Tuesday, May 16, 2000

Contractors Meeting

Chair: L. Scott Cram, LANL

Principal Investigator: **Christine L. Hartmann Siantar**

Institution: **Lawrence Livermore National Laboratory**

Research Title: **Using PEREGRINE for Treatment Verification in Radiation Therapy**

Abstract

The PEREGRINE dose calculation system provides 3D Monte Carlo transport calculations fast enough for day-to-day radiation therapy planning. It operates on low-cost, commodity hardware , enables real time visualization of dose as it is simulated, and completes a full treatment simulation in minutes. The initial version of this system, which calculates radiation dose distributions for photon therapy, has been licensed and will soon be available for commercial distribution to the radiation therapy community.

The work described here extends PEREGRINE's capabilities to serve a critical need in the verification of dose delivered to the patient. This year, we have developed online portal image-simulation tools that will enable the physician to verify that the correct dose distribution was delivered to the patient for each treatment, and that the patient is in same position every day. We have used these tools to investigate how to improve portal image quality and verify the dose delivered. This presentation describes the prototype, experimental/simulation results, and our plans for the future.

Principal Investigator: **Stan Majewski**

Institution: **Jefferson Laboratory**

Research Title: **Dedicated Diagnostic Positron Emission Mammography System**

Abstract

Evolution of a compact low rate single-gamma scintimammography imager into a high rate two-head Positron Emission Mammography (PEM) imager will be first presented. Two small PEM prototypes with field-of-view (FOV) of 4x4 inches were built and one was thoroughly tested with F-18 labeled compounds at West Virginia University. Spatial resolution of 3-4 mm FWHM was attained. The third instrument with a FOV of 8x6 inches is the subject of the present instrumentation effort with the DOE grant support. It is currently under construction and will be tested later this year at Duke University's PET center. All the single gamma and positron imaging devices built by the Detector Group at Jefferson Lab use the same compact imager technology based on an array of compact position sensitive PMTs coupled to a variety of small pixilated (pixel size 3mm) scintillator arrays, such as CsI(Na), NaI(Tl), GSO and LGSO. This development benefited from several recent technological advances in: compact PMTs, new heavy scintillators, improved production techniques of pixilated scintillator arrays, special light guides, as well as novel fast readout schemes and fast and economical data acquisition systems. All these advances put in one unique "package" resulted in a powerful dedicated breast imager capable of earlier detection of smaller lesions than currently possible with standard nuclear medicine instruments.

Principal Investigator: **Thomas F. Budinger, M.D.**

Institution: **Lawrence Berkeley National Laboratory**

Research Title: **Vascular Relaxoscope**

Abstract

The response of the human arterial system to short periods of stress, such as exercise or pressure-induced changes in blood flow, varies widely with age, drugs, alcohol, state of health and may be influenced by trace materials in some foods. We are developing practical, non-invasive and inexpensive methods of evaluating vascular reactivity in normal and diseased human subjects. Three approaches are being taken with the goal of engineering a user-friendly instrument for routine clinical use. One method involves approximately 2 minutes of tourniquet-induced blood flow occlusion in the arm and the characterization of the reactive blood flow waveform changes after tourniquet release using Doppler ultrasound. The second approach uses a device to measure the pulse pressure speed over a fixed distance of the brachial and radial arteries as a more direct measurement of vascular compliance before and after a period of schema. The third approach involves iontophoresis of vasoactive substances and inhibitors of the vascular relaxing factors, and the miniaturization of a scanner for the quantification of the skin perfusion response. In this approach we introduce novel iontophoretic chemical combinations which allow selective investigation of particular biochemical pathways involved in the dilation response of cutaneous capillaries. Our three approaches have been selected so that we will be able to evaluate the health of both conduit and resistance vessels, while elucidating the poorly understood biochemical pathways involved in the vasoactivity of each. We outline our progress to date, which includes an analysis of the many confounding variables affecting peripheral vascular response. We then present preliminary data which illustrates the effect of a fatty meal on the power of the reflected Doppler flow waveform, and illustrate our analytical methods for the processing of Doppler and skin perfusion data.

Principal Investigator: **Surya K. Mallapragada**

Institution: **Ames Laboratory**

Research Title: **Micropatterned Schwann Cell Seeded Guidance Conduits for Nerve Regeneration**

Abstract

This work investigates the influence of substrate-mediated chemical and physical and cellular guidance on the growth and alignment of neurons in vitro. These substrates will be used as inner lumens of artificial nerve conduits and implanted to enhance peripheral nerve regeneration in vivo. Compression molded and solvent cast biodegradable polymer substrates made of copolymers of lactic and glycolic acid were micropatterned to form grooves on the substrate surfaces. Laminin was selectively attached to the bottom of the grooves and rat sciatic Schwann cells were seeded on the substrates. Laminin provides chemical guidance and enhances neuronal adhesion and outgrowth while the Schwann cells align along the grooves and secrete nerve growth factor to enhance axonal regeneration. The microgrooves were found to cause the Schwann cells and neurons to align along the direction of the grooves. The influence of the groove width, depth and spacing as well as the presence of laminin and Schwann cells on neuronal alignment and growth was investigated. It was found that the groove width influenced Schwann cell alignment the most, while groove depth played a significant role in neuronal alignment. Laminin was found to accelerate the rate of growth of Schwann cells and neurons along the grooves. The degradation rates of the compression molded and the solvent cast films were compared and the microgrooves were found to last for only five days in the compression molded films, while they lasted for more than a month on the solvent cast films, making them the preferred substrates for Schwann cell and neuronal cultures.

Principal Investigator: **Mark Vaughn**

Institution: **Sandia National Laboratories**

Research Title: **Improved Corneal Keratome Surgery with Standalone Robotic Apparatus**

Abstract

The first step in LASIK surgery for vision correction is to attach an apparatus called a keratome to the eye and cut a contact lens-shaped flap away from the cornea. This corneal flap is reattached after the laser ablates enough underlying tissue to correct the refrative defect. The half dozen keratomes manufactured today suffer from some common problems which lead to majority of the problems associated with the 5% rate of unsatisfactory outcomes. Sharper blades will reduce tissue damage and reduce or eliminate the need for "sawing" of the blade. Umbilical cords and hoses pull on the keratome, requiring higher suction levels and larger suction rings to maintain attachment. Open drive systems with exposed racks and pinions can entrain eyelashes and lids, leading to suboptimal results. Methods to deal with these shortcomings and a short discussion of cutting edge procedures will be discussed.

