PI Name	Institution	Title	Project	Years Awarded	Funding Institute
Abbas, James J	University Of Kentucky	Preparatory Adjustments For Improved Standing With FNS	HD038570	3 years	NICHD

Abstract: DESCRIPTION: (adapted from Investigator's abstract) The long term goals of this research is to develop practical Functional Neuromuscular Stimulation (FNS) systems for restoring motor function in neurologically-impaired individuals. FNS has been used to restore the ability to stand, step and maneuver in persons with spinal cord injury (SCI) and other neurological disorders that impair lower extremity function. Research results have been encouraging, but lower extremity FNS systems have not yet proven to be clinically viable primarily due to the limited degree of function that has been restored. The investigators will develop and evaluate a system that provides the FNS system user the ability to make two types of preparatory adjustments prior to performing a task: the user will first place their feet in a suitable location and then the user will adjust their posture (i.e. adjust the location of the pelvis with respect to the feet). The role of proper foot placement in standing has not been well characterized, nor has it been exploited in FNS control system design. The majority of the effort will be directed towards investigating the role of foot placement and developing techniques to achieve suitable foot placement in FNS stance. To incorporate the facility for adjusting posture once the feet are in place, the investigators will utilize and build upon the results of their on-going efforts in which they are implementing techniques for on-line postural adjustments. At the completion of this project, they plan to have successfully developed and implemented a novel control system for making preparatory adjustments in FNS standing and to have demonstrated the functional benefits provided by this system. Towards this end, they propose a coordinated effort that will utilize computer simulations with detailed biomechanical models, experiments on able-bodied individuals, and several sets of experiments on spinal cord injured subjects who are standing using FNS systems.

PI Name	Institution	Title	Project	Years Awarded	Funding Institute
Alsop, David C	Beth Israel Deaconess Medical Center	Diagnostic Imaging Of Cerebral Blood Flow With MRI	AG019599	4 years	NIA

Abstract: Imaging of Cerebral Blood Flow (CBF) is a powerful technique for the diagnostic evaluation of patients with dementia, stroke and epilepsy. A technique known as Arterial Spin Labeling MRI has demonstrated the ability to provide high quality images of CBF without radioactivity or injection. The advancement of this technique has been limited, however, by the destructive effects of patient motion, the poor image quality of the fast, echoplanar imaging technique used to combat these motion effects, and the inability to acquire images from the entire brain in a reasonable exam period. The applicants propose to overcome these limitations by refining a novel background suppression approach. Multiple inversion pulses will be used to reduce the intensity of uninteresting signals prior to image acquisition. This approach can reduce motion-related errors by a factor of 100 while preserving the CBF signal. Because of the dramatic reduction in motion-related errors, a superior, 3D fast spin echo imaging approach can be employed to provide CBF images from the whole brain in under 6 minutes with twice the sensitivity of earlier approaches. We propose to realize this potential of this approach by: 1. Optimizing the design of the RF pulses used for background suppression to minimize CBF signal loss and systematic errors near the top and bottom of the brain. 2. Using a nonlinear minimization strategy to optimize the timing of the inversions so as to achieve ideal background suppression 3. Developing a strategy for T1 quantification of brain tissue that will be compatible with the 3D fast spin echo sequence and which will be insensitive to the presence of cerebrospinal fluid(CSF). TI measurement is required for CBF measurement but can be contaminated by small amounts of CSF in the voxel. 4. Measuring the efficiency of the background suppressed sequences. Efficiency will be measured as a function of labeling plane location to guide the choice of parameters for subsequent applications. 5. Measuring the test-retest reliability of the optimized CBF imaging method in normal controls and patients with dementia and comparing it to unsuppressed methods. This information is needed for the design and interpretation of diagnostic tests, pharmaceutical evaluations and other studies employing CBF MRI. These developments will make reliable CBF imaging by Arterial Spin Labeling a widely applicable technique for diagnostic imaging.

Bioengineering Research Grants (BRG) awarded in FY 2000

Ateshian, Gerard A   Columbia Univ New York Morningside   Anisotrophy And Nonlinearity Of Cartilage Mechanics   AR046532   4 years   NIAMS

Abstract: Articular cartilage is the bearing material of diarthrodial joints. Its primary mechanical function is to transmit large loads across the articular surfaces of joints with minimal friction and wear; under normal conditions, cartilage can maintain this function for seven to eight decades. From an engineering perspective, the mechanical behavior of cartilage is considered to be remarkable, unmatched by any traditional engineering bearing material. However, despite several decades of sophisticated biomechanical studies of cartilage, an accurate understanding of cartilage mechanics remains elusive due to its remarkable versatility and complexity. Studies have demonstrated that the mechanical response of articular cartilage may vary as a function of duration and rate of loading or deformation, i.e., cartilage exhibits viscoelasticity. Furthermore, it has been shown that the tensile stiffness of cartilage differs when testing the tissue parallel and perpendicular to the split line directions, i.e., it exhibits anisotropy. It has also been established that the stiffness of cartilage in compression may be one to two orders of magnitude smaller than in tension, i.e., it exhibits tension-compression nonlinearity. Various studies have also confirmed that these measured properties may vary from the superficial to the deep zone of cartilage, i.e., the tissue exhibits depth-dependent inhomogeneity. To date, no single constitutive model of articular cartilage has been able to describe its mechanical response under the various testing conditions described in the literature. The hypotheses of this proposal are that (1) cartilage is orthotropic, requiring more material constants than have been measured to date to describe its mechanical response; (2) the tension-compression nonlinearity of cartilage requires that some, but not all of these constants have different values in tension and compression; and (3) that a theoretical framework encompassing cartilage orthotropy and tension-compression nonlinearity, using mixture theory, can provide agreement between theory and experiment for all testing configurations; this agreement improves when incorporating tissue inhomogeneity in the analysis. Therefore, the specific aims of this proposal are to test human patellar cartilage samples in tension, compression, shear and permeation, along the three mutually perpendicular directions which are hypothesized to characterize the planes of material symmetry, such as to determine experimentally a complete set of elastic and permeability constants of cartilage; to determine whether these constants indeed describe an orthotropic material; to experimentally assess the depth-dependent inhomogeneity of cartilage; and to compare transient and equilibrium experimental responses to corresponding predictions from a newly proposed biphasic, octantwise orthotropic, conewise linear elasticity model with depth-dependent inhomogenous properties. To achieve these aims, it is proposed to use the most current techniques for measurement of tissue mechanical properties.

Ateshian, Gerard A   Columbia Univ New York Morningside   Biotribology Of Diarthrodial Joints   AR043628   4 years   NIAMS

Abstract: DESCRIPTION (adapted from the Investigator's abstract): This is a first renewal application of an excellent, highly productive team of a Bioengineer (G. Ateshian) with a Biochemist (W. Valhmu) who are studying the mechanisms of articular cartilage lubrication and/or failure of lubrication on loading/frictional characteristics of bovine articular cartilage. Based on previous theories and experiments, the authors propose new experiments to further characterize the relationships between friction and fluid pressurization of articular cartilage. The overall theory being tested is that pressurization shifts load away from contacting cartilage surfaces, thus decreasing friction until pressurization subsides. Three relevant hypotheses are to be tested in this renewal: 1/that friction depends on interstitial fluid support load, equilibrium frictional coefficient and solid-to-solid contact; that cartilage-on-cartilage contact fraction area is smaller than cartilage on glass. 2/ under normal loading, cartilage always maintains high interstitial fluid support with low friction and 3/ enzymatic degradation will defeat interstitial load mechanisms and increase the coefficient of friction. Using a unique load-or-displacement controlled frictional testing apparatus containing a microchip pressure transducer to measure cartilage interstitial fluid pressurization directly, the authors will systematically test these hypotheses through a series of carefully thought out permutations and combinations of load-versus-displacement controlled tests. The ability to test the fluid pressures within cartilage samples under these various, well-controlled, physiologically relevant loading conditions, in order to test various theories of cartilage lubrication and friction, is extremely important and unique. The investigators provide extensive evidence that this proposal is both logical and feasible. Their background review on the topic, along with their papers on the topic over the past few years are all outstanding. They provide both strong theoretical and experimental evidence to support the concepts that they are testing. The main concept is that fluid pressurization is critical to controlling cartilage friction. They will test that theory using cartilage-on-glass tests along with some very important and unique cartilage-on-cartilage tests at stresses from 0.05Mpa-5 Mpa, frequencies of 0.0005Hz - 0.5 Hz and up to 10 percent compressive strains, with and without enzymatic (collagenase, chondroitinase ABC and hyaluronidase) treatments.

Bioengineering Research Grants (BRG) awarded in FY 2000

Bergsneider, Marvin   University Of California Los Angeles   A Hemodynamic Model Of Intracranial Pressure Dynamics   NS040122   3 years   NINDS

Abstract: Disorders of intracranial pressure, including traumatic brain injury and hydrocephalus, can cause significant morbidity and mortality. There is increasing evidence that many of our "standard" theories explaining the pathophysiology of these disorders should be reconsidered. In this proposal, a novel theory describing the pathophysiology of elevated intracranial pressure and hydrocephalus is studied using a combination of bioengineering modeling methods and laboratory experimental investigations. The theory, which we termed the hemodynamic theory, is based on an interrelationship between intracranial compliance, cerebral blood flow impedance, and intracranial pressure. Our preliminary studies using a small animal model have demonstrated a strong correlation between compliance and disturbances in blood flow. The overall objective of this project is to construct and validate a transmission-line circuit that models intracranial pressure changes in relationship to altered hemodynamics. In order to enhance the accuracy of the model, the individual circuit parameters will be estimated from in vitro experiments. In addition, an in vivo model of acute hydrocephalus will be used to test the theoretical basis supporting the circuit model. Finally, the computer simulations of the new circuit model will be compared to the actual physiological data derived from the animal experiments. The long-term goal of this project is to establish a comprehensive, unifying theory of intracranial pressure pathophysiology that accurately represents and predicts the various clinical disorders affected by altered intracranial pressure. The use of bioengineering modeling techniques provides a powerful method to test hypotheses by simulating complex physiologic phenomenon. An improved understanding of these disorders will offer new and better treatment modalities for millions of affected patients.

