective of this project was to design proteomic procedures to identify molecular determinants of the contractile phenotype of the VSMCs. We investigated the contractile and proliferative proteins associated with two VSMC lines extracted from the rat aorta: A7r5 and A10. Cell line A7r5 is thought to be more proliferative, while cell line A10 is thought to be more contractile. These two cell lines were grown in conditions previously shown to promote either contractility or proliferation. Cell lines were cultured on a variety of surfaces, including plastic, laminin, and fibronectin, and in the case of cell line A10, in the presence of transforming growth factor-β (TGF-β) and platelet derived growth factor (PDGF). Proteins from each VSMC sample were separated using one-dimensional polyacrylamide gel electrophoresis (1-D PAGE). Proteins were digested with trypsin to obtain peptides, which were further analyzed by mass spectrometry (MS) to obtain the tryptic peptide spectra. Spectra obtained were compared to the theoretical spectra by software called SEQUEST. Matches between the theoretical and experimental sequences were considered protein identifications. Approximately 40 known contractile proteins were identified in each sample. An additional 21 potentially contractile proteins and their functions were identified from comparisons of conditions promoting contractility and proliferation. This proteomic approach is a valuable resource for researchers to identify candidate protein markers of VSMC contractile phenotype for further investigation of their significance and functionality.
Development of an integrated microfluidic system for label-free characterization of microarray binding affinities

Jessica L. Louie

To fabricate a microfluidic flow system that encloses the resonant cavity of the Resonant Cavity Imaging Biosensor (RCIB), a novel microfluidic design was developed to integrate the two Bragg reflectors of the RCIB into a flow system. The RCIB uses a resonant cavity to achieve high imaging sensitivity for label-free detection of binding between biomolecules and probe molecules fixed in a microarray. The flow system will deliver unlabeled biomolecules in-solution to the resonant cavity, allowing the RCIB to take real-time measurements necessary for kinetic study of binding affinities. Kinetic characterization of binding affinities are of particular interest when studying protein-protein interactions in drug therapy development for example. To build the flow system, polydimethylsiloxane (PDMS) was chosen because it has been used to build microfluidic systems for other biosensors and it has also been used in an optical application to define the height of a resonant cavity. PDMS is widely used in microfabrication for biological and electronics applications because it is inexpensive, easily molded, and has good biocompatibility. Specific design challenges posed by the integration into the 20-100 μm resonant cavity of the RCIB were that devices parts could not interrupt imaging optics and interconnect tubing needed to be positioned without jeopardizing the reflector’s stability or structural integrity. To realize the novel microfluidic design in PDMS, two alternate methods of fabrication were investigated. In both methods the two Bragg reflectors were embedded in PDMS in order to allow interconnect tubing to access the flow channel. In the first method PDMS was cast in a mold, and then sealed on the bottom reflector in a dome-like fashion to form a flow channel. In the second method a thin film of PDMS is stacked between the two reflectors to provide the desired reflector spacing. The thin film of PDMS was produced with specific height by spin coating. A functional microfluidic device could not be produced with the reflectors embedded in PDMS because of problems with PDMS prepolymer seeping into the optical pathway during molding and PDMS shrinkage. Prepolymer seeping was be overcome by embedding reflectors against a hydrophobic PDMS substrate. Alternate PDMS weight ratios or polymers may be used to lessen shrinkage. In conclusion, the multilayer stacking method shows promise in producing a functional flow system to enclose the resonant cavity of the RCIB.
A Design and Validation of an MRI Compatible Dynamic Spinal Testing Device

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Lower back pain is among the top five most common reasons for patient visits in the United States. Disorders of the intervertebral disc are usually manifested by changes in the disc's shape, volume, structure, and composition due to age. MRI imaging is currently the gold standard for assessment of degenerative state of the disc. Presently no method exists for the detection of degenerative signs for early detection and diagnosis of disc disease. The aim of this project is to validate the design of an MRI-compatible device for functional imaging of intervertebral discs and to identify an MRI-compatible displacement measurement device. The device is a pneumatic actuating system, controlled by a PID controller. The displacement measurement device, an optical encoder, provides location feedback in the system. Hence, this system is closed loop with the optical encoder implemented. The validation of the device design is done using MATLAB's SimuLink environment to model the actuating system. In the event the current model fails to meet specifications, another design has been identified that has potential of meeting the criteria. The new design involves a hydraulic system as opposed to a pneumatic actuating system. Upon continued validation of the device design and future testing, the device will eventually be certified MRI-compatible. The ultimate goal of this research is to get an MR image of an intervertebral disc and study the disc experiencing mechanical load.
Effect of Stretching on Cell Rheological Properties

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A fundamental question in cell biology is what determines the rheological properties of living cells. If the mechanical distending stress is a key determinant of cell rheology, then modulating this stress by cell stretching should have a major effect on cell rheological properties. If not, then other mechanisms must play a major role. The goal of this project is to study the effects of mechanical distension on the rheological behavior of human airway smooth muscle (HASM) cells. Previous work indicates that altering the active component of the distending stress using pharmacological means results in an increase in the dynamic modulus, $G^*$. In this project it is expected that modulating the passive component of stress by cell stretching should have a similar effect on $G^*$. A stretchable cell culture device has been developed that is able to rapidly stretch HASM cells, thereby generating passive mechanical stress within the cell. This device is placed inside a magnetic cytometry system to measure the change in $G^*$ with increasing strain. In this project, data that have been previously obtained from stretching experiments on HASM cells are quantitatively analyzed using newly developed software. Mathematical models, both previously developed as well as newly developed, are used to fit the data. The model parameters were related to the underlying mechanisms in living cells. The results if this project demonstrated that passive mechanical stretching produced results similar to previous studies (Wang et al. 2001, 2002; Hubmayr et al. 1996) of active agonist-induced stretching. These findings suggest that prestress is in fact indicative of cell rheological behavior.
Effect of Cyclic Loading on the Expression of TIMP3 
in Cells on Collagen-GAG Meshes

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Many shortcomings of current tissue substitutes, such as scarring and impaired healing, stem from the lack of knowledge regarding cellular interactions with tissue scaffolds. In particular, there is a lack of understanding as to how mechanical forces affect cell growth and behavior on engineered surfaces. The overall goal of this project is to use real-time polymerase chain reaction coupled with reverse transcription (RT-PCR) to determine the effect of micromotion (i.e., small cyclic loads) on the expression of tissue inhibitor of metalloproteinase-3 (TIMP3), an extracellular matrix remodeling factor, in cells grown on collagen-glycosaminoglycan (GAG) meshes. Collagen-based substrates are a natural choice for use as tissue engineering scaffolds because of the abundance of collagen in connective tissue in vivo. By itself, however, collagen is a poor scaffold because its jelly-like texture makes it difficult for cells to permeate the structure. For this reason, the collagen used to synthesize the meshes in this project was cross-linked with chondroitin 6-sulfate, a type of GAG, to form a cohesive, porous mesh for cell support. WS1 human dermal fibroblasts were cultured on three experimental surfaces: two-dimensional (2D) collagen-coated plates, three-dimensional (3D) unloaded collagen-GAG meshes, and loaded collagen-GAG meshes. In addition, cells were cultured on untreated tissue culture polystyrene (TCP) plates to establish baseline TIMP3 expression. Each sample was incubated in 5% CO₂ at 37°C for four hours. The collagen-coated plates served as the control between the 2D and 3D environments while the unloaded meshes served as the control between the loaded and unloaded environments. For the loaded meshes, small cyclic loads were applied using the Q800 Dynamic Mechanical Analyzer (DMA) from Thermal Analysis Instruments. The DMA uses submersion clamp technology, which allowed samples to remain immersed in supplemented media for the duration of the experiment. A loading frequency of 0.1 Hz was applied to individual cell-seeded meshes with a preload force of 1.0 N and an amplitude of 100 μm for four hours. Total RNA from the sample cells was isolated upon termination of the experiments using an RNeasy Mini Kit from QIAGEN. The isolated RNA was reversed transcribed into complementary DNA (cDNA), the preferred template for PCR amplification, using the SuperScript™ III First-Strand cDNA Synthesis System from Invitrogen. TaqMan® Universal Master Mix and TaqMan® Assays-on-Demand™ probes (Applied Biosystems) were used to prepare the synthesized cDNA templates for PCR. Samples were prepared in triplicate on a 384-well optical PCR plate for amplification in the Applied Biosystems 7900HT Fast Real-time PCR System. A probe for TIMP3 was used to screen the mRNA levels of the target gene and a probe for the endogenous control was also included. Glyceraldehyde-3-phosphate dehydrogenase (GAPD), a catalytic enzyme involved in glycolysis, was used as the endogenous control for the PCR experiments in this project because its expression is independent of applied mechanical force. In addition, a no template control (NTC) composed of Universal Master Mix and RNase-free water was used to calibrate the system. Expression data obtained from RT-PCR were analyzed using the accompanying Applied Biosystems SDS 2.2 software and the Relative Quantification \( \Delta \Delta C_T \) Study option. The software computed threshold cycle (\( C_T \)) values for each sample, which were used to calculate \( \Delta \Delta C_T \) values. The \( 2^{-\Delta \Delta C_T} \) method of quantifying relative changes in gene expression was applied to the results to determine the mean fold change in TIMP3 expression across the three experimental conditions relative to the baseline condition. The results of this study showed that the expression of TIMP3 in dermal fibroblasts grown on collagen-GAG meshes increased in response to cyclic loads. Since TIMP3 inhibits the proteins responsible for extracellular matrix (ECM) reorganization, the results suggest that pressure applied to a wound encourages scar formation rather than healthy remodeling of the ECM at the wound site. Though these findings conflict with the idea of using pressure therapy to minimize scar formation in healing skin, the mechanism by which cyclic loads enhance TIMP3 expression is still unknown and must be examined in order to fully characterize the effect of mechanical forces on the expression of TIMP3 in cells on bioengineered tissue scaffolds.
MODELING THE ROLE OF LUNG HYSTERESIS IN RESPONSE TO A DEEP INSPIRATION BY A BRONCHOCONSTRICTED ASTHMATIC