Principal Investigator: **Winston C. H. Chen**

Institution: **Oak Ridge National Laboratory**

Research Title: **High Throughput Hybridization Mass Spectrometry for Disease Screening**

Abstract

There is a critical need for developing a high throughput, reliable and inexpensive DNA analyzer for genome-wide disease diagnosis. Early diagnosis of diseases can save both lives and the cost of medical care. At present, there are no commercially available instruments to meet the requirements of rapidity, low cost, reliability, and applications to several diseases. However, recent development of hybridization-on-chip and mass specotrometry DNA detection technology provides good potentials for high throughput analysis. Since the development of sequencing by hybridization (SBH), it has been recognized that hybridization can become a powerful tool for DNA analysis. However, there are a few serious barriers to be overcome to make hybridization-on-chip become a high throughput and reliable diagnosis tool. Since thousands of DNA probes are needed for hybridization-on-chips, the confirmation of the correct sequences for these probes are in critical need. However, there are no good methods to quickly confirm the sequences at present time. Most hybridization detections are based on the labeling of DNA probes by either radioactivity or chromophore. These labeling process increases the cost and time drastically, especially when thousands of probes need to be prepared. It is highly desirable that the labeling process be eliminated. With the estimate of 100,000 genes in the human genome and the potential for many mutations in any single gene associated with a specific disease, it is important to further increase the throughput from present hybridization-on-chip technology. With present DNA detection technology, only single hybridization reaction can be detected at a single hybridzation site. However, the use of mass spectrometry can lead to the possibility of detecting multiple hybridizations at a single hybridization site. The capability of high multiplexing by mass spectrometry DNA detection can increase the analysis speed by orders of magnitude so that genome-wide mutation detection can become feasible.

During the past five years, we have been developing mass spectrometry for DNA detection and sequencing. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry and electrospray ionization mass spectrometry have been successfully used to detect DNA fragments. With mass spectrometry DNA detection, DNA fragments are detected by their molecular weights so that labeling is no longer required. Recently, we have succeeded in detecting DNA fragments longer than 3000 base pairs and sequencing the double-stranded DNA fragments with the size up to 200 bp. We also demonstrated the use of mass spectrometry to detect PCR products and the fragments produced by enzyme digestion.

We have been collaborating with Dr. Matteson and Dr. Potter at the University of Tennessee Medical Center on the detection of cystic fibrosis. Both base deletion (F508) and point mutation (G551) of cystic fibrosis from clinical samples have been demonstrated. Trinucleotide expansions associated with neurodegenerative diseases have also been successfully demonstrated. We also developed an innovative approach to sequence a short DNA probe or primer with mass spectrometry without the need of DNA ladder preparation. By adjusting the pH values of DNA samples and the laser fluence, a short oligonucleotide can be sequenced with mass spectrometry directly. This result indicates that a large number of probes can be sequenced in a relatively short time. It can enhance the reliability of using hybridization-on-chip for mutation diagnosis.

The multiplexing hybridization on a single hybridization site has also been demonstrated. We have demonstrated that multiple DNA probes with different lengths for hybridization can be detected by mass spectrometry simultaneously. We also tagged molecules with different molecular weights to the DNA probe with the same length for hybridization. Laser desorption mass spectrometry has also been used successfully to detect DNA probes with different tagging molecules. Experimental details will be presented in the meeting.

Principal Investigator: **A. Peter Campbell**

Institution: **Argonne National Laboratory**

Research Title: **Development and Validation of a Virtual Reality Tool for Treatment of Posttraumatic Stress Disorder in Electrical Trauma Victims**

Abstract

The University of Chicago Department of Psychiatry (UCDP) and the Argonne National Laboratory Decision and Information Sciences Division (ANL/DIS) have embarked upon a joint effort to construct a generalized capability to assemble Virtual Reality (VR) environments to aid in the treatment and/or rehabilitation of patients suffering from a wide range of conditions. As a first demonstration of the effectiveness of this approach, UCDP and ANL/DIS are constructing a VR-based approach for exposure treatment of electricians suffering from Posttraumatic Stress Disorder (PTSD) as a result of electrical accidents. The study leverages UCDP's long baseline of experience in treating electrical injury (EI) victims, and its excellent ongoing rapport with the local electrical workers' unions in the Chicago area.

Each year, 100,000 individuals in the United States suffer EI from domestic and commercial power sources, with over 1000 deaths. The most common arena of injury is from industrial or construction-related accidents. Treatment and rehabilitation can be extraordinarily lengthy and costly. The symptoms of PTSD have proven to be extremely difficult to treat, with the most effective psychological treatments typically incorporating some form of exposure to the feared event(s) either imaginally or *in vivo*. Yet many people with PTSD are not able to use imaginal treatments and *in vivo* exposures are often expensive, risky, and at times, impossible. Therefore, PTSD often remains a chronic, disabling mental disorder.

A number of clinical case reports show that VR technology may be effective in treatment of phobias, such as fear of flying, claustrophobia, and spider phobia with symptoms of obsessive-compulsive disorder. In this project, we have hypothesized that use of VR technology could enhance the effectiveness of exposure therapy for all PTSD victims by recreating the feared event through the use of virtual presence in support of personal imagination. VR treatment may have special advantages as it (1) increases a potential for sharing the virtual traumatic event by patient and therapist, (2) allows patients to set their own pace for graded exposure, and (3) provides a virtual space for safe exploration and manipulation of fear-provoking objects, thus increasing patient's sense of control and performance aptitude without placing the survivor (or coworkers) at risk. We therefore aim to develop a VR model for psychological treatment of PTSD in EI survivors. The immediate goal of the project will be to determine if the VR-enhanced psychological treatment will be more effective and improve the outcome for EI patients suffering from PTSD.

The first phase of the study focuses on developing a short series of standard vignettes for conversion into virtual reality simulations. Surveys of electrical workers and electricians who have suffered EI are used to help identify the situations that are personally relevant and anxiety provoking for the highest percentage of respondents. The vignettes are then reviewed from a computer technology standpoint, with respect to the VR experiential requirements, the feasibility, costs, and technological risks of implementation, and the potential for re-use in other applications.

The VR hardware and software suite will be constructed in the next project phase. The VR simulator will provide visual input via Head Mounted Display (HMD) with head orientation and position tracker. Two HMD's will be supported simultaneously, in order that the therapist may share a subject's experience. The subject's visual input will be based upon stereoscopic images generated from 3D computer graphics models constructed for each venue, possibly supplemented by video and audio backgrounds obtained from actual or archetypal exposure sites. Audio input will be provided via lightweight stereo headphones. A high-end PC with graphics accelerators will be used to drive scene generation, orientation and motion tracking, and collision detection activities. A second PC will handle data acquisition and archiving for the subject's psychophysiological responses from heart rate and skin conductance monitors.

A guiding principle in assembling the computer hardware and software suite for VR therapy has been that the ensemble must be affordable, maintainable, and flexible, in order to be successfully deployable on a wide scale. Thus, to the extent practicable, relatively affordable, commercial off-the-shelf components have been used in assembling the VR therapy suite.

Once the VR suite is constructed and functionally tested for the selected therapy scenarios, studies will be undertaken to assess the validity and utility of VR-based exposure as a means of treating EI survivors who suffer from PTSD symptoms. This will be accomplished by comparing patients' reactions to currently available imaginal exposure therapies and VR-enhanced application of this

therapy. An imaginal plot based on the patient's personal EI experience will be developed to use independently or in conjunction with a VR scenario. We will assess self-report and psychophysiological responses during exposure to compare evoked anxiety between the two experimental protocols. Subjects for this study will be adult EI victims treated at the University of Chicago Hospitals immediately following their accident, as well as those who were triaged and acutely managed at other hospitals then later referred for further evaluation and treatment on a post-acute basis.