Berns, Gregory S   Emory University   Integration Of Bifurcation Theory And Continuous FMRI   MH061010   4 years   NIMH

Abstract: DESCRIPTION: (Adapted from the Investigator's Abstract): This project proposes a new paradigm for the study of how the dynamics of brain activity are related to behavior. An interdisciplinary bioengineering approach will be used to integrate the theory of nonlinear dynamics with both the analysis and design of functional magnetic resonance imaging (fMRI) experiments. This will lead to the development of new algorithms specifically targeted to the analysis of dynamic fMRI studies. The algorithm development will allow the implementation of novel fMRI experiments that are no longer limited to subtractive designs. In the past, the predominate approach to studying human cognition has been the subtractive experimental design. This method relies upon the establishment of discrete cognitive states, with the data analysis aimed at identifying brain regions that show significant changes in activity between the states. While successful in identifying brain regions that are differentially activated, the subtractive approach does not reveal the more complex temporal choreography that must occur to produce a specific behavior. To go beyond spatial mapping, one would like to know not only which brain regions are activated in a specific cognitive state, but how the pattern of brain activity makes the transition from one state to another. To do this, a new technique, called continuous fMRI is proposed. In contrast to the approach of designing experiments in which discrete behavioral states are maintained for blocks of time, this method maintains a single cognitive "state," but continuously varies a single parameter of the task. Pilot data from a continuously varying finger tapping task will be presented that demonstrate the feasibility of this approach. Continuous fMRI experiments generate dynamic data sets. New methods of analysis will be developed to characterize the types of dynamic behavior that occur. 1) Coupled with continuous fMRI, bifurcation analysis will identify state transitions in the brain as a single experimental parameter is continuously varied. Bifurcation theory will allow the classification of these transitions into one of four well-described forms. 2) Using finger tapping as a prototype task, bifurcation theory will be used to analyze the transition from low tapping rate to high tapping rate. 3) The technique will be extended to include the cognitive process of uncertainty detection. Using measures of information transmission, the amount of stimulus uncertainty will be varied in a reaction-time task, and bifurcation analysis will identify the types of state transitions that occur between low and high uncertainty. The integration of bifurcation theory with continuous fMRI is anticipated to have a significant impact on the way in which fMRI experiments are conducted and will yield new techniques for the study of neuropsychiatric illness.

Boada, Fernando E   University Of Pittsburgh At Pittsburgh   Methodology For In Vivo 3D Triple Quantum Sodium MRI   HL064205   3 years   NHLBI

Abstract: Normal cells maintain a relatively low intra-cellular sodium concentration (10-40mM) against a large sodium pool in the extra- cellular space (120-150mM concentration). The large concentration gradient that develops across the cell membrane is critically important for maintenance of basic cellular functions and it is severely disrupted during the course of many pathological conditions. Disruption of this sodium gradient leads to a concomitant, and sometimes very specific, increase in intra-cellular sodium concentration. Thus, monitoring of changes in intra-cellular sodium content in vivo could provide valuable insights into specific aspects of in vivo cell metabolism during normal and diseased conditions. However, non-invasive tools for observing changes in intra-cellular sodium concentration are currently unavailable. Sodium MRI represents an attractive approach for the non-invasive monitoring of changes in sodium content in vivo. Although the NMR properties of the sodium nucleus had made sodium MRI very challenging, recent advances in MRI have made it possible to produce sodium images of diagnostic quality at clinical field strengths (1.5T) in times that are appropriate for routine clinical examinations. The sodium MRI methods demonstrated up to now can only provide quantitative maps of total tissue sodium concentration in vivo. The more demanding goal of producing in vivo maps of the intra-cellular tissue sodium concentration in humans remains a challenge, with exciting benefits, for which practical solutions can now be formulated using triple quantum (TQ) sodium imaging schemes. This R01 proposal is written in response to program announcement PA-99-009 (Biomedical Research Grants) and is aimed at developing an optimal methodology for in vivo, TQ sodium MRI in human brain. The goal is to design imaging schemes capable of producing TQ sodium images of diagnostic quality (SNR greater than 20:1, voxel size 1cc) in times acceptable for clinical studies (12 minutes). The proposed methodology is to be developed and tested on whole body clinical scanners and validated using phantom as well as in vivo data.

Bolch, Wesley E   University Of Florida   Tomographic Dosimetry Phantoms For Pediatric Radiology   HD038932   3 years   NICHD

Abstract: DESCRIPTION (Adapted from Applicant's Abstract): Both fluoroscopy and computed tomography are becoming increasingly utilized in pediatric medicine. Quantitative methods for determining organ dose in pediatric patients are thus essential for clinical decision-making and risk assessment. Even approximate methods of risk assessment, based upon measures of entrance dose or energy imparted, fundamentally rely upon knowledge or organ dose. Organ doses may be determined through either computational simulation of the diagnostic exam using anthropomorphic models, or through the use of dosimeters embedded within anthropomorphic physical phantoms. Anthropomorphic computational models may be further classified as either stylized models, where organs are delineated by 3D surface equations, or tomographic models, in which organs are determined from segmented CT or MRI images. In this project, the investigators will develop improved techniques for estimating organ doses to the newborn child in both fluoroscopic and CT examinations. The project Specific Aims are: 1) to construct a high-resolution, segmented tomographic computational model of a newborn child using helical CT images of live newborns. The model will be scaled to match the dimensions and organ masses of the MIRD newborn model; 2) to construct a high-resolution tomographic physical phantom of a live newborn using the identical CT data and also scaled to match the MIRD newborn model. A full-scale physical phantom of the stylized MIRD model will also be constructed. Internal organ doses will be assessed using embedded high-sensitivity MOSFET dosimeters; 3) to determine organ doses in the newborn child received during fluoroscopic and CT examinations using both the computational model and physical phantoms developed in Specific Aims 1 and 2, respectively; and 4) to evaluate the degree to which improved anatomic representation, in either computational models or physical phantoms, influences estimates of organ dose in newborn radiological examinations.

Campagnola, Paul J   University Of Connecticut Sch Of Med/Dnt   Multiphoton Biomedical Nanofabrication   GM060703   4 years   NIGMS

Abstract: DESCRIPTION (adapted from applicant's abstract): This application seeks to develop a new method to direct the 3-D assembly of biomolecules and synthetic polymers. This will be done by cross-linking molecules in a highly controlled manner using mutiphoton illumination. A wide range of biological molecules will be incorporated in the 3-D structures while maintaining their bioactivity. The investigators claim that their approach provides benefits over current methods including photolithography, microcontact printing and free-form microfabrication. This will be accomplished with higher optical resolution, preservation of biological function, and improved 3-D capability. Feasibility has been demonstrated by fabricating structures with synthetic polymers, proteins, hydrogels, and active enzymes. The proposed work will develop fabrication methods with wide applicability in a number of biological and bioengineering fields. Specific goals are: 1) to fabricate structure for applications in biosensors, gene chips, protein-based micro-machines, micrometer scale-enzyme factories, and biomaterials. 2) To fabricate nano and micro-scale gels for application in biosensors, drug delivery, and tissue engineering. 3) To fabricate dimensionally complex channels and structures for applications to microfluidics. 4) To fabricate composites and biomaterials for tissue engineering.

Bioengineering Research Grants (BRG) awarded in FY 2000

Carrington, Walter A   Univ Of Massachusetts Med Sch Worcester   High Resolution 4-Dimensional Fluorescence Microscopy   GM061981   3 years   NIGMS

Abstract: The Green Fluorescent Protein (GFP) has presented great opportunities for the use of fluorescence for the study of dynamic cellular processes in living cells. It has also presented great challenges for imaging technologies. This Bioengineering Research Grant proposes to develop a high resolution, high-speed fluorescence microscope for imaging single molecules or small aggregates of molecules moving at the speeds of molecular motors. This instrument will provide 3-D movies with the high temporal and spatial resolution that is needed for live cell imaging. It will be based on a fast, sensitive, low noise 640 x 480 CCD camera, wide field illumination and fast focus change. Spatial resolution of 100 nanometers (transverse) will be obtained by the use of computational methods called image restoration or deconvoluion. It will obtain images at rates of 94 frames per second for full frames images and faster for smaller images (188 frames/second) with 65 percent quantum efficiency and 8.5 electron readout noise. It will obtain 3-D images at rates up to 36 high-resolution 3-D images per second. High pixel rates are needed to provide an image at the speeds needed to follow motion at speeds up to 1 to 2 microns per second. This camera operates at about 30 Megapixels/sec, but since the whole sample is illuminated for the full frame time, fluorescence saturation does not limit signals. Signal levels in scanning confocal microscopes are severely limited by fluorescence saturation at these scanning rates. Sensitivity will be high enough to detect and image single molecules in a cultured cell's cytoplasm and to detect and image small clusters of proteins in parts of the cell with higher auto-fluorescence. Fluorescence will be calibrated so that small numbers of fluorescent proteins can be accurately counted. Imaging protocols will be developed and tested for optimizing the tasks of detecting, imaging and counting small numbers of proteins whether stationary or in motion at the speeds of molecular motors. This system will produce one gigabyte of data in less than 20 seconds. Software will be developed for proving nearly instantaneous feedback to the experimenter on the quality of this large stream of data. Sophisticated image restoration, volume visualization and data analysis software will be provided at the microscope for this purpose.

Celliers, Peter M   University Of Calif-Lawrnc Lvrmr Nat Lab   Clinical Diagnostics Using Nonlinear Optical Imaging   AR046885   3 years   NIAMS

Abstract: The overall goal of this proposal is to develop a novel imaging system based on the nonlinear optical process called higher harmonic generation. In this process two (or three) photons combine to form a single photon with twice (or three times) the frequency of the original photons that formed it. This phenomenon results from the interaction between photons from a high intensity source and the nonlinear optical properties of the object. Measurements of this "frequency-doubled and tripled" light can provide detailed information about structural and spectral properties of the object from which it emanates. In the present application we propose to use a femtosecond-pulsed laser to access an immense biological database, the extracellular matrix. There are compelling reasons for this choice. First, the matrix is far from an inert infrastructure. Rather, there is a constant reciprocal flow of information between matrix and resident cell population that reflects current physiological status. Second, collagen (the predominant component of the matrix) is, unlike most proteins, a molecule of infinite variety. With more than seventeen genetically distinct forms and an extensive menu of post-translational modifications, collagen can be thought of as a kind of structural chameleon, reflecting changes in its environment biochemically rather than chromatically. Many pathological conditions are associated with well-characterized structural changes in collagen. For example, melanoma is associated with loss of fibrillar organization of dermal collagen; diabetic complications with increased nonenzymatic glycation of collagen, and hypertrophic scarring with increased lysine hydroxylation. Our preliminary data document that these changes can be detected by higher harmonic analysis. We have assembled a uniquely strong research team to pursue these promising findings, with the goal of developing a clinically useful diagnostic tool with wide range of potential applications. To this end we propose to accomplish the following Specific Aims: 1. Design a prototype nonlinear confocal imaging system with the necessary compactness, flexibility, and sensitivity for clinical use. 2. Conduct a systematic survey of collagen preparations (purified and in native tissue) that will allow us to identify optical signatures of those structural features indicative of pathophysiological conditions. 3. Develop and refine mathematical models that will allow predictive inference about matrix structure from optical data. 4. Construct portable confocal system and begin clinical data collection.