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Asthma is a prevalent respiratory disease that is clinically defined by three hallmark characteristics: spontaneous reversible airway obstruction, airway hyper-responsiveness (AHR), and chronic inflammation of the airways. The underlying mechanisms regulating this asthmatic behavior have been studied in a variety of ways, including by characterizing the response to a deep inspiration (DI). When the airways are constricted, the DI response of an asthmatic subject has revealed two distinct trends: bronchodilation of the airways (reduction in airway resistance, $R_{aw}$) or heightened bronchoconstriction (transient increase in $R_{aw}$). The mechanisms regulating the DI response are hypothesized to be dependent on the method of constriction (spontaneous or pharmacologically induced) and initial obstruction level (quantified by $R_{aw}$). The relative magnitude of airway wall and lung tissue hysteresis (the stress-strain relationship between the expansion and deflation volumes) has also been hypothesized to regulate the DI response. The overall objective of this project was to elucidate the underlying mechanisms responsible for varying observed DI responses in asthmatic subjects. To this end, both experimental and computational modeling techniques were employed to investigate the DI response. Using transfer impedance ($Z_u$), $R_{aw}$ was calculated for two groups of asthmatic subjects, one group constricted by Methacholine (Mch) inhalation and another with spontaneous airway constriction. For both asthmatic groups, the response to a DI was quantified before, during, and after a DI by creating hysteresis loop plots of $R_{aw}$ vs lung volume during a DI and also by finding the mean pre-DI $R_{aw}$ and 3 second post-DI $R_{aw}$. From these measures, 5 of 7 subjects experimentally constricted asthmatic subjects demonstrated a transient decrease in $R_{aw}$ post-DI. A significant increase in $R_{aw}$ post-DI ($p < 0.01$) was observed in 9 out of 11 spontaneously constricted asthmatic subjects. Using the hypothesis of relative hysteresis, a computational respiratory model was created and used to identify possible airway and lung parameters responsible for the varying DI responses. Parameters in this model accounted for airway wall resistance and compliance ($R_{aww}, C_{aww}$), central and peripheral airway resistance ($R_{aw}, R_{paw}$), gas compression compliance ($C_g$) and resistance and compliance of the lung tissues ($R_{lu}, C_{lu}$). Normal dynamic measures were estimated for these parameters and each element was independently altered to determine the relative hysteresis contribution of the airways and lung tissues. Under normal baseline conditions, our model demonstrated counterclockwise hysteresis loops (consistent with findings of Froeb and Mead) indicating the relative hysteresis of the airways to be greater than that of the lung tissues, resulting in a bronchodilation in response to a DI. The only airway parameter to induce a reversal in the hysteresis loop direction was found to be $R_{paw}$. These results remain consistent with the hypothesis that initial obstruction level regulates a DI response and suggests that the caliber of the peripheral airways is a key factor regulating the DI response.
Developing analytical methods for understanding the breakdown properties of lung tissue, and applying them to emphysema

Jesse Nandhavan

In spite of what is known about the biological and biochemical processes leading to emphysema, much is still unknown how the biomechanical forces play a role in the progression of the disease, eventually leading to lung failure. In general, the breakdown properties of tissues have not been completely understood. Therefore, if new quantitative methods for understanding these properties were to be developed, they could be applied to emphysematous tissue. The overall objective of this research project was to develop more accurate analytical measures for understanding the stress-strain and failure behavior of lung tissue, and to apply them to emphysematous lung tissue. Traditional approaches to understanding the stress-strain and failure behavior of lung tissue have utilized engineering stress, which uses a static initial thickness value for the cross-sectional area used in stress calculations. This method is a gross underestimation of the true stress in the material. By using our stretching system, along with image analysis, we were able to investigate the thickness as a function of strain for the various lung tissue strip samples. We also made three types of thickness measurements: a global measurement and regional measurements at the leftmost and rightmost regions of the tissue strips during stretching. The stress-strain and failure data were then compiled. These methods were applied to control and elastase-treated tissue samples, as well as tissue samples obtained from tight-skin mice. The in vitro elastase treatment degrades elastin in the lung while the tight-skin mouse is a genetically different mouse that spontaneously develops emphysema. Using our developed methods, we found that there was a linear decreasing trend in the thicknesses for all samples as strain was applied from 0%-50%. We also found that there was a clear difference between engineering stress and the new “true stress” calculated using the thickness as a function of strain. Both the engineering and the true stress for the elastase-treated and tight-skin samples were found to be much lower than that of the control samples. A similar trend was observed for the failure stresses for each sample group. In this project, we found that true stress is a much more accurate method for calculating stress-strain and failure data for lung tissue than engineering stress. We also found through analysis of the global and regional thicknesses of the tissue strips that thickness change is not homogeneous throughout. We concluded that in order to accurately characterize the mechanical properties of soft tissues, especially during failure, it is essential to calculate proper stress.
Impact of Parenchymal Tethering and Smooth Muscle Constriction on In Situ Pressure – Area Relationships during Deep Inspirations

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Asthmatics have a deficiency in their ability to maximally dilate airways. The cause of this deficiency is either strengthening and stiffening of airway smooth muscle (ASM), or wall inflammation causing the parenchyma to de-coupling from the airway. To date, there has been no practical method for quantifying the in vivo behavior of airway wall properties in relation to the balance of parenchymal tethering and distending pressure after ASM provocation. This project designed, developed, and applied a novel system to probe the balance of airway distending forces before and after bronchial challenge in excised calf lung. Our hypothesis was that ASM stiffening de-couples airways from the parenchyma, thus reducing the influence of tethering forces after methacholine (MCh) challenge. The system uses a wall vacuum source to manually generate deep inspirations (DI) in isolated, intubated excised bovine lungs. Simultaneously, a linear motor system imposes 8Hz oscillations at the opening of the lung, allowing airway resistance ($R_{sw}$) to be tracked, as a surrogate of airway diameter ($D$), in pseudo real time using the Jensen method [6]. From obtained $R_{sw}$ and pressure data, diameter - volume expansion and in situ pressure-area (P-A) relationships can be extracted for each lung. These relationships can then be used to draw conclusions about the relative influence of distending forces before and after challenge. Experiments have been performed on nine excised lungs. Data were acquired in deep inspirations starting from lung collapse at 0 cmH$_2$O, and functional residual capacity (FRC), at 5 cmH$_2$O. Also, an experiment was performed on one of the isolated lungs to probe the effect of DI rate on airway distending forces. The relationship between minimum resistance ($R_{MIN}$) and $R_{sw}$ prior to deep inspiration was found to be fairly linear as long as the increase due to methacholine was less than 10 cmH$_2$O. After this point the relationship became quadratic and the lungs showed dramatic decrease in the ability to maximally dilate. Examination of the increase in diameter as function of volume expansion indicated that the volumes necessary to produce a given increase in diameter was the same before and after challenge. This suggests that tethering was not affect by ASM provocation. When P-A curves were examined we found a statistically significant reduction in compliance post methacholine, and that the decrease in compliance followed a quadratic relationship with $R^2$ of .828. These finding suggest the ability to dilate is completely linked to ASM stiffening in the airway wall. In conclusion this project provides preliminary evidence that decreased DI response in asthmatics is more likely due to ASM stiffening then tethering forces associated with de-coupling of airway from the parenchyma when ASM thickens and becomes inflamed.
The Effects of Informational Masking on Spatial Channels