At the completion of this demonstration/prototype development effort we plan to continue testing the application in clinical environment with a view to its early adoption at UCDP and will move to introduce the application to full-time use. The next step for clinical research would be to compare various ways of conducting VR-enhanced therapy to determine the optimum protocols for different kinds of patients.

We see several avenues for further evolutionary development of the VR system resulting from the initial study. To facilitate the above therapy studies, an abstract software object model of graduated exposure could be developed that can allow a subject to "dial up" a VR therapy vignette over an essentially continuous range of immediacy, vividness, and stress level. Such a system could be extended to allow real-time psychophysiological readings and/or real-time therapist instructions to feed back to the VR to dynamically alter the perceived intensity of the virtual experience. The VR therapy suite could also be as the springboard for an "augmented reality" application aimed at training and evaluation of electricians. In augmented reality, a subject interacts with both real and virtual environment elements. For training purposes, vignettes could be assembled in which subjects perform tasks in an environment that includes a "real" junction box they can manipulate, embedded in an otherwise virtual frame of reference. Videotape and/or telemetry returns from the subject's wired "data gloves" could be used to evaluate performance against the recorded performance "signature" of an acknowledged expert on the same tasks. Finally, we could explore the capabilities developed and demonstrated in the project for a series of other valuable applications addressing psychotherapy and rehabilitation across diagnoses, as well as more distantly related fields, such as driver acuity evaluation.

Principal Investigator: **Yuehe Lin**

Institution: **Pacific Northwest National Laboratory**

Research Title: **Microfluidic Devices for Rapid Sample Processing/Mass Spectrometric Characterization of Microbes**

Abstract

Development of capabilities to miniaturize analytical devices and components offers a number of potential economic and practical benefits. Among these are the ability to reduce sample sizes, increase sample-throughput, develop low cost, disposable devices, and improve device portability. The low flow rate characteristic of these microfluidic devices is compatible with electrospray ionization/mass spectrometry (ESI-MS). In this presentation, development of microfluidic devices fabricated on polymer substrates using excimer laser micromachining technology will be described. These include a dual-stage microdialysis device, a micro isoelectric focusing device, and a micro electrospray nozzle array. The applications of these microfluidic devices for rapid and automated cleanup, fractionation, and separation of biological samples will be discussed.

Tuesday, May 16, 2000

Artificial Limb Symposium

Chair: Morton Lieberman

Principal Investigator: **Louis A. Quatrano, Ph.D.**

Institution: **National Center for Medical Rehabilitation Research, National Institute of Child Health and Human Development, National Institutes of Health**

Research Title: **Mobility Enhancement: Bioengineering Opportunities**

Abstract

The presentation will cover the National Center for Medical Rehabilitation's interest in artificial limb research, areas of research supported and mechanisms available to support this research.

Principal Investigator: **Jan J. Stokosa, C.P.**

Institution: **Stokosa Prosthetic Clinic**

Research Title: **Amputation and Prosthetic Rehabilitation in the Lower-limb: Where We are and Where We Want to Be**

Abstract

Few experiences may be more profoundly shocking to the human body than amputation. This loss is irretrievable. At first, the impact of its finality is difficult to comprehend or believe - losing a treasured part of the body is not fully appreciated until its loss. The missing part was a major component of the body's functioning capability, without conscious effort, yet all in the established pattern of daily living.

The anatomy of the remaining portion of the limb after amputation is quantitatively and qualitatively different from the anatomy of the intact limb. The vast differences in physology, weight-bearing capability, motor and sensory function, and pain, usually become manifest several months after surgery. Conventional amputation techniques render the greatest physiologic disturbance. Amputation techniques emphasizing a biological approach, such as the Ertl technique, result in a superior physiologic and biologic end-organ.

In the design, fabrication, and fitting of any extremity prosthesis, comfort to the wearer must be an overriding concern. Other elements of the prosthesis and the fitting process are subordinate to--and dependent on--proper socket fit. Discomfort will result in rejection or improper use of the prosthesis, thwarting other benefits. The most sophisticated component part with the most accurate biomechanical alignment is of little value if walking or use causes pain or skin breakdown, or both.

The goal of amputee rehabilitation is to aid the amputee in reentering and regaining his or her place in society: working, playing, and engaging in a full range of human relationships. Progress in this endeavor will be marked by the amputee's placing a diminishing emphasis on the amputation and prosthesis. Ideally, amputaton and prosthesis will move outside the inner circle of the patient's life concerns. The prosthetist's role in this process, in the broadest terms, is to enhance the amputee's mobility and appearance, with maximum comfort.

State-of-the-art amputation surgery, prosthesis design, and discussion of areas for improvement will be discussed.

Principal Investigator: **Dudley S. Childress, Ph.D.**

Institution: **Northwestern University**

Research Title: **Artificial Limb Requirements for Human Ambulation and Manipulation--What We do now and What We Hope to do in the Future**

Abstract

Functions of the human extremities in walking and in manipulation will be described. Examples will be presented as to how currently available artificial components can be used in prostheses to provide function for persons with limb loss. Limb losses that occur below the knee and below the elbow can usually be adequately compensated, although the performance of these prostheses remains quite prescribed when compared with natural human limbs. Losses above the knee and above the elbow, particularly when limbs are lost on both sides of the body, are much more difficult to functionally replace.

Human control of natural limbs will be related to control of robotic arms. Natural methods for control of human-machine systems (e.g., aircraft control surfaces, remote manipulators, and automobile power steering) will be compared with control methods for human-prosthesis systems (e.g., Bowden cables, velocity control of motors using switches, or myoelectricity). Ways to provide easily intrepreted sensory and proprioceptive feedback (e.g., extended physiological proprioception) will be described.

Relationships between human walking with prostheses, walking robots, and passive walking machines will be discussed. Simple theoretical models of walking will be presented. The use of computational methods in the design and manufacturing of prostheses will be demonstrated.

The status of the prosthetics field currently seems similar to the status of the field of aviation around 1935. At that time some very good airplanes, such as the DC-3, had been designed and produced. Sixty five years later a few DC-3s are still in service. In 1935, aeronautics, the science and engineering of flight, was in relative infancy. One has only to look at aircraft today to understand the tremendous influence that science and engineering has had on aviation since 1935. In 2000, some very good prostheses are being designed, fabricated, and worn successfully. Some of these systems are likely to be used for decades to come but the field needs many advancements. Fortunately, a nascent field of science and engineering now exists in limb prosthetics. Consequently, many members of the prosthetics field look forward with confidence to substantial advances in this field over the next couple of decades. Direct skeletal attachments, direct surgical connections to muscles, new surgical methods, smart components, new materials (possibly nanostructures), and new design and fabrication tools are some of the areas of prosthetics where science and technology should have significant impact.