Chapin, John K   SUNY Downstate Medical Center   Robot Arm Control Using Cortical Multineuronal Recording NS040543 5 years NINDS

Abstract: This proposal addresses the possibility of utilizing "motor" information extracted from simultaneous neuronal population recordings in the brain to remedy the loss of motor function associated with paralysis, limb amputation and other neurological conditions. This effort is also scientifically significant because it directly addresses the problem of neural population coding in the brain, and the possibility of controlling such coding through biofeedback. We have recently demonstrated in rats and monkeys the feasibility of using simultaneous neuronal population recordings in the motor cortex to control movement of a robot arm. The rats, in particular, were able to utilize their brain activity to accurately position (in one dimension) the robot arm under a water dropper, and then carry the water drop back to their mouths. Moreover, over continued training in this "neuro-robotic" mode, these animals were able progressively decorrelate this neural activity from the overt movements with which they were normally associated. This proposal has three specific aims: I. To utilize chronic neural ensemble recordings in monkeys to directly control multi-directional robot arm movement. The main issue is whether neuro-robotic feasibility be demonstrated for control of movements in multiple directions and under varying load conditions. II. To develop, implement and optimize new methods for transforming neuronal population activity into realtime neuro-robotic control signals. The main issue is whether simple linear neural population coding algorithms can be used to produce optimal neuro-robotic control functions, or whether nonlinear networks will be necessary. III. To investigate the feasibility of neuro-robotic control after sensorimotor denervation. The main question is whether neuro- robotic control is feasible after paralysis. This will be investigated here in rats subject to reversible denervation or amputation of the forelimb.

Chen, Zhongping   University Of California Irvine   High Speed High Resolution Phase Resolved OCT/ODT HL064218 4 years NHLBI

Abstract: Direct visualization of tissue physiology and anatomy provides important information to the physician for the diagnosis and management of disease. High spatial resolution noninvasive techniques for imaging in vivo tissue structure and blood flow dynamics are currently not available as a diagnostic tool in clinical medicine. Such techniques could have a significant impact for biomedical research and patient treatment. The objective of the proposed research is to develop a high speed noninvasive optical technique, optical coherence tomography (OCT) and optical Doppler tomography (ODT), for imaging in vivo tissue structure and blood flow with high spatial resolution (2-10mum) in biological tissues. Preliminary results obtained in our laboratory have demonstrated the potential of this technology for a number of clinical applications where imaging tissue structure and monitoring hemodynamics are important. However, there are four limitations in our current OCT/ODT system: speed, resolution, penetration depth and speckle noise. The proposed research is directed toward the development of a high speed, high resolution, phase resolved OCT/ODT system for imaging tissue structure and microcirculation that overcomes these limitations. The specific aims of this proposal are to: (1) design and develop a high speed high resolution phase resolved OCT/ODT system for tomographic imaging of in vivo tissue structure and blood flow dynamics in highly scattering biological tissues; (2) develop signal processing and image reconstruction software and hardware for phase resolved OCT/ODT; (3) image blood flow in vitro using reconstituted canine blood and in vivo using the chick chorioallantoic membrane (CAM) model to verify and optimize OCT/ODT system operation and spatial resolution; and (4) demonstrate in animal models and clinical studies how OCT/ODT can assist in diagnosis and treatment of skin tumors and port wine stain birthmarks where imaging tissue structure and monitoring blood flow are important.

Chilkoti, Ashutosh   Duke University   Elastin Fusion Proteins   GM061232 4 years NIGMS

Abstract: DESCRIPTION (adapted from applicant's abstract): The objective of this research proposal is to develop a convenient, generic methodology to modulate the physico-chemical properties of proteins by fusing them to environmentally-responsive elastin-like polypeptides (ELPs), and to concurrently elucidate the biophysical principles which govern modulation of their properties. The underlying hypothesis of the proposed research is that incorporation of an ELP sequence at the N- or C-terminus of a target protein will impart environmentally-responsive properties to the fusion protein. This is because ELPs are oligomeric repeats of the pentapeptide sequence Val-Pro-Gly-X-Gly (VPGXG)(X is any amino acid except Pro), which undergo an "inverse" phase transition: below the inverse transition temperature [T(t)] ELPs are soluble in aqueous solution, but when the temperature is raised above their T(t), they undergo a sharp (2-3 degree C range) phase transition, leading to desolvation and aggregation of the polypeptide. The inverse transition can be induced by changes in temperature, ionic strength, or pH, and is completely reversible. In preliminary studies, Dr. Chilkoti has demonstrated that the solution and interfacial properties of ELP fusion proteins can be systematically modulated as a function of their solution environment (e.g., temperature and ionic strength). He has also shown that the inverse transition of an ELP in a fusion protein is related to the effective surface hydrophobicity (ESH) of the fusion partner. Dr. Chilkoti proposes to synthesize a set of ELP fusion proteins in which ESH of the protein and MW of the ELP is independently varied. He will experimentally determine the altered T(t), of ELP fusion proteins relative to ELP control [delta T(t)], and ESH of the fusion proteins, and investigate the relationship between delta T(t) and ESH. The proposed research will result in a fundamental biophysical understanding of the parameters which govern modulation of the inverse transition of ELP fusion proteins, which will allow rational design of parameters (e.g., temperature range, ELP MW, ionic strength) for the proposed biomolecular engineering applications of ELP fusion proteins. Specific applications that will be developed in this proposal are: (1) inverse transition cycling, a new, and convenient methodology for protein purification based upon thermally-reversible modulation of the solubility of ELP fusion proteins; and (2) biosensor regeneration, which utilizes the thermally-reversible adsorption of ELP fusion proteins on hydrophobic surfaces.

Dembo, Micah   Boston University   The Biophysics Of Cell-Substratum Traction Stress GM061806 4 years NIGMS

Abstract: By virtue of recent advances in the technology of the elastic substratum method (ESM) it is now possible to generate accurate vector maps of the traction stresses exerted against a substratum due to the cytoskeletal activity of a single biological cell. We here propose to exploit th ESM so as to answer several fundamental questions about the biological significance of traction stresses, about the physical and molecular origin of these stresses and about the dynamics and control of the cytoskeleton in fibroblasts. AIM number 1 to test the role of traction in the modalities by which cells sense and respond to mechanical perturbations. This will be accomplished by measuring traction stresses during and following controlled deformations to the substratum. AIM number 2 to analyze the dynamics of traction, motion and shape in pairs of normal and transformed cells as they come into contact. AIM number 3 to invent, analyze and test a variety of quantitative mechanical models of the mechanism and molecular origin of the fibroblast-substratum traction stress. AIM number 4 to test the functional linkage between the transmission to traction forces to the substratum, the presence of various integrin isotypes and the presence of Zxyin containing adhesion sites.

Duncan, James S   Yale University   Automatic Image Registration For Prostate Radiotherapy CA080894 4 years NCI

Abstract: The effectiveness of externam beam radiation treatment for prostate cancer is decreased due to a variety of uncertainties in the treatment setup, including the physical characteristics of the treatment beam, patient positioning issues, patient organ motion and operator non-reproducibility. The development and administration of a treatment plan using image- guided techniques to account for some of these uncertainties can positively impact its effectiveness. However, the use of these techniques to date has been limited by i.) a lack of accuracy, robustness and reproducibility in the registration of the high resolution 3D computed tomographic (3DCT) or simulator images acquired in a reference)or planning) frame to the highly noisy and blurry portal images, acquired in the treatment environment and ii.) the difficulty in measuring organ motion and relating it to these data. Thus, we first propose to develop a new automated, accurate, and robust system for performing bony anatomy- based 3DCT-to- multiple- (2D) portal image registration by simultaneously incorporating portal image segmentation. The system will rely on a combination of dense field (region-based) and sparse field (gradient/boundary features) information and will use information- theoretic metrics in an optimization framework to solve for the mapping parameters. This approach will be validated using a gold standard developed from serial CT acquisitions taken each week during the treatment. Next, we will study the relationship between setup variation due to bony structure movement and that due to organ motion in preparation for the design of a future complete system that can acquire treatment- environment images of the prostate using an ultrasound probe attached to an articulated arm in an external- skin- marker-based frame, and the 3DCT-to-multiple portal registration algorithm described above. The feasibility of using external markers to relate portal and ultrasound information will be a key part of this study as well. Finally, we will evaluate the utility of the 3DCT-to-multiple portal registration approach by applying it to the problem of quantitatively studying the sensitivity of errors in the delivery of an optimal dose distribution for a particular patient on a particular day to variations in patient- positioning-related setup for treatment plans of different complexity. These studies will help us understand the utility of more complex treatment plans and planning systems in today's health care environment.

Bioengineering Research Grants (BRG) awarded in FY 2000

Fields, Alan P University Of Texas Medical BR Galveston Lipid Signalling In The Cell Nucleus TW001381 3 years FIC

Abstract: The U.S. PI has a long-standing interest in the various aspects of protein kinase C (PKC) isozyme signaling within cells. The PI has previously investigated in detail one particular pKC isozyme, PKC B2, and has generated a considerable amount of knowledge regarding the mechanisms surrounding activation of this isozyme. The present parent project for this FIRCA application by the PI has now shifted to explore the functional characterization of an atypical PKC isozyme, PKCi, in human leukemia cell survival. In examining factors responsible for the nuclear activation of PKC B2 prior to mitosis, the PI's laboratory isolated a nuclear PI-PLC from G2 phase nuclei. Preliminary experiments using antibodies to known PI-PLC isozymes indicated that this nuclear PI-PLC did not correspond to any of the previously identified PI-PLC isozymes. The foreign collaborator, while working with regenerating rat hepatocytes, also observed the presence of a novel nuclear PI-PLC activity involved in cell cycle regulation. Given these common findings and interests, and given the foreign collaborator's expertise in the biochemical analysis of phosphatidylinositol-metabolizing enzymes, a new collaborative effort has arisen between these investigators. Therefore, the main thrust of this proposal is to identify this novel nuclear PI-PLC activity. In addition, recent data suggests that a phosphatidylinositol 3-kinase (PI3K) signaling system exists within the nucleus and that this nuclear PI3K signaling system is distinct from the well described cytoplasmic-cell membrane PI3K system. The novel nuclear PI3K pathway is responsible for PKB activation. These preliminary results suggest that PI3K and PKB activation may play a direct physiologic role in nuclear events associated with cellular proliferation and cell cycle progression. The second and third specific aims therefore propose to expand and confirm these preliminary results of the roles of nuclear PI3K and PKB in these cellular events.

Glucksberg, Matthew R Northwestern University Color Doppler Imaging Of The Retina And Choroid EY013002 3 years NEI

Abstract: Defects in the regulation of retinal and choroidal flow are part of the etiology of diabetic retinopathy, glaucoma, and other vision-threatening disorders, yet the physics and physiology controlling of blood flow to the retina is poorly understood, at least in part because of the limitations of current methods of measuring blood flow. The goal of this research is to quantitatively study the control of flow and the hemodynamics in the choroidal and retinal circulations and their relationships to retinal disease. The hypothesis is that blood flow in the retinal and choroidal circulations is not homogeneous and that increased heterogeneity in blood flow may be an early indicator of dysfunction of the retinal and choroidal circulations. As part of this work simultaneous, continuous and quantitative measurements of tissue perfusion in the choroidal and retinal circulations will be made to allow study of how the retina and choroidal circulations interact in response to physiological conditions. Previous investigations of the role of the vasculature in health and disease have been hampered by the limits of technology. In this project Color Doppler Optical Coherence Tomography (CDOCT), a novel non-invasive imaging technology, will be adapted to measure hemodynamic parameters in the circulations that serve the retina. The specific aims will first address the instrumentation and quantification of blood flow and then validate the results using in-vivo comparison to Laser Doppler Flowmetery, the most commonly used current method of assessing perfusion. The method will then be used in animal experiments to determine the effects of perfusion pressure and blood gasses on the regional distribution of blood flow and local hematocrit in the retinal and choroidal circulations, with and without ganglionic blockade and other maneuvers which act differently on the two circulations.