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Informational masking (IM) is defined as non-energetic masking which results in stimulus uncertainty that causes an elevation in threshold when detecting the target. Currently, there is a lack of research on the effects of IM on spatial channels. The goal of this project is to determine how well a person can stay focused on one spatial channel with either a stable or an irregular pattern of activity on other spatial channels. This irregular pattern of activity is expected to cause IM. To determine the effects of informational masking, four conditions are introduced to the listener: a fixed-position fixed-intensity (FPFI) condition, a random-position fixed-intensity (RPFI) condition, a fixed-position random-intensity (FPRI) condition, and a random-position random-intensity (RPRI) condition. Each condition has a unique combination of target sound levels and masking triplets. A triplet is made up of three masker noises, each at a random location in virtual space. The task of the subject is to detect the target sound in the presence of this triplet. A one-interval two alternative forced-choice (1I-2AFC) paradigm is used to measure the performance of the subject in percent correct and sensitivity. Differences in results between the four conditions are used to characterize the subject’s susceptibility to IM. The performance of each condition, listed in a descending order (i.e., from best performance to the worst performance) is: FIFP, FIRP, RJFP, and RIRP. An energy detector model which includes a spatial filter and internal noise was used to predict the performance of some conditions. A flow chart of the model is shown in the figure on the bottom. The model was able to predict the performance of the FIRP conditions in a fairly accurate fashion and shows promising results for the other conditions. The final outcome of this project, implementing the energy detector model, will provide a better understanding of IM on spatial channels.
IMPROVING THE MULTI-ELECTRODE CHRONIC RECORDING TECHNIQUES IN THE HIPPOCAMPUS

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Multi-electrode recording experiments from ensembles of single cells in freely behaving animals are widely used in a variety of neuroscience research fields. Two challenging problems in multi-electrode recording are that assembly of micro-electrode drives and spike sorting procedures are both highly time-consuming and subjective. Furthermore, large-scale parallel recording data are challenging for data management, visualization and analysis. The overall goal of the project, therefore is twofold: 1.) To improve upon the design of the multi-electrode drive and 2.) To develop an effective identification program for observable neural activity states. The newly developed design for the multi-electrode drive drastically reduced the manufacturing time and labor intensiveness common to more traditional approaches. This was accomplished by essentially separating what was an embedded and continuous design into three distinct steps that were later recombined into a more stable micro-electrode drive. To increase the recording efficiency from multiple electrodes, silica tubing and sonication were introduced into the procedure. Computer aided design drawings were created to detail the new procedure. The amplified brain signals are transmitted from the multi-electrode drive to an acquisition system in the computer and recorded via a high-density parallel recording system. To deal with the large-scale parallel recording data from these signals, a user-friendly and interactive software program was developed to concurrently view the x-position, y-position, EEG, and spike trains corresponding to one session of experimental data collection from single neurons recorded. Development of this data analysis software was done through MATLAB's Graphical User Interface Development Environment (GUIDE) and uicontrols. The standardized procedure for micro-electrode drive assembly, coupled with an effective neural identification program will allow for comparison and extensive data mining between different Neuroscience field laboratories.
Monaural Intensity Discrimination:
Effects of Perceptual Fusion of Target and Distractor

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When two acoustic signals, similar in frequency and location, are presented simultaneously to the auditory system, the two signals fuse together and are perceived as one sound object. When two signals fuse, it is difficult to listen to one of the signals (the target) and ignore the other (the distractor). The overall goal of this project was to quantitatively determine how perceived properties of the distractor (pitch and location) affected target-distractor fusion. The experiments quantified target-distractor fusion by measuring the ability of a listener to discriminate intensity differences in the target in the presence of a distractor. The properties of the distractor (perceived pitch and location) were the independent variables and the intensity discrimination thresholds were the dependent variables. Performance was measured using a 4-interval 2-Alternative Forced Choice adaptive paradigm, and threshold was defined as the minimum intensity difference in the target (in dB) required for 70% correct discrimination. The target was a 60 dB, 600-Hz tone presented to the left ear with a reference intensity of 60 dB. The intensity and phase of the distractor were varied uniformly between 60-90 dB and ±π/2 respectively, and the distractor frequency was parametrically varied. In the first experiment, the distractor was presented to the ipsilateral ear, the contralateral ear, and binaurally (to three perceived locations in the horizontal plane around the head). The greatest degree of target-distractor fusion was seen when the distractor was presented to the same ear as the target. We did not see a large effect on target-distractor fusion due to the perceived location of the distractor in the binaural case. The second experiment measured the effect of perceived pitch of pure-tone (single frequency) distractors and complex-tone distractors (two frequencies either harmonically related or unrelated to the target frequency) on performance. The greatest degree of target-distractor fusion was seen when the frequency component(s) of the distractor were close to the target frequency. The complex tone distractors that had frequency components harmonically related to the target frequency did not have an effect on target-distractor fusion relative to harmonically unrelated distractor frequencies with approximately the same frequency separation from the target. In the preliminary model of the results, the total energy of the distractor, regardless of the ear to which it was presented, was passed through a filter centered at the 600-Hz target. The decision variable is based on the amount of distractor energy passing through the filter. Consistent with the experimental results, the model predicts a strong dependence of distractor frequency on target intensity discrimination. Studies of intensity discrimination in the presence of distractor stimuli will lead to a better understanding of binaural auditory processing, potentially leading to improved prosthetic hearing devices.
Temporal Context Sensitivity of Field L Neurons in Zebra Finches

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The brain’s sensitivity to temporal sequences underlies our ability to learn and perform complex motor tasks such as speech. Despite the importance of this sensitivity, little is known about the learning and detection of complex sequences in the brain, specifically in the cortex. Zebra Finches provide us with a good model to explore the neural coding of complex temporal sequences because of the similarity of their vocal communication system with that of humans. This project will focus on the temporal context sensitivity of neurons in the field L region of the Zebra Finch forebrain, which is the avian analogue of the primary auditory cortex in humans. Our goal was to quantify the temporal linearity/non-linearity of responses in field L neurons in order to gain new insight on the hierarchical processing of information in the auditory system. A database of Zebra Finch songs was compiled. The Zebra Finch song is composed of syllables which are analogous to words in human speech. The songs were segmented into the syllables that form it. These syllables were then used to generate synthetic stimuli. The various stimuli consisted of two given syllables separated by different gap lengths. Zebra Finches with a surgically implanted electrode were presented with these stimuli, and the neural activity of the field L region was recorded using standard electrophysiological methods. We analyzed two aspects of temporal context sensitivity in the neural responses. How does the response of a syllable depend on 1) the delay that separates it from the previous syllable, 2) the identity of the syllable that precedes it? For most of the neurons that we recorded from, we found that responses were non-linear. The responses to the same syllable depended on the gap that separated it from the previous syllable. Specifically, the non-linear effects were typically observed in the range of 10-30ms, which is within the natural range of inter-syllable intervals in the Zebra Finch songs. Furthermore, we found that the response to some syllables also depended on the identity of the syllable that preceded it. In conclusion, our results suggest that the response to a given natural sound at the cortical level depends not only on the sound itself, but also on the history of sounds that preceded it.
“Characterization of an EMG Signal from a Surface Array Electrode”