Principal Investigator: **Peter Thomas, Esq.**

Institution: **Law Firm of Powers, Pyles, Sutter & Verville, P.C.**

Research Title: **The Consumer and Public Policy Perspectives on Rehabilitation Research**

Abstract

This presentation will focus on the needs of consumers with disabilities in the area of rehabilitation research, particularly prosthetic research and development. The speaker will attempt to compare and contrast the vast scientific and technological potential with the real needs of everyday persons with disabilities and draw several preliminary conclusions about the research priority-setting process. Long-term and more recent trends in public policy will also be offered for consideration, including the federal appropriations process, the view of legislative advocates on these issues, and the health costs associated with technological advancements in the areas of medical rehabilitation and prosthetics. Specific attention will be devoted to the trends of third party payors of rehabilitation technology and how public policy can be helpful in this area.

Principal Investigator: **Terry Supan**

Institution: **Southern Illinois University School of Medicine**

Research Title: **Where Prosthetic Research and Development Needs To Go—A Clinical Prosthetist's Viewpoint**

Abstract

The perceived need for prosthetic development will vary from the viewpoint of amputees, prosthetists, engineers, and other researchers. The intent of this presentation is to give the clinical prosthetist's viewpoint on what is currently available and where we should go from here. Both upper and lower limb prostheses will be reviewed. Why current prostheses are rejected by the amputees will also be discussed. Specific recommendations will be made on who should have input into the research and development process.

Principal Investigator: **Maurice LeBlanc**

Institution: **Veterans Affairs Rehabilitation R & D Center**

Research Title: **Upper-Limb Prostheses, Crutches, and Children**

Abstract:

Limb prosthetics research and development got a big impetus after WWII. Research and education programs were started because of all the amputees returning from the war. There are now both body-powered and externally powered upper-limb prostheses available. Most arm amputees use body-powered prostheses because of their simplicity, low cost, and sensory proprioception. However, these prostheses have not changed a great deal since the 1950s. They still use Bowden control cables and housings introduced from the aircraft industry. Arm amputees would like to have upper-limb prostheses which function well and look more natural and aesthetic.

We know from artwork that crutches have been used for 5000 years. First they were just a stick, then a stick with a "Y" at the top, and then a stick with a "Y" and a hand grip. It was not until the late 1800s when a saw was developed that could split the stick that the present configuration of the underarm crutch was developed with the double tube incorporating the hand grip. For users of crutches, it takes about twice as much energy to ambulate as compared with normal gait. This taxes the energy and limits mobility of people who use crutches. They would benefit from crutches which promote ambulation in a more energy efficient way, are lightweight, and which are more aesthetic.

Prostheses and other assistive technology for children must not be scaled-down versions for adults. Children have special needs in that they grow in different proportions; they grow in spurts; the technology must be useful at home and school; the technology must be acceptable to parents and teachers; and the technology must allow and support their psychological as well as physical growth and development.

Principal Investigator: **Morton L. Lieberman**

Institution:

Research Title: **Artificial Limb Activities at Sandia National Laboratories**

Abstract

Sandia National Laboratories has been involved in various aspects of research and development associated with the development of artifical limbs. Early research addressed ultrasonic imaging of limbs that provided a new means of fitting sockets of prostheses. Subsequently, activities sponsored by NIH/NCMRR and DOE/NN established a basis for converting Russian nuclear weapons developers into prosthetics developers. Multiple projects that address various aspects of lower limb prosthetics are now being addressed. This has created the world's largest center in lower limb prosthetics research, ironically located at a Russian nuclear weapons laboratory. The development and status of these projects will be discussed.

Wednesday, May 17, 2000

Contractors Meeting

Chair: Patrick Fitch, LLNL

Principal Investigator: **Sharon Stansfield**

Institution: **Sandia National Laboratory**

Research Title: **Emergency Medicine and the Rural Community: Virtual Reality to Address Training Shortfalls**

Abstract

Abstract not available.

Principal Investigator: **Anna Gutowska**

Institution: **Pacific NorthWest National Laboratory**

Research Title: **Polymer Formulations for Cartilage Repair**

Abstract

Regeneration of destroyed articular cartilage can be induced by transplantation of cartilage cells into a defect. The best results are obtained by the use of autologus cells. However, obtaining large amounts of autologus cartilage cells causes a problem of creating a large cartilage defect in a donor site. Techniques are currently being developed to harvest a small number of cells and propagate them in vitro. It is a challenging task, however, due to the fact that ordinarily, in a cell culture on flat surfaces, chondrocytes do not maintain their in vivo phenotype and irreversibly diminish or cease the synthesis of aggregating proteoglycans. Therefore, the research is continuing to develop culture conditions for chondrocytes with the preserved phenotype. We are investigating the use of reversibly gelling polymers for the in vitro cell culture of chondrocytes. Our hypothesis is that a 3-D matrix formed by a gelling polymer may provide the optimal culturing conditions, resembling the in vivo environment in which the chondrocytes normally grow. We propose to use reversible stimuli-sensitive gels for the in vitro cell culture of chondrocytes as well as for the injectable formulations suitable for in vivo repair of cartilage defects.

Principal Investigator: **Duncan Maitland**

Institution: **Lawrence Livermore National Laboratory**

Research Title: **Shape Memory Polymer Microcatheter for Treating Ischemic Stroke**

Abstract

Researchers in the Medical Technology Program from Lawrence Livermore National Laboratory have developed a micro-mechanical shape memory polymer (SMP) device that can be used to treat ischemic strokes that are seen daily in emergency rooms across the U.S. Ischemic strokes result when blood flow stoppage occurs due to a blocked artery in the brain. Stroke is the third leading cause of death (150,000/year) and the leading cause of disability in the United States. Approximately 700,000 strokes occur annually in the U.S., accounting for costs of over $26 billion/year for treatment and rehabilitation. Ischemic strokes account for approximately 80% of strokes; hemorrhagic strokes make up the remainder.

Current ischemic stroke treatment modalities include mechanical intervention or pharmacologic thrombolytic (drug) therapy to disrupt or dissolve thrombus (blood clots). Current mechanical interventions cannot address most occlusions that occur in smaller, more deeply seated vessels such as the middle cerebral artery. The pharmacologic treatments are ineffective. Successful development of a new treatment modality could have significant benefits to the outcomes of stroke patients, ultimately improving mortality rates and decreasing morbidity, thereby decreasing the cost of rehabilitation and improving the quality of life.

We have built and demonstrated a prototype SMP opto-mechanical device that will be tested for extracting blood clots. The microactuator is delivered through a 0.018" inner-diameter guide catheter and deploys to 0.040" for extraction. The device uses an optical fiber to carry laser energy to SMP. The SMP is a material in which the elastic modulus or “softness” can be reduced by three orders of magnitude when heated above a transition temperature. This softening combined with engineered residual stresses, results in an actuation of the SMP from a closed, low profile shape to an open state suitable for extracting the clot. This work has been carried out in collaboration with a neurological surgeon, Chip Jungreis, from the University of Pittsburgh.