Griffin, Lanny V California State Poly U San Louis Obispo Interfacial Properties Of Haversian Bone DE013579 3 years NIDCR

Abstract: DESCRIPTION (Adapted from the Applicant's Abstract): Cortical bone is a brittle, circumferentially laminated, multiphase composite structure that has been shown to exhibit microdamage similar to that found in advanced composite materials. Microcracks are an important manifestation of fatigue damage and are clinically associated with stress fractures, bone fragility, and remodeling. The goal of this study is to quantitatively investigate properties, such as fracture toughness and shear strength, of major interfaces in cortical bone, such as cement lines and interlamellar interfaces of osteons. Additionally, the effects of collagen fiber orientation and physiologic region on these fracture properties will be evaluated. The relevance to structural fracture resistance is that these bone interfaces have been shown to deflect microcracks, and may contribute to the overall fracture resistance of whole bones. The experiments are based on a standard fiber push-out procedure used for testing interfacial properties of fiber-reinforced composite materials. Human bone will be used to evaluate the dependence of interfacial properties of osteons as a function of collagen fiber orientation within the osteon and the adjacent matrix, and to assess the effect of the anatomic region. Equine bone will be used to evaluate differences between primary and secondary osteons. Micromechanics and constitutive modeling will be performed.

Bioengineering Research Grants (BRG) awarded in FY 2000

Griffith, Bartley P   University Of Pittsburgh At Pittsburgh   Bioengineering-Biologic Study Of Non-Pulsatile Perfusion   HL064950   4 years   NHLBI

Abstract: The decade of the 1990s has seen considerable progress toward the development of innovative ventricular assist blood pump systems suitable for the chronic support of adult patients in refractory cardiac failure. Particularly noteworthy are the centrifugal and axial flow rotary blood pumps which are now undergoing long-term animal testing in anticipation of the first U.S. clinical trials. Several of these pump systems are also currently being tested overseas in humans in acute implant trials. One long-standing question remains unanswered regarding these rotary blood pumps relates to the chronic effect of a non- physiologic flow pulse on the anatomy and physiology of the host. This question is assuming considerable clinical importance as these rotary pump systems approach the clinical application for which they are intended, namely long-term total cardiac support. Consequently, the proposed study is being undertaken to investigate chronic non-pulsatile flow from the point of view of physiologic endpoints which are known to be important in the clinical setting of left ventricular and biventricular assistance. To that end, we will complete a series of in vivo (calf) experiments in which diminished pulse flow or totally non- pulsatile flow is generated for either 30 days or 180 days duration via implantation of an axial flow blood pump system. Using this well-validated animal model and robust pump system, we will evaluate the effects of diminished pulsatility and non- pulsatile flow on vasomotor response, arterial microstructure, biomechanical properties of the carotid arteries, and tissue capillary flow. From these experiments, we believe that we will provide significant new information regarding tissue perfusion and arterial adaptation to, and possible impairment from, diminished or non-existent flow pulse.

Griffith, Bartley P   University Of Pittsburgh At Pittsburgh   Development Of A Chronic Artificial Lung   HL065740   4 years   NHLBI

Abstract: The investigators propose to develop a compact wearable pump-lung to support total respiratory needs in adults with either acute respiratory distress or chronic lung failure. The need for such device is considerable and advancements in materials, biocompatibility, and design have enabled us to develop a promising prototype (chronic artificial pump-lung, CAL). We have combined our clinical experience and bioengineering strengths to propose a design criteria that include: Compact wearable device, oxygen delivery of 250 cc/min, CO2 elimination of 200 cc/min, blood pumping of 5 liters/min, modular design facilitate oxygenator replacement (disposable component), use of oral anticoagulation, and fail-safe flow-regulating control. In operation the CAL will achieve extremely efficient gas transfer by utilizing active convecting mixture of the blood via rotation of discs comprised of microporous hollow fiber membranes. Rotation of the fiber discs draws and pumps blood though the device and over the fibers. To date, compact prototypes are five times more efficient (per m2) in O2 delivery than commercial oxygenators and pump at physiologic flows against anticipated afterloads. Preliminary work on biocompatibility has encouraged us that the device can have an optimized blood flow path, platelet resisting surface, and gentleness to RBC, WBC, and platelets. Specific aims of this proposal are: 1) Evaluate the functional pumping and mass exchange characteristics, in vitro of candidate 0.5 m2 devices in a water-based circulation loop while modeling the flow path of the CAL with computer flow design to predict pumping characteristics and aid in optimization of flow path. 2) Evaluate flow path biocompatibility of candidate CAL designs developed in bovine blood-based circulatory loop to assess hemolysis, thrombotic deposition, and platelet activation. Functional pumping and mass transfer characteristics of candidate CAL prototypes will concurrently be evaluated with this flow loop. In parallel, the CFD model developed in Specific Aim 1 will be extended to blood and refined into a predictive design tool. 3) Characterize the membrane transport and platelet attacking properties of uncoated and candidate siloxane-based fiber coatings. 4) Perform chronic (21-day) in vivo bovine experiments to assess both the gas exchange and pumping functionality and overall long-term biocompatibility of the CAL prototype. 5) Develop and validate a closed-loop, flow control algorithm to ensure fail-safe pumping by the CAL spinning disc(s); incorporate algorithm into a controller unit to be part of the overall CAL system.

Haskell-Luevano, Carrie   University Of Florida   Structural Determinants Of Neuroendocrine Receptors   DK057080   5 years   NIDDK

Abstract: DESCRIPTION (Adapted from the application): In both mice and humans the neuroendocrine melanocortin system has been linked to weight regulation and obesity. Of the multiple receptor subtypes involved, the melanocortin-4 receptor subtype (MC4R), which is located entirely in the central nervous system, appears to play an important role in body weight homeostasis. This is suggested most strongly by knockout and mutational studies in animals. Endogenous agonists for this receptor include proopiomelanocortin-derived peptides, whereas the agouti-related protein is a natural antagonist. However, based on the use of available agonists and antagonists, function of the MC4R is difficult to distinguish from that of other melanocortin receptor subtypes, especially MC3R, for which a function has not been defined. This lack of specificity in reagents makes it difficult to assess structure-function relationships of MC4R, and to differentiate its functions from those of MC3R. Thus, the overall goal of this proposal is to develop new peptide and non-peptide MC4R probes that can be used to define the function of the MC4R, both in vitro and in vivo. The specific aims are to 1) identify selective MC4R agonists and antagonists using peptide libraries and a combinatorial chemistry approach, 2) identify structural features of a constitutively active MC4R that will allow differentiation between agonist and antagonist behavior of ligands, and 3) test available parenteral and potential orally active compounds selective for MC4R in vivo.

Bioengineering Research Grants (BRG) awarded in FY 2000

Heidemann, Steven R   Michigan State University   Cytomechanics Of Cell Crawling   GM061339   4 years   NIGMS

Abstract: This proposal addresses the mechanical linkages within the cell that underlie cell migration and shape change. Such linkages are involved in invasion and metastasis by tumor cells; in regulated migration of leukocytes during immune surveillance and response; in human embryonic development; and in wound healing. Recent evidence indicates that cell motility involves a continuously acting cortical motor that engages and disengages, as with an automobile transmission with a clutch. Our goal is to understand the various mechanical couplings among the motor, the MT-rich bulk cytoplasm, and adhesions to the environment that underlie fibroblast motility during directed cell migration (Specific Aim 1), in non-migratory motility such as cell spreading (Specific Aim 2), and in cells poisoned with anti-cytoskeletal drugs (Specific Aim 3). These various motility states of fibroblasts are analyzed quantitatively for three sub-mechanisms of cell movement: cell adhesion, cortical motor activity, and engagement and disengagement of the motor to the cell surface and bulk cytoplasm. For example, we test the hypothesis that mechanical strength of adhesion is the result of recruitment of actin to the cytoplasmic side of the adhesion site, and that this actin recruitment, in turn, leads to engagement of the cortical motor to produce cytoplasmic movements. These analyses are carried out combining four methodologies: 1) calibrated glass needles to apply and measure forces to individual fibroblasts; 2) Visualization of the actin and microtuble cytoskeletons by transfection and expression of cytoskeletal proteins labeled cytoskeletal proteins labeled with green-fluorescent protein (GFP- technology); 3) Assessment of the continuously acting cortical motor through the centripetal movement of variously treated vinyl beads or calibrated needles adhering to the surface; and 4) manipulating the extent of cytoskeletal coupling to the motor and environmental by differential adhesion of surface-attached beads or needles. The proposed experiments are intended to substantially improve our understanding of the physical mechanisms of cellular motility and shape change, which understanding is poor compared to our knowledge of the molecules involved.

Herzenberg, Leonard A   Stanford University   Multi Colors FACS--Advancement For Extended Applications   CA089499   5 years   NCI

Abstract: We propose to maintain the momentum of new discoveries using multicolor fluorescence cell analysis and sorting by developing a new instrument to provide more light generation per cell, better light collection, improved signal evaluation and optimized sorting capability. We recently developed a FACS instrument able to measure up to 11 fluorescent reagents, and experiments using 8 and 9 colors are being performed routinely. The move to higher order multicolor analysis has been very successful in producing new biological results, and it has increased the dye choices and flexibility in work using fewer colors. However, in multicolor experiments the data quality in individual measurement channels is often not as good as what we obtain with comparable single color stains on these channels. We have analyzed the signals and concluded that, while there are systematic problems such as logamp scaling inaccuracy and mismatches between logamps which degrade the accuracy of spectral overlap corrections, the fundamental problem is lack of sufficient light in some of the single measurements and, more generally, lack of sufficient light to accurately evaluate and correct spectral overlaps. Further work on new dyes and different laser sources will help to decrease spectral overlaps between dyes, but efforts to increase the number of usable reagents and to use particular probes whose spectra crowd other dyes of interest will assure that spectral overlap and spectral overlap corrections continue to be limiting factors in flow cytometry. To address these limitations we will develop a FACS yielding at least 20 times the signal levels we obtain with the current system. Initially, we will build separate analytical and sorting prototyping systems. Improved signal evaluation electronics and procedures will be developed. A series of new developments will also be carried out to facilitate high quality cell sorting. Based on developments in these systems, we will assemble a combined biologically useful FACS. We will begin to carry out biological experiments at as early a stage in the work as possible, and the complete instrument will be made available to the full array of users in our FACS service center.