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When the muscle is innervated, electrical signals are propagated along the motor neurons. The propagation of these electrical signals generates a motor unit action potential (MUAP). An electromyographic (EMG) electrode detects the sum of all the action potentials elicited by the recruited motor units (MU). Currently, the needle electrode, our gold standard and the surface array electrode are used to detect EMG signals from an active muscle. The surface array electrode offers a noninvasive technique for detecting an EMG signal but it lacks specificity and selectivity in detecting the signal. A MUAP provides information about the control properties of the corresponding MU. An EMG signal is resolved into MUAP of a given MU using the Precision Decomposition Algorithm. The objective of this investigation is to use parameters to characterize the sEMG sensor. The calculated parameters helped determine the suitability of the sEMG signals for decomposition. The parameters that were assessed were the peak to peak amplitudes (Vpp), the duration and the energies which were extracted from the MUAP waveform. This investigation is unique in that it is the first of its kind to detect an EMG signal using both sEMG and intramuscular (iEMG) sensors simultaneously. The EMG signal was obtained from the first dorsal interoseous (FDI) using quadrifilar needle electrode. The iEMG signal was detected at the 10%, 20% and 50% maximal voluntary contraction level (MVC) and decomposed using the Precision Decomposition Algorithm. The sEMG signal was constructed from the iEMG signal using spiked triggered averaging. On average, the needle iEMG electrode was found to have MUAP waves with significantly larger Vpp and energies. On the contrast, the sEMG detected MUAP shapes with longer durations. Overall the iEMG MUAP showed more variability in its coefficient of variation for a corresponding MU and within each channel. These findings suggest that incorporating the characterization scheme in future construction of the sEMG will optimize the decomposition performance of the sEMG signals. This will ultimately provide a noninvasive approach to detecting EMG signals that will allow for the analysis of the neuromuscular system.
A Pilot Study: Improving Mediolateral Balance Using a 90° Tilted Room

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The cost of medical care for patients with balance disorders is estimated to exceed one billion dollars per year in the United States. Neurological afflictions such as stroke, Parkinson's disease, Cerebral Palsy, and spinal cord injuries can destroy balance. Current methods of balance training use partial body weight support (BWS), a neurorehabilitation technique, which is being used to enhance locomotor recovery in patients with motor disorders. A new type of body weight support device has been developed that trains the subject by having them lay down in a 90 degree tilted room, reducing the subject's reliance on the vestibular apparatus, increasing the reliance on the somatosensory and visual system. The goal of this project was to determine the effects of training in the tilted environment blindfolded, forcing subjects to rely completely on the somatosensory system during training. To measure balance, testing was done on a movable platform which contained a Kistler 9284 multi-component force plate sampling vertical reaction forces at 100 Hz from which center of pressure (COP) was derived. A computer simultaneously sent out a perturbation signal to the platform and recorded the subject's COP for 30 seconds. Parameters such as mean velocity, root mean squared of COP and median frequency were extracted to give an indication of balance. Subjects were tested before and after training in the same tilted room. Training lasted for 60 minutes per session, on average three sessions per week, subjects completed a total of 8 to 10 training sessions. A Matlab program was used to compute and compare the balance parameters from before and after tests. For control group, subjects were tested twice without training in between. The results showed an improvement in long term balance control of subjects after balance training in the tilted environment compared to the control group. 3 out of the 4 subjects had an improvement in balance, including 2 out of the 3 who trained blindfolded. There does not appear to be any extra benefit to training with only 1 input.
QUANTITATIVE MRI: 1.5T AND 3.0T COMPARISON

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Recent advances in Magnetic Resonance Imaging (MRI) technology have made 3.0T magnetic field scanners economically feasible for clinical and research use. Compared to the currently standard 1.5T scanners, 3.0T scanners offer increased image quality and decreased imaging time. Three tissue-specific parameters, T1, the longitudinal relaxation time, T2, the transverse relaxation time, and proton density, PD, which reflect the effect of the magnetic field on the tissue, are routinely measured during MRI scans and used for diagnosis. Numerical ranges for T1, T2 and PD parameter values have been empirically determined for various normal tissues, and are used for interpreting 1.5T imaging data. Since increasing the scanner magnetic field non-linearly affects the T1, T2 and PD parameters, it is necessary to develop similar numerical ranges for 3.0T to take advantage of the improved image quality at this field and to ensure proper data interpretation. Previous research has shown that the T1, T2 and PD non-linear behavior deviates from the theoretically predicted values. However, no studies were done to quantitatively compare the relaxometric parameters' field-dependence. The goal of this project was to quantitatively analyze the effect of magnetic field increase on the T1, T2 and PD parameters in phantom and human brain tissue by scanning at maximally identical conditions and quantitatively post-processing the resulting imaging data. Phantoms consisting of various fruits and a healthy human volunteer were scanned at 1.5T and 3.0T Philips Intera scanners using mix-Turbo Spin Echo (mix-TSE) pulse sequence to measure the T1, T2 and PD parameters. An in-house model-conforming MathCAD algorithm was used to remove the experimental settings-dependent information from the measured values and to generate quantitative parameter maps from the scan data. The map pixel intensity represented the relaxometric parameter value, with bright pixels indicating high values and vice versa. The quantitative parameter maps were employed to calculate the T1, T2 and PD histograms. Further, an additional MathCAD segmentation algorithm was used to isolate several tissue types to analyze tissue-specific relaxometric field dependence. Lastly, system identification Wiener-Hopf modeling was used to estimate the hypothetical orange tissue T1 transfer function to relate values measured at 1.5T and 3.0T. It was found that most tissues inspected exhibited behavior consistent with the MR theory: the T1 values lengthened and the T2 values shortened with increased magnetic field. Some tissues exhibited the opposite trend. The hypothetical T1 transfer function was modeling showed that two linear filters can be used to estimate the varying behavior for T1 values below and above 1250ms. Overall, the effect of magnetic field increase on T1, T2 and PD relaxometric parameters has been quantitatively analyzed, resulting in data which can be used for further 1.5T and 3.0T comparison.
Improved Techniques for the Design and Construction of
Implantable Multi-electrode Microdrive Arrays

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Electrical activity in the hippocampus is associated with learning and memory. Localized action potential signals from this brain region are measured using implantable multielectrode microdrives. These microdrives allow careful placement of sensing electrodes into precise locations inside the brain. When operating a device in such delicate and sensitive regions during neurobiology experiments, there are a number of special requirements. A microdrive must be lightweight and suitable for use in freely moving animals. Microdrives must house an array of microscopic electrodes, which are used to transmit and relay action potentials to data acquisition equipment. Multiple electrodes are desired for the ability to record simultaneously from large numbers of neurons and to analyze neuronal activity at the network level. The fine adjustability of electrodes is also required in order to target individual neurons and capture highly localized action potential signals. Current technology for measuring neurosignals provides two solutions, purchasing extremely expensive commercial devices or fabricating custom, handcrafted microdrives. This project proposes a third solution that demonstrates an engineered, CAD-based approach that will ultimately produce an easy to fabricate, robust and reusable microdrive. Prototype design concepts were produced with the use of AutoDesk Inventor, a solid modeling CAD design software package. A prototype was fabricated, implanted into an animal specimen, and judged using the following criteria: 1) cost per implantation 2) ease of assembly and 3) ability to remove and reuse for successive implantations. The first prototype device demonstrated the feasibility of our design methods, reduced device fabrication time and confirmed the use of robust materials for device construction. The second prototype further improved device design in the areas of assembly and reusability. This project has transformed microdrive fabrication from tedious and time consuming handmade approaches towards CAD – engineered prototypes that are durable, reusable and less complicated to assemble.
Mathematical Modeling of the Horseshoe Crab Eye

Eileen Leung

The brain constructs the visual images that we see from the trains of electrical impulses that the eye transmits. Horseshoe crab processes the visual scene using basic mechanisms found in higher animals, including humans. As a result, the horseshoe crab's lateral eye is the largest neural network for which a quantitative cell-based mathematical model exists. However, an internal biological clock (circadian clock), in the horseshoe crab's brain changes the properties of the eye as a function of the time of day. At night, the circadian clock sends out signals that initiate profound changes in the structure and function of the receptors. The objective of this project is to incorporate these physiological changes into a "night time" model of the horseshoe crab eye. First, a model of the night time state of the eye was produced based on the horseshoe crab eye model from its daytime state using MATLAB. Then, the daytime model was verified by assigning different inputs in forms of video images. Lastly, the phototransduction module in the daytime model was replaced with a small potential fluctuations (SPFs) and large potential fluctuation (LPFs) generator module because LPF generations are not presented during the day. This new module produced SPFs and LPFs with the rates and variability reported in published studies. From this nighttime model of the horseshoe crab eye, we were able to help (a) explain the results of behavioral studies which show that horseshoe crabs can see objects equally well day and night despite the dramatic difference in light level and (b) suggest a reason for how human and other animals are able to see well in the dark. The results found in this project shows that occurrence of LPFs may be the reason that a horseshoe crab is able to see at night. In summary, the proposed study aims to simulate the output of the crab's eye in its "night-time" state and this helped insight into how the animal achieves the described visual performances at a different light level.
Improving Balance through Noise-Enhanced Sensorimotor Function