Principal Investigator: **Anthony Makarewicz**

Institution: **Lawrence Livermore National Laboratory**

Research Title: **Acoustic Focusing of Optically-Generated Shock Waves in the Treatment of Kidney Stones**

Abstract

One half million people suffer the debilitating pain of kidney stones in the United States each year. Of these, approximately 60% can not be successfully treated with medication and dietary restrictions and must be treated more aggressively, either with surgery or one of many modalities of lithotripsy. These aggressive treatments cost between $5,000 to $10,000 per occurrence, for an annual national cost of up to $3 billion. High costs limit the availability of these aggressive treatments to large medical centers.

We are developing a novel medical technology for destroying kidney stones (lithotripsy) via intracorporeal application of an optically-generated focused shockwave. This technique will be an efficacious, safer, and lower-cost alternative to the currently available technologies for kidney stone destruction. The device will be introduced through the urethra and bladder, using a flexible optical fiber to deliver laser energy. The tip of the fiber will be capped with an opto-acoustic transducer and an acoustic lens to focus the generated shock wave on the kidney stone. Our new device combines the beneficial characteristics of current technologies used for kidney stone destruction (localized application of energy, maneuverable fiber optic delivery system, relative safety of an acoustic shock wave) while eliminating the potential dangers (perforation of soft tissue by the direct application of laser energy and the cumulative effects of multiple high-energy shock waves on soft tissue far from the stone).

Device development requires the investigation of several parameters including: optical fiber tip shape, absorber properties, lens shape, and acoustic waveform shape, which is controlled by the lens shape and the laser pulse duration. We have undertaken the design using computational techniques. The numerical results of acoustic pulse focusing will be compared to experiments of system mock ups. Plans for reduction of the system size and shock wave characteristics for kidney stone destruction will also be discussed.

This work was performed under the auspices of the U.S. Department of Energy by the University of California Lawrence Livermore National Laboratory under contract No. W-7405-Eng-48.

Principal Investigator: **David Schlyer**

Institution: **Brookhaven National Laboratory**

Research Title: **Beta Microprobe for Radiotracer Kinetics in Freely Moving Animals**

Abstract

A scintillation microprobe has been developed to directly measure positron decays in living tissue. The probe consists of a small LSO crystal coupled to an optical fiber that is read out with a photomultiplier tube operated to a single photon counting mode. Positron conversions in the crystal are detected with high efficiency due to the excellent stopping power and high light output of LSO, and allows for the direct determination of the positron decay activity in a highly localized region of tissue. The probe can be used in the study of chemical kinetics and the development of new radiotracers in awake and freely moving animals.

Principal Investigator: **Tuan Vo-Dinh**

Institution: **Oak Ridge National Laboratory**

Research Title: **Advanced Fluorescence Techniques for In-Vivo Diagnosis**

Abstract

Tuan Vo-Dinh (1*), Brian Cullum (1), Masoud Panjehpour (2), and Bergein F. Overholt (2)

(1) Oak Ridge National Laboratory, Oak Ridge, Tennessee 37831-6101, USA
(2) Thompson Cancer Survival Center, Knoxville, Tennessee 37916, USA

An optical diagnostic procedure based on laser-induced fluorescence (LIF) has been developed for direct in-vivo cancer diagnosis without requiring biopsy. Endogenous fluorescence of normal and malignant tissues were measured directly using a fiberoptic probe inserted through an endoscope. A nitrogen dye laser tuned to 410 nm was used as the excitation source. The fiberoptic probe was inserted into the biopsy channel of an endoscope and lightly touched the surface of the tissue being monitored. Each measurement was completed in approximately 0.6 second for each tissue site. We have developed a technique using the differential normalized fluorescence (DNF) to enhance small but consistent spectral differences between the normal and malignant tissues. This technique greatly improves the accuracy of diagnosis for malignant tissue. The LIF methodology has been applied in a clinical study involving over 200 patients in order to differentiate normal tissue from malignant tumors of the esophagus. The results of this DNF approach were compared with histopathology results of the biopsy samples and indicated excellent agreement in the classification of normal tissue and malignant tumors for the samples investigated. The effect of inflammation on the diagnosis was also investigated.

Advanced techniques such as synchronous fluorescence and time-resolved detection are currently being developed to further improve the optical diagnostic method. These techniques are aimed at developing an improved and novel system to diagnose esophageal cancer and high-grade dysplasia as well as low-grade dysplasia in Barrett's esophagus. A technical innovation of this project is the development of a unique real-time synchronous luminescence (SL) monitor for detecting small differences in fluorescence profiles of tissues. Molecular fluorescence is a sensitive technique that can be used to measure endogenous fluorescence spectra of biological samples. However, fixed-excitation fluorescence spectra tend to be similar for normal and dysplastic tissues. A methodology that is capable of improving the specificity of the fluorescence technique is the synchronous scanning method, often referred to SL. The proposed SL monitor could lead to significant advances in rapid and effective detection of cancer and dysplasia of the esophagus.

Principal Investigator: **Liaohai Chen**

Institution: **Los Alamos National Laboratory**

Research Title: **Novel Biosensors Based on Nanosized Conjugated Polymer: Detection of Hepatitis C Virus and Broken DNA Strand**

Abstract

An entirely new class of highly-sensitive, selective, robust and economical biosensors for rapid detection of Hepatitis C virus and broken DNA strands has been developed. These are based on a recent scientific breakthrough in which the photophysical properties (e. g., fluorescence) of nanosized conjugated polyelectrolytes can be greatly altered by certain types of electron acceptor molecules with a quenching sensitivity ten-million fold higher than that for conventional small molecule-based materials. Coupling the reversal of quenched polymer fluorescence with a bio-recognition event, we constructed a "turn on" biosensor which is capable of identifying toxins, viruses and broken DNA strands at nano to pico molar concentrations. Herein, diads which contain the quencher molecules linked to bio-ligands such as a recombinant antibody (single-chain Fv) for Hepatitis C core protein or a DNA-binding domain of poly(ADP-ribose) polymerase have been synthesized. In the absence of virus or broken DNA strand, these diads can efficiently quench the polymer fluorescence, yet by adding small amount of the bioanalytes, dramatic increase of fluorescence was observed due to the antibody-antigen interaction or complex formation between the DNA-Binding protein and broken DNA strand. It is anticipated that this novel sensor array could replace currently used ELISA and related assays in the clinics for identification of Hepatitis C virus in serum. It will also provide a new tool to study DNA damage and repair mechanism inside cells.

Principal Investigator: **John George**

Institution: **Los Alamos National Laboratory**

Research Title: **Advanced Magnetic Resonance Imaging System Evaluation of a Novel Diagnostic Technique for Emphysema**

Abstract

Abstract not available.