Holschneider, Daniel P   University Of Southern California   An Implantable Bolus Infusion Pump For The Neurosciences   MH062148   3 years   NIMH

Abstract: DESCRIPTION: (Adapted from the Applicant's Abstract) The applicants propose the development of a subcutaneously implantable microbolus infusion pump (MIP) for neuroscience research in small animals, where the research paradigms require conscious, behaving animals in a non-tethered state. The MIP will allow in vivo incremental dosing of drugs by remote activation, as well as sequential administration of different pharmacologic agents, via the external jugular vein. This capability will make the MIP a powerful tool for examining acute behavioral and physiologic effects of pharmacologic agents in animal models of human disease. Use of the MIP should allow investigations of the acute effects of pharmacologic agents on animal behaviors sensitive to interference by handling (e.g., mating, aggression, sleep, circadian rhythms). Furthermore, the MIP will allow noninvasive study of the acute effect of pharmacologic agents on physiologic parameters that are typically confounded by the effects of handling stress on the animal (e.g., stress hormones, cardiovascular parameters, brain electrical activity, temperature). Pilot data are provided which suggest that infusion of radiotracers with the MIP in the freely moving animal allows imaging of acute changes in regional blood flow associated with brain activation. Such functional neuroimaging of complex animal behaviors cannot be undertaken with the current technologies. In transgenic mice, the MIP promises to improve the characterization of the phenotypic effects of gene deletions/insertions. The 4 goals of this project are: (1) to optimize and develop the design of the MIP for rats, (2) to validate the ability of MIP to provide precise, remotely activated bolus infusion of a drug in freely behaving rats, without interfering with the normal behavior and physiological parameters, and allowing the generation of cerebral blood flow images, (3) to miniaturize the MIP for mice, and (4) to design and test a dual chamber MIP that allows independent, controlled release of two separate pharmacologic agents.

Bioengineering Research Grants (BRG) awarded in FY 2000

Hu, Xiaoping P   University Of Minnesota Twin Cities   Improvement And Applications Of Functional MRI   MH055346   5 years   NIMH

Abstract: DESCRIPTION (Adapted from Applicant's Abstract): In the last few years, a significant new development in fMRI is the introduction of event-related techniques that are also known as single-trial or time-resolved approaches. By providing temporally-resolved fMRI response evoked by individual events, event-related fMRI can elucidate temporal profiles of events taking place in the neural circuit and provide trial-specific information. Therefore, event-related techniques represent a major breakthrough in fMRI, hold a great potential for imaging the function of brain with an added dimension and have become widely utilized since its introduction. However, since event-related studies differ from those based on the traditional block design, and the associated temporal response is often small and unknown a priori, technical difficulties are still present. The first part of this application is thus aimed at developing a set of tools to improve event-related fMRI. Specifically, the applicants propose to develop and validate: 1) methods for improving the signal-to-noise ratio in event-related fMRI data; 2) methods for time course feature extraction and activation identification in event-related fMRI; and 3) analysis techniques for characterizing event-related fMRI time courses. In addition, the propose to also develop 4) adaptive imaging techniques for event-related fMR] with improved temporal resolution. After their development and validation, the techniques will be further demonstrated with two cognitive tasks that have not been previously examined with event-related fMRI. The first paradigm is use-word generation task that was previously demonstrated by PET studies to involve spatially separate areas that were shown by ERP to exhibit unique temporal relationships. The applicants propose to use event-related fMRI to investigate these areas and compare the timing derived from event-related fMRI with that reported by ERP to test the hypothesis that event-related fMRI can ascertain temporal differences in neuronal response to the use-word generation in the domain of hundreds of milliseconds. The second task to be studied is a delayed non-match to sample (DNMS) task which is thought to involve both cortical areas and medial temporal lobe, in a temporally differential manner. Specifically, the applicants propose to examine a modified DNMS paradigm using event-related fMRI to ascertain the activation in areas involved in the task and to elucidate temporal profiles of the activity in these areas. The hypotheses are that the medial temporal lobe is involved, differences exist in activation profiles of different areas, and the differences can be elucidated with event-related fMRI to aid in the understanding of the roles played by these areas.

Hunter, David G   Johns Hopkins University   Retinal Birefringence Analysis In Strabismus & Amblyopia   EY012883   4 years   NEI

Abstract: DESCRIPTION (Author Abstract): Amblyopia is the leading treatable cause of vision loss in childhood, with a prevalence of 2-5%. It is responsive to treatment early in life, but delayed treatment can result in life-long visual impairment. Unfortunately, health care practitioners are often unable to identify amblyopia risk factors, including strabismus, media opacities, and anisometropia, in patients under age 5, so that many cases of amblyopia go undetected and untreated. There is a need for a more effective method of detecting amblyopia risk factors. The fovea of the eye is surrounded by a distinctive pattern of birefrefringent fibers that change the polarization state of transmitted light. Our laboratory has developed a specialized form of retinal birefringence scanning (RBS), in which a small spot of polarized fight is scanned in a circle on the retina, and the returning fight measured for changes in polarization. We have demonstrated that RBS accurately (+/- 1 deg) detects foveal fixation in real time, in unrestrained subjects (including infants and children), making it possible to study patients with amblyopia and young children at risk for developing amblyopia. RBS has been characterized in only a small number of subjects, however, and little is known about individual variability. We have also developed binocular RBS (BRBS), which detects fixation of both eyes simultaneously and hence detects interocular alignment. The specific aims are to more fully characterize the RBS signal in normal and amblyopic subjects to enhance accuracy (hence sensitivity and specificity), and to screen normal and strabismic subjects using BRBS to identify amblyopia risk factors. BRBS may make it possible to screen infants and children automatically for the presence of amblyopia risk factors, including ocular misalignment, media opacity, and possibly refractive error, thereby facilitating early detection and treatment of this preventable form of blindness. The ability to screen for early, small deviations may help resolve conflicting findings on the efficacy of early amblyopia detection and treatment.

Bioengineering Research Grants (BRG) awarded in FY 2000

Khoobehi, Bahram   Louisiana State Univ HSC New Orleans   Retinal And Choroidal Blood Flow Imaging   EY012887   3 years   NEI

Abstract: DESCRIPTION (Author supplied): This proposed study focuses on fluorescent cell imaging (FCI) in which erythrocyte membranes or leukocyte nuclei from one animal are stained with different fluorescent dyes of different wavelengths, injected systemically in the same animal, excited transcorneally, and tracked and analyzed to quantify blood flow. After imaging fluorescent cells in the blood vessels of the posterior pole of the eye, video frames are analyzed to infer maximum and average blood cell velocities, and relative and absolute volumetric blood flow using an automated data extraction system. The diameters of large ocular blood vessels are measured and mapped. Cell velocities are spectrally analyzed to determine pulsatility. The five objectives of the study are: 1) to establish FCI safety and potential use in humans by performing toxicity tests in rats and monkeys; 2) to develop a statistical framework for comparing parameter maps; 3) to validate FCI by evaluating measurements made in vitro of stained erythrocytes in capillary tubes and in vivo by comparing FCI measurements of velocities and flow rates in the monkey eye to measurements obtained using laser Doppler methods; 4) to compare erythrocyte and leukocyte blood flow velocities in the microcirculation; and 5) to assess the clinical utility of FCI. The fifth goal has four parts. First, FCI will be used to compare blood parameters in a rat model before and after inducing symptoms of diabetes using streptozocin, and in a researcher-blind study, an attempt will be made to use FCI parameter maps to diagnose diabetes. Second, quantification and mapping of blood speeds, pulsatility, and flow rates in the microcirculation of the macula and optic nerve head of a normal monkey will be performed using FCI. Third, those hemodynamic parameters will be mapped in the macular microcirculation of the monkey choroid using FCI. Finally, changes in hemodynamic parameter maps of the monkey eye in response to an acute increase in intraocular pressure will be quantified. With FCI, changes in blood flow rates in diabetic retinopathy and glaucoma might be determined, as well as the effect of consumption of vasoactive drugs.

Ledbetter, Jeffrey A   Pacific Northwest Research Institute   Gene Therapy With MAB Derivatives Expressed On Tumors   CA090143   4 years   NCI

Abstract: DESCRIPTION: (Applicant's Abstract) Previous work in the applicant's laboratory has demonstrated that costimulation plays a key role in the induction of an immune response, including one to tumors. This costimulation can be provided by either transfecting a gene encoding a ligand, such as CD80 and/or CD86 into tumor cells, or by transfecting a gene encoding a single chain Fv (scFv) from the appropriate anti-receptor mAb. The scFv approach can have an advantage over the use of natural ligands. For example, CD80 and CD86 bind with high avidity to CTLA-4, which produces a strong negative signal, while the anti-CD28 scFv does not. In addition, scFvs can be used when natural ligands are unknown, such as for CD3-epsilon. In this application, variable region genes from hybridoma antibodies specific for human costimulatory receptors will be expressed as cell surface scFvs to modulate antigen-specific immune responses to tumor cells. Genes encoding scFvs that retain specificity and high binding affinity for CD3-epsilon, CD28, CD2, CD4, CD8, and CD154 have been constructed and expressed as soluble Ig-fusion proteins. Transmembrane domains have been added to some of the scFv gene constructs to direct their expression to the cell surface. These genes will be expressed on the surface of human tumor cell lines to determine their potential for amplification of T cell responses. The applicant hypothesizes that use of antibody derivatives can improve the specificity and potency of cancer gene therapy, and that cell surface expression of scFvs will enhance the immune response to specific antigens when compared with expression of native ligands for T cell surface receptors. He will determine whether expression of scFvs specific for T cell stimulatory and costimulatory molecules on the surface of tumor cells will increase T cell activation, including both CD4+ Th1 responses and CD8+ cytotoxic responses important for tumor rejection.

Liao, James   University Of California Los Angeles   Nitric Oxide Diffusion And Reaction With Erythrocytes   HL065741   4 years   NHLBI

Abstract: The broad, long-term goal of this project is to investigate the diffusion and reaction of nitric oxide (NO) in blood, particularly its interaction with red blood cells (RBCs). It is hypothesized that RBCs possess specific mechanisms that regulate the NO consumption rate through modulation of membrane permeability to NO. Specifically the following aims will be pursued. Specific Aim 1: Is NO consumption by RBC regulated by transmembrane diffusion? Specific Aim 2: Do any specific intra- erythrocytic molecules participate in the regulation of NO quenching? Specific Aim 3: How does the regulation of NO consumption by RBCs affect vessel regulation? The first two aims will be addressed by use of a competitive experiment and a differential membrane bioreactor specifically designed to measure the NO-RBC reaction rate. Kinetic models will be used to analyze the data. Biophysical (EPR and fluorescence) and biochemical (characterization of enzymes, metabolites, and lipids) techniques will be applied to RBCs, RBC ghosts, and synthetic liposomes in order to answer these questions. The last aim will be addressed using isolated porcine coronary microvessels as a bio-assay to determine the functional role of NO quenching and its regulation. The hypotheses proposed above are a significant departure from the current understanding that NO consumption is not regulated and that the RBC membrane is "completely permeable" to NO. In addition to its contribution to fundamental physiology, the proposed work directly impacts multiple aspects of clinical medicine, including NO inhalation therapy and the design of blood substitutes. Furthermore, the proposed mechanism might contribute to the pathology of several diseases, such as essential and pulmonary hypertension, peripheral vascular disease associated with diabetes mellitus, sickle cell anemia, and other hereditary RBC disorders. In these situations, altered RBC membrane consumption by RBCs is essential to the development of clinical intervention and understanding of the complex roles that NO plays under physiological and pathological conditions.