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Dynamic balance control depends, in part, on somatosensory signals from the legs and feet. It has been shown that, during quiet standing, subsensory mechanical noise applied to the soles of the feet by vibrating insoles can reduce postural sway, and therefore improve balance control in healthy young and elderly individuals. The overall goal for this project was to determine if subsensory mechanical noise applied to the soles of the feet by vibrating insoles could reduce postural sway and improve dynamic balance control in healthy young and elderly subjects standing on a motorized motion platform. The platform perturbed subjects in either the mediolateral (ML) or anteroposterior (AP) direction, moving as the sum of seven sinusoids with frequencies that were non-integer multiples of a fundamental frequency. Platform position and whole-body postural sway were recorded using a motion capture system and reflective markers placed on the subject's hip and shoulder. Twenty young subjects (18-35 years old) and 10 elderly subjects (65 or older) were perturbed in the ML direction, and 10 young subjects and 9 elderly subjects were perturbed in the AP direction for twelve trials, which included six control trials, in which there was no random vibration applied by the insoles. For all trials, root mean square (RMS) and path length were calculated and compared between the stimulation and control trials. Path length was calculated separately over the first and second halves of each trial to determine if adaptation to insole vibration or platform motion occurred over the course of each trial. Also, AP data were used to estimate a transfer function for the balance control system, using a third-order autoregressive model with exogenous input. Transfer function relative stability was calculated and compared between stimulation and control conditions. Decreases in RMS or path length or an increase in relative stability suggested an improvement in balance control, and a paired t-test was used to determine if any of the improvements were statistically significant (p < 0.05). For young subjects, perturbed in the AP direction, there were statistically significant decreases in the second half of hip and shoulder path length (p = 0.01 and p = 0.04) with the application of random vibration to the sole of the feet. Also, there was an increase in relative stability, but it was not statistically significant (p = 0.69). For elderly subjects, there were no statistically significant changes in RMS, path length, or relative stability with the application of random vibration. These results suggest that postural sway decreased in young subjects with the application of random vibration to the soles of the feet and that dynamic balance control may have improved. It is unclear from the results if postural sway decreased or if dynamic balance control improved in elderly subjects. Additional elderly subjects need to be tested to assess the statistical significance of the possible effect of the insoles on dynamic balance control. Overall, this work indicates that noise-based devices such as vibrating shoe insoles may improve deficits in dynamic balance control related to decreased somatosensory function in healthy young and elderly subjects.
LINEAR MODEL APPROXIMATION OF AMACRINE, BIPOLAR, AND GANGLION CELLS IN SALAMANDER RETINA

KIAN SETAYESH

Ganglion cells in salamander retina are depolarized by the excitatory synapses of bipolar cells and are hyperpolarized by the inhibitory synapses of amacrine cells. Amacrine cells in turn hyperpolarize bipolar cells via inhibitory synapses. ON and OFF bipolar and ganglion cells in the retina depolarize to light onset and offset respectively. Morphological structures depicting synaptic interactions between these cells have been created, but there has been no attempt to model the temporal characteristics of the synapses. This project hopes to show that ganglion cell output is linearly correlated to the stimulus intensity and frequency from a sinusoidally modulated light source. A sinusoidal light stimulus allows for quick cell classification by showing ganglion cell responses relative to periods of light increase and decrease. Measured currents are recorded from ganglion cells using whole-cell patch-clamp techniques. Glycinergic inhibition from amacrine cells is blocked with strychnine, while GABAergic inhibition from amacrine cells to ganglion and bipolar cells is blocked with bicuculline and picrotoxin. Obtaining excitatory post-synaptic current (EPSC) traces with toxins applied provides an indication of how each inhibitory branch contributes to the ganglion cell response. Fourier analysis shows the frequency components of each current trace for the first ten harmonics of the stimulus frequency. Averages of the magnitudes of sine and cosine components provide the basis to predict ganglion cell current response. OFF responses are faster and less sustained than are ON responses. ON-OFF ganglion cells rectify current responses relative to a sinusoidal light stimulus. Higher frequency stimuli do not correlate well in evoking sinusoidal current responses as do lower frequency stimuli due to the low flicker-rate in salamander retina. Higher contrast gains tend to evoke larger EPSCs and IPSCs in ganglion cells. Primary results show that the majority of ganglion cell responses are determined within the first two harmonics of the response. Within the first ten harmonics for a 1 Hz sinusoidal stimulus the power is approximately 99% of the entire power in the signal. For higher frequency stimuli the power is beyond the first 10 Hz since the harmonic frequencies range higher. These higher frequencies act as noise in relation to the fundamental frequency. Transient and sustained bipolar cells provide excitation to ganglion cells. Transient Bipolar cells transmit fast, transient EPSCs while sustained bipolar cells are responsible for slow, periodic EPSCs. Sustained bipolar cells also synapse with amacrine cells to regulate IPSC current. Amacrine cells releasing glycine (Glycinergic) are responsible for the sinusoidal component to the IPSC responses, while amacrine cells releasing GABA (Gamma-aminobutylic acid) are responsible for governing the transient responses from transient bipolar cells. Transient bipolar cells also possibly operate in an L-AP4 independent pathway, which implies that transient ON bipolar cells are morphologically different than sustained ON bipolar cells. Further experimentation includes patching from amacrine and bipolar cells to isolate transient and sustained responses, as well as to differentiate between glycinerigic and GABAergic currents from amacrine cells to a modulated sinusoidal stimulus.
Effect of an Object on Heading Perception

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Heading perception is one’s ability to determine self-motion and is necessary to navigate in real environments containing both moving and stationary objects. The visual presentation of self-motion is provided by an expanding visual field, termed optic flow. Psychophysical studies have shown that heading perception is not affected by the presence of moving objects, except when the object crosses the heading point. The overall objective of this study was to understand the effects on heading perception caused by the timing and duration of an object (a square box) blocking the heading point. Blocking the heading point during the middle interval of the stimulus reduced the accuracy of heading judgments. When the duration of blocking was varied, shorter durations were found to cause the worst performance in heading perception. These results reveal that humans judge heading within a certain amount of time and are more accurate when this time is not interrupted.
Quantitative MRI: Humans vs. Other Species
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Over the past thirty years, considerable amounts of MRI information have been accumulated on humans and other species. Baselines for comparison of specific tissues within and between any two species however have not yet been stated. The overall objective of this project is to devise a systematic routine for comparing the similarities and dissimilarities between the heads of humans and Rhesus monkeys using quantitative magnetic resonance imaging (Q-MRI). The specific focus is on the main intra-cranial (white matter, gray matter and cerebral spinal fluid) and extra-cranial (fat and muscle) tissues. Q-MRI is an imaging modality, which unlike conventional qualitative MRI, the value assigned to an image pixel has meaning and pertains to the tissues present in a specific pixel. The analysis between the two species was focused on the common major organ needed for general function and survival -- the brain. Though the brain of a human and Rhesus monkey is complex, the brain is a most suitable organ for comparison between the two species, since it can be examined as a whole or as individual components. Our approach is first to separate the Q-MRI head images acquired of the two species into two categories: intra-cranial matter, which are tissues inside the brain, and that of extra-cranial matter, which consists of all tissues in the head except those of the brain. The next step is to decide if and how to divide the Q-MRI brain images (intra- and extra-cranial matter) of the species from the original Q-MRI head images into left and right halves using a bisecting plane subroutine we created in MathCAD. Once the intra-cranial or extra-cranial matter of the head is separated, the images are then split into left and right hemispheres before being categorized and then further subdivided (i.e. the brain is sub-divided into white matter (WM), gray matter (GM), and cerebral spinal fluid (CSF)). The components of interest regarding the left and right portions of the head in Q-MRI images of the two species are specifically those of muscle, fat, WM, GM, CSF, and the ratio of GM/WM. The methods used to extract these measures involve Q-MRI segmentation, region of interest (ROI) spectroscopy, and tri-Gaussian curve-fitting. In analyzing the data, results show that the ratio of GM/WM for the whole male Rhesus monkey brain is roughly double that of the GM/WM for the human brain, regardless of gender. This finding is significant because of its implicit indications of how other species, especially Rhesus monkeys, are similar yet dissimilar to humans in terms of Q-MRI weighted images and measurements.
Design of a Novel Inhalation Device for Large Volume Liquid Aerosol Delivery