Wednesday, May 17, 2000

Artificial Sight Symposium

Co-Chairs: Elias Greenbaum, ORNL and

Mark Humayun, Johns Hopkins Wilmer Eye Institute

Principal Investigator: **Peter Dudley**

Institution: **National Eye Institute/National Institutes of Health**

Research Title: **Introduction to Current Status of Retinal Disease Research at NIH**

Abstract

The retina is a specialized light-sensitive tissue that contains photoreceptor cells (rods and cones) and neurons connected to a neural network for the processing of visual information. Visual information is sent from the retina to the brain for decoding into an image. The intimate association of the neural retina with the adjoining pigmented epithelium is essential for normal function. Over the past two decades much has been learned about the basic biology and physiology of the retina. The fundamental structural anatomy and physiology of the retina will be reviewed. Retinal degenerative diseases will be discussed and illustrated with specific examples of retinal degenerations such as retinitis pigmentosa and macular degeneration.

Information on the programs and support of retinal disease research by the National Eye Institute will be presented.

Principal Investigator: **Gerald Chader**

Institution: **The Foundation Fighting Blindness**

Research Title:

Abstract

Abstract not available.

Principal Investigator: **Srinivas R. Sadda, M.D.**

Institution: **Wilmer Eye Institute, Johns Hopkins**

Research Title: **Retinal Cell Transplantation as a means of Visual Restoration**

Abstract

Currently there is no treatment that can restore lost vision to the 20,000 people left totally blind by retinal degeneration or the 500,000 people left visually impaired from retinal causes in the United States. Although there is extensive loss of the outer retinal layers (photoreceptors) in retinal degenerations such as retinitis pigmentosa, the inner nuclear layers remain relatively well-preserved. Replacement of photoreceptors by transplantation has been suggested as a possible method of restoring vision to these patients. Retinal transplantation was first performed in 1946, but significant interest did not develop until the mid-1980s. Through the efforts of a number of investigators, early experiments in retinal degenerate animal models (mouse, rat) demonstrated that transplanted tissue could survive and differentiate in the subretinal space. It also became established that fetal retinal tissue was the optimal source of donor tissue, possibly due to its greater immunologic tolerance. In addition, it was noted by several investigators, that organization/ orientation of the transplanted cells could be affected by the method of transplantation. It was found that after transplantation, dissociated retinal cells (microaggregates) would often form rosettes, whereas retinal sheet transplants tended to form more orderly and normal-appearing retinal layers. Subsequent experiments demonstrated that transplanted photoreceptors were functionally active, as evidenced by normal light-dependent shifts of phototransduction proteins, as well as normal electroretinographic responses. Despite this apparent functional capability of transplanted tissue, restoration of vision or ganglion cell activity has not been well established. This shortcoming has been attributed to the failure of transplanted tissue to form functional connections with remaining host neurons. Some investigators have suggested that a physical glial cell barrier may develop between the transplant and the host, thereby preventing integration. However, careful histologic/ immunohistochemical studies have shown that processes can extend from the transplant to the host. Another possible explanation for failure of functional integration is the loss of synaptic receptivity of the host retinal neurons. Despite the limited success of animal studies, pilot studies of retinal transplantation have been performed in human patients with retinal degenerations. Thus far, conclusive evidence for sustained visual improvement has not been demonstrated. Future efforts in the field of retinal transplantation are being directed towards the enhancement of functional host-transplant integration.

Principal Investigator: **William Heetderks, M.D.**

Institution: **NINDS, NIH**

Research Title: **Feasibility of a Visual Prosthesis Based on Intracortical Microstimulation**

Abstract

Electrical stimulation in the visual cortex with a microelectrode produces the percept of a spot of light in space. Microstimulation at multiple sites can produce the percept of connected points or a line. If this observation can be generalized to microstimulation at a large number of points, it may be possible to create percepts of simple shapes that could be useful for navigation or reading.

This presentation will briefly review the experimental results of intracortical microstimulation in human volunteers that support this concept. Then it will describe some of the technical and safety issues encountered in generalizing from one to a large number of electrodes. Finally it will describe the microelectrode arrays currently under development for intracortical microstimulation.

Principal Investigator: **Mark S. Humayan, M.D., Ph.D.**

Institution: **Johns Hopkins Wilmer Eye Institute**

Research Title: **Electrical Stimulation of Blind Human Retinas; Is an Intaocular Retinal Prosthesis Feasbile?**

Abstract

Wentai Liu Ph.D.[c], Jim D. Weiland M.D.[a],
Satoshi Suzuki M.D. Ph.D.[b], Chris Damarco[c], Duke V. Piyathaisere B.S.[a],
Salvatore A. D'Anna M.S.[a], Eugene de Juan, Jr M.D.[a].
[a] The Intraocular Prosthesis Group, Wilmer Ophthalmological Institute, Johns Hopkins University, Baltimore MD, USA.
[b] Ophthalmology Department, Nagoya University, Nagoya, Japan.
[c] North Carolina State University, NC, USA.

Purpose: To study if electrical stimulation of the retina can elicit visual sensation in individuals blind from retinitis pigmentosa (RP) or age-related macular degeneration (AMD) and to develop an epiretinal prosthesis to benefit the visually-impaired.

Methods: The histology of the deceased patients' retinas blind from RP was studied. Clinical experiments included single retinal electrical stimulation site, resolution tests with up to three sites and patterned stimulation with up to 25 sites. Prosthesis' components and functionality were characterized, from the extraocular unit including a video camera, video processing chip, RF telemetry unit and primary coil, to the intraocular unit, including a secondary coil, processing chips, and the electrode array.

Results: 78%-88% of the inner retinal neurons remained intact in eyes of RP patients. 5/6 blind RP and AMD patients could localize electrical stimulation of the retina (threshold charge densities- 0.16-70 mC/cm^2). 2/2 could resolve simultaneous stimulation sites. 2/2 patients perceived simple forms in response to pattern electrical stimulation. A 100-channel chip, which is capable of being powered via a radio frequency pulse, was developed.

Conclusions: These results support the feasibility of providing useful vision via patterned electrical stimulation of the retinas of individuals blinded by outer retinal degeneration.

Acknowledgements: National Science Foundation, grant #IIS9801684. National Science Foundation, grant #BES-9810914. National Eye Institute, grant #R29EY11888. Foundation Fighting Blindness. The Alfred E. Mann Fund. Second Sight, Valencia CA, USA.

Principal Investigator: **Elias Greenbaum**

Institution: **Oak Ridge National Laboratory**

Research Title: **Application of Biomolecular Photovoltaic Structures to Sight Restoration**

Abstract

This presentation will describe recent progress on the integration of bioactive nanostructures into microchannel glass for the construction of a retinal prosthesis. The bioactive nanostructure is the isolated and purified Photosystem I (PS I) reaction center derived from green plant tissue. We have performed the first measurements of photovoltages (.1 V) from single PS I reaction centers [Lee et al., *J. Phys. Chem B.* **104**, 2439 (2000)]. The goal of this team project is to use the PS I reaction center, to build on the successful research on visual perception elicited by electrical stimulation of the retina in blind humans (Johns Hopkins University Medical School) and development of nano- and microchannel glass, a novel material with many potentially important applications (Naval Research Laboratory). We propose to use the PS I reaction centers, integrated onto two-dimensional microelectrode arrays, to provide photoelectrical stimulation of the retina in blind humans. A retinal implant based on current medical implant technology would be limited to 16 stimulation channel or pixels. A visual scene based on such little information would provide a blind person with a marginal benefit. The combination of the PS I reaction center and channel glass electrodes has the potential to instrument the retina with thousands of electrodes, each driven by a highly efficient photodetector. The metal wire arrays are fabricated by depositing platinum throughout the hollow channels of thin wafers of nanochannel glass. The nanochannel glass provides hexagonal close packed arrays of highly uniform channels in a glass host. The glass can be fabricated with any desired channel diameter varying from ~0.2 Fm to ~10 Fm. The platinum metal is deposited within the channels using standard electroplating solutions and methods.