Bioengineering Research Grants (BRG) awarded in FY 2000

Lotz, Jeffrey C   University Of California San Francisco   Analysis Of Injury Avoidance Strategies During Falls   AR046890   3 years   NIAMS

Abstract: At least 280,000 hip fractures occur annually in the U.S., at an estimated cost of $9 billion. While over 90% of these are caused by falls, only about 2% of all falls result in hip fracture. Considerable evidence now exists that the most important determinants of hip fracture risk during a fall are the body's impact velocity and configuration (and in particular, whether contact occurs to the hip region). Accordingly, protective responses for reducing impact velocity, and the likelihood for direct impact to the hip, strongly influence fracture risk. Improved understanding of the nature of such responses, and how these are affected by age-related declines in neuromuscular variables, would enhance our ability to develop exercise- based strategies for hip fracture prevention. Based on the results of epidemiological and biomechanical studies, we hypothesize that two protective responses central to safe landing during a fall are (a) absorbing energy in the lower extremity muscles during the descent phase of the fall, and (b) braking the fall with the outstretched hands. We also hypothesize, based on epidemiological evidence, that the efficacy of these responses associate with strength, flexibility, and reaction time. To test these hypotheses, we will address four aims. Aim 1 is to test whether use of the above protective responses influences young females' ability to avoid impact to the hip, and reduce the impact velocity of the body during falls onto a soft gymnasium mat. Aim 2 is to test whether ancillary measures of balance and lower extremity flexibility and reaction time associate with young and elderly subjects' ability to absorb energy in their lower extremity muscles, and reduce impact velocity when descending from standing to sitting. Aim 3 is to test whether balance and upper extremity strength, flexibility, and reaction time associate with young and elderly subjects' ability to quickly contact an impact surface with the outstretched hands, and absorb energy in the upper extremity muscles during simulated falls. Finally, Aim 4 is to develop and validate complementary mathematical models of falling, and use these to determine how specific impairments (or exercise-induced enhancements) in muscle strength, joint flexibility. Finally, Aim 4 is to develop and validate complementary mathematical models of falling, and use these to determine how specific impairments (or exercise-induced enhancements) in muscle strength, joint flexibility, and reaction time affect fall protective responses and fall severity. By identifying the biomechanical and neuromuscular variables which govern safe landing during a fall, these studies should lead to novel and effective interventions for reducing hip fractures in the elderly.

Loughlin, Patrick J   University Of Pittsburgh At Pittsburgh   Time Varying Characteristics Of Human Postural Sway   DC004435   3 years   NIDCD

Abstract: DESCRIPTION: (Adapted from the Investigator's Abstract) This study seeks to gain understanding of the human postural system and its ability to adapt to external visual perturbations. The adaptation, habituation and saturation characteristics of postural sway in healthy individuals standing on different support surfaces will be studied as will as the same characteristics in patients with diseases that impair balance such as vestibular deficits and cerebellar deficits. The focus will be on the time-varying aspects of the postural response to visual perturbations. Preliminary data indicate that the ability to adapt to perturbations can be used to distinguish between classes of subjects. The primary tool for data collection is a center of pressure (COP) platform type with a moving visual field device attached. Data processing methods such as time-frequency analysis are employed to allow the calculation of adaptation (per-stimulus response decline within a trial), habituation (a decrease in response to stimuli across repeated trials) and saturation (compression of the response to increasing stimulus) statistics with high confidence. An objective of the research is to improve the evaluation and rehabilitation of individuals with balance disorders.

Mewes, Klaus   Emory University   Advanced Methods For Microelectrode Guided Neurosurgery   NS040548   4 years   NINDS

Abstract: DESCRIPTION: (Verbatim from the Applicant's Abstract) Development and clinical testing of an improved brain mapping and lesioning system is proposed. An improved MRI scan protocol, the intraoperative use of patient-specific MRI data and automation of major components of the microelectrode-guided neurosurgical procedure are key features of this system. These efforts are anticipated to improve the accuracy of lesion and/or deep brain stimulating electrode placement and to increase the efficiency and safety of this procedure. Increased usage and availability of this class of procedures is expected due to 'ease of use' characteristics achieved by automating many of the difficult and time consuming tasks. System development and enhancement will be based on the microelectrode-guided pallidotomy procedure pioneered at Emory University. A high resolution, high contrast MRI protocol will be developed for better visualization basal ganglia (BG) structures and greater spatial accuracy. It will be used to generate 3D mapping templates from patient-specific data volumes. Software for intra-operative useage will have the following functions: 1) automatic classification of neuronal discharge patterns and detection of BG nuclear boundaries, 2) automated detection of sensory-motor driving and visual evoked responses, 3) generation and co-registration of microelectrode trajectory plots with MRI incorporating data from 1 and 2, and 4) automated best-fit analysis to correlate recording track information with the MRI-based patient-specific MRI data volume. The system performance for neuronal pattern classification and BG nuclear boundary detection, sensory-motor driving and visual evoked response detection, microelectrode track generation, and track to template best-fit analysis will be compared individually to that of human experts. Upon achieving successful performance, a working prototype will be developed near the end of the second year that integrates these components and the clinical evaluation phase of the system will begin. Lesion accuracy, operating time, and a number of tracks required using the proposed system will be compared to similar data from procedures performed at Emory University using previous methods and technology.

Bioengineering Research Grants (BRG) awarded in FY 2000

Miller, Christine E   University Of Rochester   Control Of Stress And Strain In The Embryonic Heart   HL065908   4 years   NHLBI

Abstract: There is substantial evidence that morphogenesis and cardiovascular phenotype depend upon mechanical loading of the heart during early stages of development. The actual mechanisms, however, have not been determined. We hypothesize that a control law exists, which governs the state of stress and/or strain in the embryonic heart cell through growth and morphogenesis. The control system is parametric in nature and operates in a closed- loop feedback regime to alter both the passive and active components of the heart. As a step towards documenting the existence of such a control law, we propose to identify the control of stress and strain in the normal heart and examine the response to perturbed hemodynamic pressure. The experimental model is the embryonic chick heart between stages 18 to 31. The specific aims are to: (1) Use confocal scanning laser microscopy to obtain morphological data and information on trabecular and myofibrillar patterns and densities. The three-dimensional geometry of the heart will be reconstructed from these scans. Both the normal and perturbed heart will be characterized. (2) Measure the mechanical properties of the embryonic heart under normal and perturbed loading. Extension, ramp-and-hold, and inflation tests will be used and appropriate forms of a constitutive relationship constructed. (3) Identify a relationship governing reduction in error between the controlled variables and the reference input by combining the results from Aims (1) and (2). The geometrical models from Aim (1) will be used to construct a realistic finite element representation of the heart with the results of Aim (2) providing material properties. The models will be solved and various measures of stress and strain compared between the normal and pressure-perturbed hearts. These comparisons, in addition to comparisons of geometrical data from Aim (1) and material property data from Aim (2), will be used to indicate possible forms of the control law and growth laws. The results of this study will provide insight into the mechanisms of mechanical sensing and control in heart development and into the relationship between mechanical environment and phenotype. Further study may also yield insight into congenital cardiovascular malformations, a major cause of morbidity and mortality in children and adults.

Munn, Lance L   Massachusetts General Hospital   Cell-Surface Adhesion--Influence Of Blood Rheology   HL064240   4 years   NHLBI

Abstract: The capture of circulating cells such as lymphocytes and metastatic tumor cells to the blood vessel wall is a complex process. Cell adhesion to the vascular endothelium depends on the forces of adhesion, the fluid dynamics, and the kinetics of adhesion molecule association-dissociation in the contact region. As a cell interacts with the surface, the participation of various adhesion molecules is determined by the force of contact (which must overcome surface protein electrostatic repulsive forces to bring the receptor-ligand pair into close proximity) and the time of contact (which must be long enough to allow at least one bond formation). Even though RBCs constitute 95% of the particles in blood and 30-45% of the total volume, they have largely been ignored as contributors to the process of adhesion. Since erythrocytes may increase both the contact force and contact time, studies performed in the absence of these cells may be inadequate for extrapolating the in vivo flow. For example, a receptor-ligand pair that does not extend very far above the glycocalyx (the glycoprotein-rich envelope surrounding the cell) may not be able to engage in saline solution, but with the additional forces imparted by RBCs, the cell membranes may come into closer contact, allowing bond formation. Also, larger contact forces should result in larger contact areas, thereby increasing the number of adhesion molecules available for binding; this would increase the probability of cell arrest. The presence of RBCs may also change the spatial distribution of leukocytes in the flow stream, pushing them from the bulk toward the wall. The proposed study will quantify the physical forces and rheological characteristics an adhering cell experiences in the bloodstream. The resulting information will be invaluable in 1) the extrapolation of flow chamber studies to in vivo adhesion, 2) the development of more physiologic blood substitutes, 3) explaining and overcoming immune surveillance by solid tumors and 4) formulation of novel strategies for prevention of atherosclerosis.

Bioengineering Research Grants (BRG) awarded in FY 2000

Normann, Richard A   University Of Utah   A Peripheral Nerve, Intrafascicular Multielectrode Array   NS039677   4 years   NINDS

Abstract: Spinal cord injuries and stroke afflict a significant component of our population (both the young and the aging). The lack of effective therapeutic solutions to these problems results in the need for lifetime care and expensive assistive technologies for these individuals. The decrease in the quality of life of these patients, the costs of their chronic care, and the reduction in their productivity present strong motivations to develop new therapeutic approaches to this problem. The goal of restoring motor function to individuals with spinal cord injuries or stroke victims has been hampered by the lack of an appropriate interface to the peripheral nervous system. The development of a minimal error control system for restoration of motor function will require acquisition of sensory information from a large number of cutaneous, muscle and joint receptors, and the capability of independent excitation of a large number of muscle groups. Existing neural interfaces cannot provide such multichannel independent access to sensory and motor nerve fibers. We have developed a new neural interface, the Utah Slant Array (or USA) that will provide unprecedented access to large number of sensory and motor neurons. The array has been designed to be implanted in peripheral nerves, and will provide up to 100 channels of neural communication. We will evaluate the recording and stimulating capabilities of the USA in acute experiments in feline sciatic nerve. We will develop a chronic USA implant system based upon what we have learned in our acute experiments, and evaluate its chronic recording and stimulating stability in an ambulating cat. We will demonstrate that sensory information recorded with the USA can be used to control the motor stimulation of efferent fibers to achieve a reliable control of a cat's ankle and foot movements when walking on a treadmill. Our overall goal is to acquire sufficient information about the USA and how it can be chronically applied so that human application would be feasible and ethically acceptable in a future granting period.