Diana Manzanedo

Pulmatrix

During normal breathing, humans commonly exhale small liquid particles, referred to as “bioaerosols”, into the environment. Bioaerosols are prone to carry airborne pathogens, which in turn increase the spread of inhaled infectious diseases such as influenza, tuberculosis and severe acute respiratory syndrome (SARS). These bioaerosols are formed during inhalation and exhalation, when air passes over the mucus layer that lines the lungs. The interaction of viscous forces and surface tension produced by the displacement of air leads to the formation of the airborne droplets. The overall goal of this project was to reduce the number of particles released into the environment as bioaerosols through momentarily altering the balance of physical forces acting inside the lung. The approach is to administer aerosolized isotonic saline solution, which is proved to produce such effect when administered as a large volume of aerosol. The specific goal was to collaborate with Pulmatrix, Inc. to create a prototype of an inhalation device to deliver the saline aerosol into the respiratory tract, or alternatively find a commercially available device that met required specifications. It is necessary for the device to produce 1 mL of aerosolized saline with particle size of 1-10 microns. The aerosol flow rate should be larger than 1 mL/min to achieve a fast and comfortable delivery of saline to the patient. The device will be developed into an over-the-counter, low cost product intended for widespread use. It will be introduced into the market for use in cleanrooms, clinics and hospitals to enhance sterility and protect both personnel and patients. The ultimate goal is for the device to become a common, reusable household item, and for people to be able to buy canisters with saline at any pharmacy. Therefore, its use will have a large effect in reducing morbidity of SARS, TB and influenza. Consequently, there will be a positive economic impact through decrease in health care costs incurred from treating patients. The resulting device will also provide an aid against bioterrorist hazards, which might be launched in the form of inhaled pathogens.
DEVELOPMENT, DESIGN AND EVALUATION OF A HUMAN DIAGNOSTIC FOR THE MEASUREMENT OF EXHALED PARTICLES

Karim Kokash and Matthew Brande

Pulmatrix Inc.

Exhaled bioaerosol particles contribute significantly to the spread of airborne respiratory infectious disease (ARID). Reducing the number of particles exhaled by individuals might considerably reduce the spread of ARID. A research-level diagnostic and anti-infectivity aerosol (AIA) have been developed and shown in a pilot study involving 11 subjects to evaluate particle exhalation from patients and following AIA treatment, reduce the number of particles emitted up to 72.9 ± 8.0% for six hours (Edwards, et al. 2004, PNAS, 50, 1783-1788). The goal of this project was to design and construct a compact human diagnostic device for the measurement of exhaled particle counts in human subjects that could be deployed into a clinic and commercialized. The core components of the device were an optical particle counter (OPC), for measurement of the size and number of particles detected and a pneumotach in parallel with a pressure transducer for measurement of flow rates. The subjects inhaled particle-free air through a filter and exhaled bioaerosols which were measured by the OPC, while the flow rate was also displayed and stored in a database.

A clinical trial was performed at the Brigham and Woman’s Hospital using the constructed human diagnostic device to measure the particle counts of patients with underlying respiratory problems, and healthy subjects. After 114 subjects were tested, inter-subject and intra-subject statistical analyses were used to evaluate the particles exhaled by each subject. It was found that 30% of the subjects were super-spreaders, or individuals who exhale an excessive particle count, who produced 97% of the total particles measured. In-house experiments were also performed on seven subjects to better characterize the formation and production of bioaerosols. A steady particle production was observed in normal producers at flow rates below 30 Liters per minute (LPM) but seemed to increase sharply with flow rates greater than 30 LPM. Tidal mouth breathing was found to be the mode that produced the highest number of particles greater than 0.3 microns in diameter. Nose breathing produced 20% less particles in the 0.3-0.5 micron range and 80% less particles greater than 0.5 microns, while talking produced the lowest number of particles across the size ranges studied.

The clinical diagnostic is a marketable product for use with the previously described aerosol inhalant, which suppresses particle production in those who exhale an excessive number of particles. Targeting those who produce a large number of particles with this diagnostic device and administering the inhalant, provides a novel method for controlling the transmission of airborne respiratory diseases. Another potential market and application for this device is in clean room contamination control.
In Vitro Characterization of Pulmonary Technologies for the Control of Respiratory Infection

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Pulmatrix

Airborne infectious disease can spread from person-to-person via exhaled pathogen-containing droplets. There has been little research into the topic of exhaled droplet formation and specifically if suppressing these exhaled droplets corresponds to a decrease in the spread of disease. The objective of this project was to refine an in vitro model of the upper airways to be successfully and accurately used to screen novel formulations for reduction of exhaled particle counts. The system used for this in vitro study, i.e. Simulated Respiratory Machine (SRM), was optimized by altering the properties of the mucus mimetic used for the tests as well as the physical aspects of the system itself. The mucus mimetic was optimized by determining its biophysical properties and comparing them to that of human tracheobronchial mucus. The main objective of the mucus mimetic optimization work was to develop consistent, reproducible mucus mimetic and to minimize its production time. The viscoelastic properties of the mimetic were determined using an ARES strain-controlled oscillatory rheometer in the cone and plate configuration and were found to closely resemble the viscoelastic properties of human mucus. The surface tension of the mucus was measured using the Du Nouy Ring method (measured the free surface tension) as well as a SITA tensiometer (measured the surface tension of a created surface). Comparison of these values revealed a lower surface tension on the free surface of the mimetic, indicating the presence of surface active agents which mimic the phospholipid monolayer of human tracheobronchial mucus. The physical aspects of the machine were optimized by designing and building a new model trachea as well as making the entire system air-tight by optimizing connections. Various filters were added and the entire system was placed inside of a biohood to eliminate contamination of the data by ambient particles. To validate the SRM as a screening tool for novel formulations in their ability to suppress bioaerosol formation, effects of various novel formulations on particle counts were determined using the SRM. Each formulation was applied to the surface of the mucus mimetic via a nebulizer. Then an air flow at a certain flow rate/pressure was prescribed over the mimetic and the numbers of sheared particles were counted using a 1 CFM Climet optical particle counter. The numbers obtained from different formulations were compared to those obtained from mucus mimetic alone. Using the in vitro model, increasing the surface tension of the mucus mimetic, via the nebulization of a novel formulation to its surface, was determined to be a method of decreasing particle formation. Isotonic saline solution (0.9%) was found to be one of the most effective formulations at lowering the number of particles formed, supporting a previously conducted in vivo study. In summary, refinement of the cough machine has led to an enhanced understanding of the formation of exhaled bioaerosols and has, and will continue to aid in the development of a formulation which suppresses the number of particles formed and exhaled by a person during respiratory activities. This formulation will impact contagion of airborne disease and, if used properly, will generally decrease the spread of disease, improving the quality of life for the general population.
Development of an Isolated Airway System for In-Vitro Studies of Airway Wall Properties