Tuesday, May 16, 2000

Poster Session

Principal Investigator: R. R. Alfano and Al Katz

Institution: City College of New York

Research Title: Clinical Applications of Photonics Technology for the Detection of Disease: Raman Spectroscopy for Detection of Diseases of the Eye as a Representative Project

Abstract

This presentation will review projects in progress at the DOE-funded Center for Laser Imaging and Cancer Diagnostics at City College of New York (CCNY). Clinical applications of photonic technology under development at the CCNY Institute for Ultrafast Spectroscopy and Lasers are carried out with the close cooperation with Lawrence Livermore National Laboratory and several local metropolitan medical centers, including: Memorial Sloan Kettering Cancer Center, Yale School of Medicine and Yale New Haven Hospital, New York Eye and Ear Infirmary, and Hackensack University Medical Center. The research areas include: Raman spectroscopy to detect eye diseases, intracerebral hemodynamics probed by near infrared spectroscopy, monitoring female hormone levels using fluorescence spectroscopy, polarization dermatoscopy for enhanced visualization of skin melanoma, fluorescence imaging of cancerous tissue, and spectral polarization imaging or prostate and other subsurface tissue imaging.

The following highlights the R&D under DOE support:

Raman Spectroscopy of the Eye

Macular degeneration is accompanied by an increase in glutamate in the vitreous. Glutamate accelerates cell death which in turn increases glutamate concentration. A non-invasive method to monitor glutamate concentration in the vitreous would provide an important tool to detect and/or monitor progression of macular degeneration. In this current work, Raman spectra were acquired from ex vivo porcine eyes injected with glutamate. While Raman spectra from the eye was dominated by signals from the lens, Raman scattering from the glutamate was detectable. An optical geometry has been implemented that significantly reduces the dominant lens signal. Raman spectra from porcine whole eyes, eye cups (lens and cornea removed) will be presented, with and without glutamate injection.

Intracerebral Hemodynamics Probed by Near Infrared Spectroscopy

Infrared absorption measurements of oxygenated and deoxygenated blood were used to investigate intracerebral hemodynamics during sleep and at the sleep-wake transition.

Monitoring of Hormone Levels by Fluorescence Spectroscopy

Flourescence measurements are taken from the female genitalia of volunteer subjects at different times during the menstrual cycle. Changes in the fluorescence intensity and profile are correlated with hormone levels as determined by blood and urine tests. The goal of this work is to develop a non-invasive real-time method to monitor the menstrual cycle to determine the optimal period of fertility.

Spectral Polorization Dermatoscope

A hand held digital dermatoscope is being developed that exploits the depolarizing properties of scattered light to enhance the visualization of subsurface images to detect skin melanoma. The use of red, green, and blue light emitting diodes, and an RGB CCD camera allows for the capture and digitalization of color images. Different colors allows imaging at different penetration depths. Image processing software is under development to improve identification of melanoma.

Fluorescence Imaging of Cancerous Tissue

Fluorescence images of head and neck tissues have been acquired at ultraviolet wavelengths corresponding to emission from key tissue fluorophores. Ratio maps generated from these images identify regions of tumors and other structures in tissue. A ratio map is a 2-D presentation of the ratio of fluorescence intensities at specific, disease-sensitive wavelengths.

Spectral Poloraization Imaging

This work employs polarization imaging technology to detect tumors of the prostate, and hidden objects beneath the surface.

Principal Investigator: Helen L. Bandey

Institution: Sandia National Laboratories

Research Title: Biofluid Studies Using the Thickness-Shear Mode Resonator

Abstract

The thickness-shear mode (TSM) resonator is employed to monitor the physical properties of biofluids (blood and urine) in contact with the resonator surface. This acoustic based sensor has been widely used for the study of materials in which physical parameters can be extracted via equivalent circuit analysis.

The first study involves monitoring the rheological properties of whole blood. It is extremely important to develop new methods that would provide real-time measurements in vitro and in vivo. For the TSM resonator, unlike many in vitro diagnostic hemorheological tests that are often end-point oriented, measurements can be made continuously in real time. Also, any new procedures that reduce sample size and analysis time would be a significant new contribution to both clinical and basic science investigations of whole blood. The TSM resonator has the advantage of being small and lightweight, provides rapid results, and uses small volumes of whole blood. Preliminary studies involve measuring the erythrocyte sedimentation rate (ESR) - a measure of the speed at which red blood cells (RBCs) settle in a prescribed time period. Note: One hour is the standard for the present technique, but shorter times could be used if any new application warranted. The settling behavior of the RBCs onto our sensor surface is monitored in real time; rheological characteristics change continuously just at the device surface as the red blood cells are increasingly compacted. In a separate experiment, preliminary data clearly suggests that the progress of blood clotting can be easily monitored. Contacting fluid begins in the liquid phase, progressing through a gel phase to a solid mass-like final state. We have also shown that it is possible, with less sample preparation, to extract plasma viscosity directly from a blood sample where no separation is necessary.

The second study involves determining the dilution of urine samples. A critical factor in urine screening is the normalization of samples for fluid dilution. Many current screening technologies involve monitoring serum properties where dilution is not a factor; however, it is cheaper and easier (both for the patient and clinician) to take a urine sample. The current standard normalization factor is the urine creatinine concentration. This is a multiple step process that can give inaccurate results. The TSM resonator can give a direct measure of dilution in terms of sensor frequency and damping and can be used in situ. Preliminary experiments were carried out on urine samples obtained from pregnant women. A strong correlation between measured sensor response and creatinine concentration is observed.

Principal Investigator: Florian Bender

Institution: Sandia National Laboratories

Research Title: Receptor-Based Biosensors

Abstract

For about 40 years, acoustic sensors have been used for gas-phase detection. In the recent years, however, large efforts have been made to develop acoustic sensors suitable for in situ liquid phase detection. A number of different concepts has been demonstrated employing various acoustic waves, including thickness shear mode (TSM), shear horizontal acoustic plate mode (SH-APM), shear horizontal surface acoustic wave (SH-SAW), and flexural plate wave (FPW).

Most often, acoustic sensors are used to detect the mass of an analyte. However, they are generally capable of detecting other physical parameters as well, including changes in viscosity and elastic constants, conductivity and dielectric constants, etc. Acoustic sensors can be made selective for the detection of a desired biomolecule by attaching specific receptor layers to their surface, e.g. antibodies, enzymes, protein receptors, or peptides.