Peterka, Robert J   Oregon Health & Science University   New Method To Identify Unilateral Vestibular Dysfunction   DC004592   3 years   NIDCD

Abstract: DESCRIPTION:(adapted from applicant's abstract) The long-term goal of this project is to develop a new clinical test that can identify and characterize the severity of an asymmetry of vestibular function between the two ears. Preliminary results suggest that a test based on measurement of vestibulo-ocular reflex (VOR) eye movements evoked by a novel rotational stimulus can overcome the significant limitations of the two main clinical tests (caloric and conventional rotation) currently used to evaluate vestibular function. If proven effective, this diagnostic test could be rapidly adopted into clinical practice since rotation test equipment capable of delivering the proposed new rotational stimulus is currently in used in most major medical centers. There are three specific aims in the proposal. The first aim is to use modeling and simulation studies to investigate how physiological properties of vestibular-nerve afferents and VOR are likely to influence the ability of the new rotational stimulus to accurately identify a vestibular asymmetry. These properties include static and dynamic characteristics of primary semicircular canal afferents, orientation of the semicircular canals with respect to one another and with respect to the rotation axis, and dynamic characteristics of nystagmus generated in response to large amplitude rotational motions. The second aim is to use experimental studies to determine exact specifications for the new rotational stimulus, and to investigate methodological factors that influence the sensitivity of the new test. The third aim is to verify the clinical applicability of the proposed new test by comparing results from caloric and conventional rotation tests with results from the proposed new rotation test. Experimental results from subjects with different levels of partial unilateral vestibular loss will determine the effectiveness and reliability of the proposed new rotation test.

Rebrin, Kerstin   Minimed, Inc.   Support System For Subcutaneous Insulin Delivery By Pump   DK057210   3 years   NIDDK

Abstract: DESCRIPTION (Adapted from the application: Control of the blood glucose concentration in diabetes mellitus is crucial to avoiding complications of this disease. However, optimal glucose control is difficult, if not impossible for most patients with insulin-dependent diabetes to achieve with currently available therapy. This consists of either multiple daily insulin injections or use of an insulin pump, with dosage adjustment based on finger stick blood glucose readings one or more times each day. This revised application proposes to develop a feedback-controlled insulin delivery system consisting of an implantable glucose sensor linked to an insulin pump. This closed-loop system will be under the control of an algorithm that mimics the function of normal pancreatic beta cells. This algorithm will also be developed and tested in the proposed studies. Experiments will be performed in normal and diabetic dogs, as well as in human subjects with diabetes. In the first specific aim, the glucose sensor and insulin pump will be linked with a feedback algorithm and tested first in normal and then in diabetic dogs under various conditions designed to reflect clinical situations. In the second specific aim, the closed loop system and control algorithms will be tested in humans, with close attention to the sensor response to hypoglycemic challenge. In the third specific aim, the control algorithm will be refined and validated in diabetic humans with varying degrees of insulin sensitivity. In the fourth specific aim, the efficacy and safety of the closed-loop system will be tested for its ability to control blood glucose in diabetic humans. The overall goal is the same: to implement a working closed-loop insulin delivery system for Type I diabetic patients within three years.

Bioengineering Research Grants (BRG) awarded in FY 2000

Smith, George M University Of Kentucky Bioresorbable Microfilaments For Nervous System Repair NS040592 4 years NINDS

Abstract: Peripheral nerve grafts are known to support axonal regeneration across a lesion in the central nervous system or a lesioned nerve gap in the peripheral nervous system. Enhanced axon growth through these nerve segments is most likely caused by increased production of neurotrophins, adhesion molecules, and growth promoting extracellular matrix molecules such as laminin. These nerve segments also contain channels that act to Organize and direct axon growth. This proposal will test the hypothesis that an artificial matrix mimicking the features of peripheral nerve grafts will influence glial attachment, migration, and enhance axonal regeneration. To test this hypothesis, we constructed microfilaments from bioresorbable polymers that can be modified to promote axon growth and release neurotrophins. When bundled, these microfilaments provide channels that orient cell migration and axonal growth. To develop a more complete understanding of cellular-material interaction, microfilaments will be fabricated from two polymers with selective physical and biochemical properties and examined after implantation into either the sciatic nerve or spinal cord. To examine cell responses to changes in physical properties, porosity, protein-release rates, cross-sectional shape, and filament diameters will be altered. The primary polymers also have different biochemical properties that can be further modified by incorporating extracellular matrix molecules (matrigel Or laminin) or neurotrophins. These biochemical modifications should greatly influence microfilament interactions with glia and regenerating axons by providing necessary chemotactic and chemoaffinity signals. The most important aspect of this study is the consolidation and utilization of both the physical and biochemical properties to explore, influence, and organize the cellular- material interaction to enhance integration, wound healing, and regeneration. Cellular responses to microfilament implants will be examined using immunohistology, semi-thin plastic sections, and electron microscopy. These experiments will elicit a better understanding of how cells interact with bioresorbable materials and how these interactions can be manipulated by altering the physical and biochemical properties of the material. The ultimate goal of this research is to achieve a better understanding of the mechanisms that influence injury repair and to use these insights to improve the development and fabrication of biomaterials that can promote wound healing and regeneration of the nervous system.

Taber, Larry A Washington University Biomechanics Of Looping In The Embryonic Heart HL064347 4 years NHLBI

Abstract: Cardiac looping is a vital morphogenetic event during early development. During looping, the relatively straight heart tube bends and twists, moving the future atria and ventricles into their correct relative anatomical positions. Even relatively minor perturbations in looping geometry can lead to major congenital heart defects. Thus, it is important to determine the factors that drive and regulate this process. Several ideas have been proposed for the mechanism of looping, but experimental results have been inconclusive and sometimes conflicting. Thus, cardiac looping remains a poorly understood process. Looping likely involves a dynamic interaction between genetic and epigenetic factors, with biomechanics being a major epigenetic component. The main objective of this research is to investigate the role that biomechanical forces play in the looping process. The specific aims of the proposed research will test the following main hypotheses: (1) Residual stress, in particular longitudinal tension in the cardiac tube near the dorsal mesocardium, plays a role in looping. (2) Looping is driven in part by swelling of the cardiac jelly, coupled with regional variations in stiffness and anisotropy of the myocardium. (3) Cytoskeletal contraction in the myocardium plays a role in looping. These hypotheses will be tested using a combination of experimental and theoretical methods. Experiments conducted on chick embryo hearts will perturb the mechanism studied in each specific aim and measure the effects on looping morphology and the material properties of the cardiac tube. The material properties, measured by "cell poker" and atomic force microscopy, and geometry reconstructed from serial sections will be used to develop computational models for the embryonic heart based on fundamental physical principles. These models will include the effects of large deformation, anisotropy, active contraction, growth, and complex three-dimensional geometry. The models will predict looping geometry for each experimental perturbation, and the actual looping mechanism(s) will be determined by comparing measured and predicted looping morphologies. Defining the biomechanical forces involved in looping would provide insight into this morphogenetic process and thereby help researchers searching for the link between gene expression and looping morphology.

Titze, Ingo R University Of Iowa Neuromuscular Control Of The Larynx During Phonation DC004347 5 years NIDCD

Abstract: DESCRIPTION: (Adapted from the Investigator's Abstract) The long range aim of this project is to predict vocal fold movement and sound generation in the larynx from neural inputs. Central to the research project is the design and implementation of a complete quantitative neuromuscular model of the larynx and to adapt this model to existing data or to data to be experimentally obtained as part of the project. The planned work consists in: establishing the dynamic contractile properties and constitutive equations for all laryngeal muscles; to develop a new 3D finite element model that allows simulation of laryngeal posturing; investigating to which degree the compartments of the thyroarytenoid muscle effect adduction, pitch and vocal register in phonation; to determine the role of laryngeal reflexes in vocal fold posturing and in neurologic instabilities of voicing; and finally to develop a set of test utterances that will test the motor capabilities of the larynx and vocal disorders of laryngeal control.

Bioengineering Research Grants (BRG) awarded in FY 2000

Triolo, Ronald J   Case Western Reserve University   Automatic Control Of Standing Balance With FNS   NS040547   3 years   NINDS

Abstract: This project will develop a novel control system to automatically regulate posture and actively restore balance to users of neuroprostheses for standing after spinal cord injury. Current standing neuroprostheses utilizing functional neuromuscular stimulation (FNS) only provide support and prevent collapse by stiffening the lower extremities through continuous supramaximal stimulation of the knee, hip and trunk extensors. They include no mechanism to actively maintain balance or compensate for disturbances, and rely on the upper extremities to make the postural corrections required to remain balanced in the upright position. This project will address the shortcomings of currently available FNS standing systems by developing a sensor-driven "artificial vestibular system" that will actively monitor posture, anticipate perturbations to balance and automatically modulate stimulation to keep the user upright. This will be accomplished by combining innovative feed-forward, feedback and adaptive control techniques at multiple joints and in three dimensions. A small number of simple, but information-rich, body-mounted sensors will capture the actions of the torso as well as the lower extremities. Dynamic stability will be achieved by using accelerations of the trunk to predict and rapidly respond to disturbances in a feed-forward manner. Static stability will be achieved by regulating center of pressure within the base of support using feedback control, and adaptive algorithms will be applied to compensate for fatigue. A model-based approach to controller development will be adopted that relies on computer simulation, optimization and performance verification prior human testing. This new control system should reduce reliance on the upper extremities while standing with FNS, thus advancing the goal of providing neuroprosthesis users with freer use of their hands to manipulate objects in the environment by automatically maintaining balance in the presence of intrinsic and extrinsic disturbances.

Udapa, Jayaram K   University Of Pennsylvania   Biomechanics Of Foot/Ankle Injuries Using 3D Imaging   AR046902   3 years   NIAMS

Abstract: DESCRIPTION (Adapted from the Applicant's Abstract): The broad goal of this research is to apply advanced imaging techniques to develop, in a patient-specific manner, a quantitative understanding of how the joints function, and of how they are affected by soft-tissue injuries and by their surgical treatment. The central hypothesis is that this understanding will lead to reliable, early and improved diagnostic and therapeutic procedures for joint ailments involving soft-tissue injuries. The focus of this proposal is on the ankle joint and its ligament injuries. The Specific Aims are: (1) to investigate ankle flexibility characteristics associated with specific ligament injuries; (2) to determine relative internal bone movements at the ankle and subtalar joints associated with ligament injuries; (3) to develop stress radiography and stress slice MRI that are optimum to show bone displacements associated with specific ligament injuries; and (4) to objectively assess the stabilization achieved by surgical reconstruction techniques for treating ligament damage. To fulfill Aim 1, a special mechanical device will be built and flexibility data will be gathered from normal injured, and post-surgical joints. To fulfill Aim 2, methods of MRI imaging under stress, image segmentation, 3-D reconstruction, and 3-D analysis will be developed. The resulting injury-specific internal displacement data will be utilized to devise simple, cost-effective methods, such as stress radiography and stress slice MRI, that best show the effect of injury (Aim 3). Such data will be used to objectively assess surgical reconstruction techniques based on pre- and post-operative scans and measurements (Aim 4). The expected outcomes of this research are twofold: (1) simple, cost-effective and high specificity methods of diagnosing ankle ligament injuries; and (2) new knowledge about the exact displacements occurring at the ankle and subtalar joints as a result of ligament injuries or their surgical repair.