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Airway smooth muscle (ASM) and airway walls can play crucial roles in asthma. In particular, asthmatic ASM appears capable of generating abnormally high forces that can cause airway closures, which are not resolvable with a deep inspiration. Previous studies have examined the static length-tension relations of isolated ASM strips and of isolated airways in-vitro but could not apply in-vivo like perturbations. Also, dynamic length cycling of ASM has been shown to have profound effects on ASM behavior. This project designed, developed, and applied a system to probe how constricted ASM alters the mechanical properties of isolated calf airways when exposed to static pressures and breathing-like pressure oscillations. The system uses a computer-controlled stepper motor system to deliver typical breathing pressure oscillations to isolated airways. The motor drives a syringe pump, which pumps Krebs solution into a pressure column. The height of the pressure column determines the pressure of the Krebs solution that is delivered into the isolated airway. The pressures experienced by the airway are measured by a 0-50 cmH2O Celesco pressure transducer. To measure airway radius changes in real-time, a novel Panametrics ultrasound system was used, which sends and receives acoustical pulses that reflect off the airway wall. The fully developed system has been used to test first and second generation isolated airways (5.10 +/- 0.68 mm outer diameter, 1.11 +/- 0.24 mm wall thickness) excised from calf lungs. The isolated airways were tested statically and dynamically, both before and after ASM stimulation. In the static tests, the airways were held at pressures of 0 to 25 cmH2O in steps of 5 cmH2O. In the dynamic tests, the airways were exposed to 0.1 Hz sinusoidal pressure oscillations of 5 to 10 cmH2O. The pressure and radius data were analyzed to produce static and dynamic pressure-area relationships and airway wall compliance values, both before and after ASM stimulation. Two populations of airways were found: those that reacted to ASM stimulation and those that did not react to ASM stimulation. Reactive, post-ASM stimulated airways had smaller cross-sectional areas than pre-ASM stimulated airways for higher pressures (15-25 cmH2O). ASM stimulation also caused the airway wall compliance to decrease significantly over the pressure range of 5-10 cmH2O (43.8% mean decrease). Dynamic oscillations of isolated airways appeared to also cause a decrease in cross-sectional area and compliance. This could be due to competing phenomena associated with viscoelastic properties of airway wall soft tissue versus softening of the ASM from dynamic oscillations. In summary, this study begins to probe, for the first time, how ASM constriction during dynamic periods of stretching alters fundamental properties of airway walls. These initial findings provide a basis for future tests that can be performed on the Isolated Airways System. These findings can be used to modify and enhance current mathematical models of the airways that are present in three-dimensional lung models.
Optimization of Current Generation from the Breakdown of Glucose by *Rhodoferax ferrireducens* in a Microbial Fuel Cell

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Abundant energy is stored in the form of carbohydrates such simple sugars or waste biomass. This energy can be harvested by utilizing the metabolic pathways of bacteria to catalyze the breakdown of these high energy compounds. A Microbial Fuel Cell (MFC) is a device that converts organic matter to electricity using microorganisms as the biocatalyst. A recently discovered strain of bacteria, *Rhodoferax ferrireducens* has shown the ability to completely oxidize glucose and deposit electrons directly onto a graphite electrode without the need for an added mediator. This project has identified limiting factors in MFC output and demonstrated modifications for improved performance. An MFC consists of two electrodes separated into chambers by a proton permeable membrane. The reduction of the negative electrode (anode) by the bacteria is coupled to oxidation by oxygen at the positive electrode (cathode). Usable energy is extracted as electrons produced at the anode flow through a resistive load to the cathode. In this project the breakdown of glucose by *R. ferrireducens* was used to power a Teflon fuel cell with 250 mL electrode chambers. Improvements in MFC voltage and current were achieved by modifying the (i) surface area and catalytic properties of electrodes (ii) the circulation rates of air through the fuel cell and (iii) geometric configuration of the fuel cell itself. A 50% rise in maximum fuel cell voltage is demonstrated with the addition of a platinum catalyst and increased exposure to air. A peak open circuit potential of 417 mV was measured out of a total theoretical value of 1.24 V based on the change in free energy from glucose to carbon dioxide and water. The energy available to the fuel cell represents roughly one third of the total available energy while supporting the metabolism of *R. ferrireducens*. Voltage-Current relationships for MFC operation were established using data collected from an automated Dataq™ voltage recording system. Experimental results from this project show 15% efficiency for the utilization of chemical energy in glucose at maximum power of 0.01 mW. A new fuel cell prototype made out of Ultem® and Lexan® Polycarbonate has been developed to facilitate future studies and combat sources of inefficiency within the fuel cell. With the new prototype and the experimental data concerning rate loss it should be possible to continue the development of microbial fuel cells to further increase voltage and current output.
Relative Influence of Autonomic Stimulation on SA and AV Nodes of Human Subjects

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The sinoatrial (SA) and atrioventricular (AV) nodes of the human heart are influenced by the balance of the sympathetic and parasympathetic (also termed vagal) branches of the autonomic nervous system, which are constantly active to varying degrees. Thus, the overall effect on the cardiovascular status reflects which dominates at any one time. The former increases both the SA node firing rate and AV node conduction, whereas the latter slows the heart rate and tends to slow conduction through the AV node. At any given autonomic state, however, the SA node rate also influences AV nodal conduction, such that increasing rates result in slower AV nodal conduction. Therefore, an important, yet unidentified, understanding in electrophysiology of the heart is the competing influence of autonomic activation with the effect of heart rate on the electrical conduction of the AV node at any given time. The overall objective of this project is to quantitatively assess the relative influence of each competing factor on AV node conduction. P-P and P-R intervals—representing the SA and AV conduction rates, respectively—were extracted from the electrocardiogram (ECG) recording of 27 patients, who participated in a clinical diagnostic test known as an exercise treadmill test (ETT). These patients were divided into 3 groups to investigate the effects of age and diabetic status on AV nodal response to exercise. It was concluded that the frequency of inputs (i.e. the heart rate) had a greater effect on AV conduction than the relative autonomic influence in all 3 groups. Interestingly, consequences of autonomic blunting may have been the limiting factor in the rate of AV nodal conduction in the diabetic group due to consequences of the disorder. Our simple statistical approach and analysis provided a quantitative way to investigate the relationship between the SA and AV nodes under competing influences, which may have application in the development of pace-making algorithms that are used in artificial pacemakers to respond to dynamic AV delay in a physiological way.
Development and Characterization of a Porous Patterned Microtextured Scaffold for Vascular Tissue Engineering Applications

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One of the challenges in creating a living tissue replacement for damaged blood vessels has been the development of a scaffold with the appropriate properties: support vascular tissue formation, mechanical stability, and biocompatibility. The medial layer of blood vessels is made up of several organized layers of vascular smooth muscle cells (VSMCs). Therefore scaffolding for such tissue must have surface features that provide cellular organization, and a porous structure to allow nutrient flow to cells in underlying layers. The objective of this project was to develop and characterize techniques using polycaprolactone (PCL), a biocompatible and biodegradable polymer, for creating a porous, patterned, thin membrane produced by microfabrication for vascular tissue engineering applications. Conventional techniques for creating porous scaffolds using salt leaching have been shown to leave pores that disrupt the micron scale features on microfabricated scaffold surfaces. A novel method using biodegradable and biocompatible micro/nanospheres in particulate leaching was used to create submicron pores in the PCL scaffold without disrupting micropatterns. Micro/nanospheres fabricated out of the biodegradable polymer poly(DL-lactic-co-glycolic acid) (PLGA) were incorporated into PCL. Parallel grooved microtextures (48 μm grooves with groove depths of 5 μm and 12 μm spacing between each groove) were introduced onto the PCL/PLGA composite surface by a mechanical heat press resulting in a scaffold with thickness on the micron scale (50±10 μm). The fast degradation properties of PLGA were then exploited to degrade away the PLGA spheres while leaving the slow degrading PCL component of the scaffold intact thus producing a porous micropatterned PCL scaffold membrane. Scaffold structure and particle distribution through the scaffold were evaluated using Scanning Electron Microscopy and Confocal Laser Microscopy. Diffusion tests were then performed to confirm the presence of through pores in the scaffold. Vascular smooth muscle cell reaction to the scaffolds was also investigated. It was determined that pores produced through the novel particulate leaching method were not disruptive to cellular organization. Through our development process we have been able to fabricate micropatterned, porous thin film scaffolds that allow nutrient diffusion through the scaffold and cell alignment, similar to that seen in vivo. These 2-D scaffolds can be used to create 3-D tissues with cells aligned and viable throughout the construct. This novel fabrication process for patterned, porous, biodegradable and biocompatible membranes that provide structural support for VSMCs may have applications in vessel replacement, drug testing, and other future tissue engineering research.
Tissue Engineering the Medial Layer of Small Diameter Arteries