Vorp, David A   University Of Pittsburgh At Pittsburgh   Biomechanical Preconditioning Of Human Vein Grafts   HL065745   4 years   NHLBI

Abstract: DESCRIPTION (Adapted from Applicant's Abstract): Five-hundred thousand coronary artery bypass surgeries are performed every year, and the human saphenous vein (HSV) is the most often used conduit in this procedure. Unfortunately, a significant number of coronary artery vein grafts (CAVG) fail within the first post-operative month due to thrombotic occlusion. There is significant evidence which implicates in this prothrombotic response the new biomechanical environment to which the vein is abruptly exposed when transposed to the coronary arterial circulation. This includes an increase in flow (and shear stress), an increase in intraluminal pressure (and radial and circumferential wall stresses), and dynamic wall motion. The latter consists of cyclic radial wall excursion due to the pulsatile arterial pressure, and cyclic longitudinal stretching, bending and twisting due to the attachment of CAVG to the beating heart. We believe that the adverse prothrombotic response by HSV to the coronary arterial circulation may be reduced or eliminated by preconditioning them to this new environment. The particular hypothesis that we will address in this proposal is that, compared to an acute, abrupt exposure of HSV to the coronary arterial biomechanical environment, a gradual, incremental imposition results in a reduced thrombotic response. The applicant has performed clinical measurements and developed a unique biomechanical model to simulate realistic CAVG biomechanics. When interfaced with a physiologic perfusion system that enables metabolic support of freshly excised HSV specimens, novel investigations such as those proposed here are possible. Therefore, to address our hypothesis, we will utilize our unique experimental capabilities and freshly excised HSV specimens. Specifically, our aims are: AIM 1: Quantitatively measure the thrombotic response of freshly excised HSV +_____ segments abruptly exposed to simulated CAVG biomechanical conditions. AIM 2: Determine the mitigating effects of a biomechanical preconditioning +_____ regimen on the thrombotic response of freshly excised HSV segments to simulated CAVG biomechanical conditions. As markers of acute thrombogenesis, we will measure platelet deposition and tissue factor generation by HSV. Preliminary data is presented which indicate that these are appropriate end-points in the proposed study.

Bioengineering Research Grants (BRG) awarded in FY 2000

Wang, Kenneth K   Mayo Clinic Rochester   A Novel Technique For Screening Barrett's Esophagus   CA085992   4 years   NCI

Abstract: Gastroesophageal cancers are the most rapidly increasing cancer in Caucasian males and are a consequence of Barrett's esophagus. Barrett's esophagus is a pre-malignant condition that is produced by gastroesophageal reflux disease (heartburn). Screening for Barrett's esophagus can only be accomplished by endoscopy that is expensive and impractical given the population at risk. The purpose of this proposal is to design an "optical biopsy" system that can be applied by a wide range of health care providers to screen for Barrett's esophagus. This system will consist of an optical probe that can be placed into the esophagus with minimal discomfort to the patient that is connected to an optical biopsy console that will provide real time results. The primary design issues will be in constructing a small caliber probe that can be comfortably placed into the esophagus and yet expandable to provide contact with the esophageal wall for an optical biopsy. The second design consideration would be in constructing an algorithm that would analyze the spectroscopic signal from the "optical biopsy" which would distinguish normal and abnormal tissue in the upper gastrointestinal tract. Three proposed probe designs will be evaluated initially in the resected porcine esophagus and stomach to assess deployment of the probes and their safety. Subsequently, the probes will be assessed in the pig model to evaluate their performance characteristics. The best design will be selected for clinical testing. The clinical trials will involve the use of the probe in patients with known Barrett's esophagus and a control group undergoing endoscopy for other indications. The probe would be passed prior to endoscopy and the results compared to the endoscopic findings. The algorithms will be derived from optical and histological biopsies taken simultaneously at endoscopy from patients undergoing surveillance endoscopy for Barrett's esophagus. The development of a screening device for Barrett's esophagus that could be operated by paramedical personnel would enable large-scale low cost screening to identify patients at risk for esophageal cancer.

White, Moreno J   Sparta, Inc.   Advanced Biofidolic Lower Extremity Prosthesis Research   HD038933   4 years   NICHD

Abstract: The aim of the proposed research is to develop and validate the function of a flexible, multi-axial, lower limb prosthesis designed from high strength composite materials. The Advanced Biofidelic Lower Extremity (ABLE) Prosthesis concept utilizes a composite material bi-phasic and asymmetric stiffness ankle to improve function/improve durability over existing at a comparable weight and cost. Structurally, the use of high strength composites as the structural and elastic elements in the prosthesis will provide greater service life and lighter weight for the amputee as well as high design flexibility in the elastic element mechanical response. Functionally, the unique bi-phasic of the ABLE elastic elements more closely mimics the function of the triceps surae and tibialis anterior muscles, enhancing mid-stance stability while still providing for the dynamic elastic responds beneficial at heel strike and push. Studies indicate that a limb providing enhanced function will: 1. Allow the amputee to be more active in their daily lives and 2. Improve their perception of their prosthesis as compared to the amputees' baseline condition. The program: 1. Establishes the biomechanical design parameters-where the desired performance is more clearly quantified on the basis of non- amputee gait, 2. Translates the design goals into the physical geometry and materials properties of the device, 3. Assures satisfactory performance by analyzing the design using state of the art finite element analysis prior to fabrication and 4. Tests the fabrication device mechanically (static loading and fatigue cycling) on both a component and assembly level and by amputees' in a clinical environment. The limb will be evaluated in the design phase by a small group of amputees to: 1. elicit feedback and 2. Measure actual performance. Finding will be used as input for the subsequent design iteration. At the third and final iteration we will evaluate the ABLE Perosthesis in an extensive real-world testing using validated outcomes measures to assess the performance or the limb versus subjects' prescribed limb, using a statistically significant pool. These outcomes will be measured through long tern evaluation using previously validated objective measures of amputee function, the Step Activity Monitor and Prosthesis Evaluation Questionnaire.

Wilson, David L   Case Western Reserve University   Tissue Response In iMRI Guided Cancer Therapy   CA084433   4 years   NCI

Abstract: (Adapted from Applicant's Abstract): This research project is part of a larger, long-term effort to develop a minimally invasive and cost-effective method to ablate solid tumors using interventional MRI (iMRI) to guide and monitor therapy. A low-field, open magnet system is used to guide the tip of an ablation probe into the tumor and to monitor tissue destruction during the ablation procedure. Ablation occurs by heating from a radiofrequency (RF) energy source at the probe tip. Not only does MR provide tumor visualization, it can reveal the thermal lesion in various acquisition sequences (T2, STIR, etc.) and measure temperature changes. Potentially, these measurements can be used during clinical ablation procedures to determine tumor cell death and to minimize damage to normal surrounding tissue. The research addresses how well these MR measurements predict the actual tissue response. In this proposal, the applicants propose to address this issue using animal models. They will develop three-dimensional techniques to accurately register and correlate MR images with gross pathology and histology techniques. Ultimately, the goal will be to quantitatively predict cell damage and death using MR image acquisition and analysis methods, and a probabilistic state model that accounts for the cellular response to temperature history. With this research, the applicants expect to establish an analysis paradigm suitable for many future studies of contrast agents, ablation techniques, localized drug release, and other iMRI-guided therapies.

Bioengineering Research Grants (BRG) awarded in FY 2000

Wolf, Patrick D   Duke University   Very Low Energy Cardioversion For Atrial Fibrillation   HL064238   4 years   NHLBI

Abstract: Internal atrial defibrillation is a successful therapy for the treatment of atrial fibrillation(AF). Current internal atrial defibrillators(IAD) use conventional defibrillation technology to deliver high energy shocks with a high likelihood of success. The applied shock strength of 3-10 Joules is above a patient's pain threshold and this limits the broad application of IAD therapy. A technology is proposed that utilizes multiple very low energy (less than .5J) shocks(VLES) with a low probability of first shock success but a high cumulative probability of conversion. A telemetry system will be implanted in an ovine model of AF. The combined animal model and telemetry system will be used as a test bed for VLES atrial cardioversion. The telemetry unit transmits 4 electrograms a distance of 10 meters and delivers continuous and programmed pacing by remote control. This system will be enhanced by adding pressure monitoring and VLES circuitry. It will be used 1) to characterize electrical remodeling and to track changes in infra-atrial pressure induced by the rapid pacing protocol and 2) to measure the energy that corresponds to a 5 percent level of success, and 3) to test three strategies for increasing the VLES probability of success. The three strategies are: 1) pre-VLES overdrive pacing 2) pre-VLES non-linear dynamics based pacing, and 3) use of class III antiarrhythmic drugs with VLES. Epicardial mapping will be used to identify the mechanism of VLES defibrillation and to characterize the effects of the 3 enhancement strategies. The work proposed in this grant will advance the science of remote testing in unanesthetized animals, will characterize the development of electrical modeling and myocardial pathology produced by rapid pacing in sheep, and will test a total of four strategies for very low energy atrial defibrillation. These advances will increase our understanding of the progression of AF and allow a successful therapy for this debilitating disease to be more broadly applied.

Young, Mark A   Montana State University (Bozeman)   Virus Based Bio-Imaging & Therapeutic Delivery Systems   GM061340   3 years   NIGMS

Abstract: Many viruses form stable self-assembled protein cages that function to store, protect and transport nucleic acid. We have previously shown that the cage structure of viruses can be used as constrained reaction vessels for the encapsulation and release of a wide range of materials other than its native RNA genome. In this way virus protein cages can be thought of as nanometer sized containers able to encapsulate other molecules through well-defined chemical interactions. The current proposal will explore the use of these virus cage structures for encapsulation and targeted delivery of therapeutic agents as well as development of these cages as magnetic resonance imaging contrast agents based on our demonstrated ability to engineer the coat protein. The principle objective of this proposal is to develop a model viral system for the use of virus cage structures in the high- density packing and release of therapeutic materials (molecules and polymers). Packaging within the virus can be driven by electrostatic complementarily between the inner protein interface and the relevant therapeutic material(s). One objective will be to extend the range of therapeutic materials that can be entrapped within the viral protein cage by engineering the electrostatic properties of the inner surface of the protein cage. A second major objective is to develop viral protein cages as potential magnetic resonance imaging contrast agents by engineering the inherent metal binding sites on the virion for binding 180 molecules of the paramagnetic Gd(III) ion. A third major objective is to express peptide 11 from the laminin protein on the outer surface of the virion and to determine its effectiveness at specifically targeting viral cages to cells expressing laminin-binding protein. A fourth major objective is to utilize inherent structural transitions in the virion to engineer new well defined chemical switches (based on redox potential and pH) to induce gating for selective entrapment and release of therapeutic materials. Virion gating results in the reversible opening/closing of 60 separate 20Angstrom units holes in the protein cage. We propose to use site-directed mutagenesis to engineer disulfide linkages and altered pH gating switches at these pores and test for their ability to entrap and release therapeutic materials.

Bioengineering Research Grants (BRG) awarded in FY 2000