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Current materials being used for the replacement of small diameter arteries (SDA) are inadequate partly due to a lack of elastin, an extracellular matrix (ECM) protein that gives arteries their compliance. In native vessels elastin fibers are present in highly organized networks, the structure of which may influence the mechanics of the vessel. The goal of this study is to see if elastin secreted by vascular smooth muscle cells (VSMCs) can be organized into a similar structure to elastin in native SDAs through use of microtextured scaffolding as a template. Neonatal rat VSMCs (NRVSMCs), VSMCs from rodents less than 4 weeks old, have been shown to secrete large amounts of elastin in culture, but the structural organization of this elastin does not compare to that found in native vessels. These cells were grown to confluence on textured polymer scaffolding, imprinted with cell sized lanes through use of photolithography. This was done with the aim of ordering the secreted elastin into parallel networks of fibers such as found in native arteries. The elastin generated by NRVMSC cultures was visualized by immunostaining and fluorescence microscopy to confirm the presence of elastin. Images were also taken through polarization microscopy and scanning electron microscopy (SEM) to visualize small elastin fibers and their orientation. Through the SEM images it was seen that many small fibrous structures were present on the textured scaffolding, while few of these structures were seen on the flat scaffolding. From the cracks present in the ECM the small fibrous structures appeared to have a preferred direction of orientation parallel to the direction of the lanes in the textured scaffolding, while no preferred orientation was seen on the flat scaffolding. This orientation was seen throughout both the lanes and spaces of the textured scaffolding. This preferred alignment was supported by polarization microscopy, which showed highly aligned structures present in the ECM on the textured scaffolding, both inside and outside the lanes, while none of these structures were seen on the flat scaffolding. Immunostaining for elastin also confirmed that elastin covered the surfaces of both the flat and textured scaffolding, suggesting that the aligned fibrous structures were elastin fibers. The combined results from the SEM, polarization microscopy and immunostaining for elastin suggest that aligned elastin fibers were present on the textured scaffolding, while none were on the flat scaffolding. More research must be done to confirm these results. Once confirmed, this method can be used as a model to test the relative importance of elastin organization on the mechanical properties of native arteries.
Novel Modeling of Nature’s Design in Genomic Regulatory Networks

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Cells respond to incoming molecular signals through a series of biochemical reactions. These biochemical reactions comprise a network of ligands, proteins, and small molecule messengers that communicate with one another to control the cell’s total behavior. In order to better understand the cell’s response, a mathematical model of the network can be used to simulate complex network behavior, as done in this project. A novel linear model is presented based on discrete state modeling. This model implements the logic of Markov modeling in that each state of the system depends solely on the previous state. Most models to date have largely been based on the kinetics of each biochemical reaction of the network. Such models are comprised of nonlinear equations that include two parameters for each system component. The goal of this project was to develop a computational model of a genomic regulatory network in cardiac myocyte cells. It was necessary to identify only the most necessary components in order to reconstruct a simplified version of the network. Transition equations for each component state, with the equations’ corresponding probabilities, which were stored in the transition probability matrix, were found based on this network. A cell’s response to an input or ligand first produces changes in experimentally measurable cytosol calcium concentrations. In the implemented model, an input switch acts to turn this system on, producing simulated time course cytosolic calcium data as the model’s output. The algorithm to simulate the cell’s behavior of the accumulation and degradation of cytosol calcium concentrations was implemented in MATLAB. This algorithm carried out iterative matrix multiplication between a state vector of system component states with the transition probability matrix. Certain network behaviors were included in the model: delay of calcium efflux, feedback due to the protein cadmodulin, and amplification due to internal calcium storage. The logical limits of the system were tested and verified by performing in silico RNAi knockout experiments, done by testing the system’s response to knocking out certain components. The model output has been shown to behave as biologically expected. A final count of cytosol calcium with all the implementations and transition probabilities produce a curve that fits experimental data. We have shown that a discrete state model of a regulatory network based on transition probabilities and matrix multiplication behaves logically with expected biological limits and fits well with calcium data.
Stringent Response vs. Stationary Phase: Expression Analysis of *Escherichia coli* Through Proteome Identification

Alex Tamburino

The stringent response of *Escherichia coli* is a protective and preventative response brought about by the failure of tRNA aminoacylation to keep up with protein synthesis. In the stringent response, a reorganization of gene expression results in widespread cellular changes that include general stress responses, downregulation of nucleotide biosynthesis, upregulation of amino acid biosynthesis and the stimulation of other global effectors. These changes pose a difficulty for many antibiotics and treatments that gain their effectiveness by attacking these altered processes. A better understanding of the stringent response will therefore aid in preventing and controlling these reactions. Research has focused on the proteomic comparison of *Escherichia coli* stringent cells versus stationary phase cells in order to improve upon previous mRNA analysis. *E. coli* MG1655 cells were grown to an optical density with 600 nanometer light (OD600) of 1.4 on Luria Broth (LB) medium and M9 minimal medium. These served as stationary controls for comparison with *E. coli* PSL879 cells containing a vector that allowed for overexpression of relA upon the addition of IPTG at 1 M concentration. The relA gene stimulates the synthesis of (p)ppGpp, the major effector of the stringent response. The proteomes of all conditions were then identified via mass spectrometry. Analysis of the proteomes revealed protein expression during the stringent response contained significant differences from early stationary phase in both rich and minimal media. Osmotic stress proteins were found to be similar, however heat shock and cold shock proteins were increased during the stringent response. Nucleotide biosynthesis was found to be downregulated, while amino acid biosynthesis was found to be upregulated. Global regulators were also observed that affected expression of glycogen synthesis, gluconeogenesis, and outer membrane proteins.
Proteomic Profiling and Analysis of Lymphocytes Related to Chronic Obstructive Pulmonary Disease

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Inflammation of lung tissue is a major factor in determining the severity of chronic obstructive pulmonary disease (COPD). COPD is characterized by deterioration of alveolar wall tissue resulting in reduced oxygen exchange with the blood. Lymphocytes infiltrate the lungs in response to inflammatory stimuli produced when tissue damage occurs. The severity of the disease seems to progress with increased presence of lymphocytes in lung tissue. Lymphocytes in the blood become active at the site of inflammation, however, the level of inflammatory “awareness” of circulating lymphocytes in the blood is not clear. The object of this study was to compare the proteomes of circulating lymphocytes in the presence or absence of COPD. Additionally, lymphocytes isolated from healthy volunteers were activated \textit{in vitro}, and the proteomic changes recorded. CD4+ T lymphocytes from healthy volunteers and COPD patients were isolated from whole blood. Proteins in the resting, activated, and COPD samples were determined from peptide sequences identified using reverse phase chromatography and mass spectrometry (MS). Peptides were identified using SEQUEST software, which matches the observed, experimental peptide spectrum with idealized spectra derived from protein sequence. Using the identified proteins, comparisons were made among the three samples to determine connections between circulating blood lymphocytes in COPD and the resting and activated samples. COPD lymphocytes were found to have many similarities to both resting and activated cell types indicating a level of partial peripheral activation in response to inflammation. Several proteins specific to activating inflammatory mediators, including myotrophin (MTPN) and a macrophage migration inhibitor factor (MIF) were found exclusively in lymphocyte of a patient with COPD. MTPN and MIF activation indicates that peripheral lymphocytes play a role in the inflammatory response characteristic in severe COPD. The goal of this project was to develop a peripheral link between circulating lymphocyte and those activated in the lungs. This project is the first step towards defining proteomic patterns in circulating lymphocytes that could potentially be used as an aid in diagnosis and prognosis for patients afflicted with COPD.
Identifying the Proteins Involved in the Cell Cycle and the Cellular Response to DNA Damage

Joseph Canavan
Mike Lamprecht

Errors in DNA synthesis during cell replication can lead to the proliferation of mutated cells and the possible transformation from normal cells to cancerous cells. DNA damage checkpoints exist within the cell cycle to ensure DNA integrity during replication. These checkpoints allow the cell time to repair damaged DNA or mark the cell for death (apoptosis). The pathways by which DNA damage is detected and communicated to cell cycle checkpoints are not completely understood. Past research on DNA damage checkpoints used microarrays that monitor thousands of genes at the level of RNA, however, proteins are the key effector molecules of the pathways, and their activity is greatly influenced by post-translational modifications made by the cell. We employed a method known as mass spectrometry-based proteomics to study DNA repair proteins and their connections to cell cycle progression directly at the protein level. The method entailed subjecting cultured cells to varying degrees of DNA damage. Mass spectrometer analysis was used to identify the proteins present in the different samples and the abundance of the proteins. Using this technique we identified specific proteins involved in DNA repair that change their abundance in response to DNA damage, and are likely to play an important regulatory role controlling cell's response to DNA damage, whether to continue cycling, pause for repair or trigger apoptosis.