The most recent development at Sandia National Laboratories is a Love-mode biosensor. This is a particular type of SH-SAW sensor, using an overlayer with low shear wave velocity that helps trap the acoustic energy near the surface, thus increasing the sensitivity, and at the same time provides electrical shielding and chemical protection of the interdigital transducers (IDT) launching and receiving the acoustic wave. An antibody-antigen reaction has been chosen to demonstrate the capabilities of the device for in situ biosensing. The sensor employs a lithium tantalate substrate, poly (methyl methacrylate) overlayer, and 103 MHz IDTs. For the detection of rabbit anti-goat antibodies, frequency shifts of over 20,000 Hz can be obtained, with the rms noise level being below 10 Hz.

Acoustic sensors represent a very universal sensing technique. By attaching appropriate receptors to the surface of the device, they can be adapted to a variety of applications, including medical diagnostics, water and environmental monitoring, food pathogen detection, and process control.

Principal Investigator: Irving J. Bigio

Institution: Los Alamos National Laboratory

Research Title: A Comparison of Artificial Intelligence Techniques for Spectral Classification in the Diagnosis of Human Pathologies Based Upon Optical Biopsy

Abstract

In order to establish the benefits of tissue diagnosis based upon optical biopsy, some form of decision making process is required to determine the pathology. When spectral information is highly variable, and model-based analysis is difficult, artificial-intelligence pattern recognition methods become valuable tools for spectral classification. We have compared Neural Networks with Hierarchical clustering for the diagnosis of pathologies in the breast, upper GI, and bladder.

This work has been supported by the National Institutes of Health (NIH) and by the Department of Defense Breast Cancer Initiative.

Principal Investigator: Stephen Burastero, M.D.

Institution: Lawrence Livermore National Laboratory

Research Title: Modeling and Experimental Measurements Applied to Joint Kinematics and Injury Prevention

Abstract

Modeling and Experimental Measurements Applied to Joint Kinematics and Injury Prevention

Stephen Burastero, M.D.,* Scott Perfect, Ph.D.,** Dale Schauer, Ph.D.,** Pat Tittiranonda, Ph.D.,* Monika Witte, M.S.**

The $100 billion problem of musculoskeletal injuries plaguing America's work force requires an interdisciplinary team committed to applying expertise in ergonomics, industrial medicine, computational modeling, and biomechanics. A biomechanical working group has been formed at LLNL to encourage collaborative efforts among computational analysts, physicians, and ergonomists. Collaborations have included the University of California at Berkeley and San Francisco, the University of Michigan Center for Ergonomics, Ohio State University Biomedical Engineering Center, and the National Institute of Working Life, Sweden

Computational Modeling

Engineers at LLNL are developing computational models of human biological joints, specifically finger, knee, and spine joints. Ergonomic exposure assessment data collected at LLNL and our expertise related to ergonomic issues of the wrist and spine may provide a method of benchmarking computational models, which, in turn could provide a method for predicting limit capabilities for persons at risk for wrist or back injuries.

Computed tomography imaging is used to generate digitized surface descriptions of the bones in a human hand and wrist. From the surface descriptions, high quality three dimensional finite element meshes of the bones are generated. Attention is currently focused on the thumb and index finger as these two fingers are frequently subjected to orthopedic surgery as a result of acute injury, repetitive motion injuries, and degenerative diseases. The model includes meshes of ligaments and tendons to the index finger, establishing a finite element model that permits articulation of the metacarpophalangeal and proximal and distal interphalangeal joints. The bones are represented as elastic materials and the ligaments and tendons are modeled as transversely isotropic hyperelastic materials. Using the finite element code NIKE3D, we have been able to articulate and perform pinch functions with the index finger by displacing the proximal ends of the two flexor tendons.

Contact is inherent in biological joints. Examples include contact between articulating surfaces of joints and between soft tissues and bone. To accurately simulate the mechanics of joints using the finite element method, a robust treatment of contact is essential. A finite element mesh was constructed for the human femur-medial collateral ligament (MCL)-tibia complex. Only the elements representing the MCL were allowed to deform. The distal femur and proximal tibia were modeled as separate rigid bodies. The MCL was modeled using a transversely isotropic hyperelastic material model. Two contact surfaces were defined, one between the MCL and the distal femur, and one between the MCL and proximal tibia. The tibia and femur were rotated 10 degrees of valgus rotation. Analyses were performed using NIKE3D. Frictionless contact was assumed for the sliding surfaces. We were successful in simulating valgus rotation. The MCL developed large tensile stresses along its long axis and these forces were transferred to the femur and tibia through the contact surfaces. The forces on the tibia (700 N) were higher than those for the femur (70 N) due to the curvature at the end of the femur.

Ergonomics/Biomechanics Laboratory at LLNL

The LLNL Ergonomics / Biomechanics Laboratory specializes in the development of instrumentation for ergonomic exposure assessment. It is outfitted with modern three-dimensional motion analysis equipment, electromyography, electrogoniometry, a sensor based hand-tracking system, image processing facilities as well as instrumentation for measuring back biomechanics. It has actively furthered the science of upper limb exposure assessment and wrist biomechanics. The ergonomics lab also benefits from a close affiliation with the Structural and Applied Mechanics Group, in the Mechanical Engineering Department at LLNL, which has focussed its biomechanics effort on computational modeling of the human hand and knee.

Field Applications

Ergonomic research solutions are often piloted in the LLNL workforce, which consists of over 8,000 innovative high-tech employees who are enthusiastic about ergonomic solutions. Some of our research staff are actively providing ergonomic consultations in the field. Specific projects have included: (1) clinical evaluation of medical screening tests for carpal tunnel syndrome (CTS) and other

musculoskeletal disorders, (2) clinical and biomechanical design and evaluation of computer keyboards and pointing devices, (3) vision ergonomics at video display terminal workstations, (4) computational modeling of upper extremity thumb biomechanics, (5) rehabilitation systems for patients with CTDs, (6) enhancing visualization in endoscopic carpal tunnel release (ECTR) surgical equipment, and (7) back injury biomechanics among hazardous waste workers.

* Health Services Department, Lawrence Livermore National Laboratory
** Structural and Applied Mechanics Group, Lawrence Livermore National Laboratory

Principal Investigator: John Chang, Ph.D.

Institution: Lawrence Livermore National Laboratory

Research Title: Intracranial Hematoma Detection Using Impulse Radar

Abstract

In the United States alone, 2 million people are treated for head injuries each year. Positive identification of intracranial hemorrhage (bleeding within the skull) is achieved through in-hospital computed tomography (CT) scans. This scenario predisposes the injured to potentially deadly delays in delivering definitive treatment. A recently developed enabling technology suggests the potential of providing in-field diagnosis of intracranial hematoma as well as providing a novel neural scanning modality. The device is based upon the technology known as the Micropower Impulse Radar (MIR). The MIR device emits electromagnetic pulses with extremely short duration and low power toward objects such as the head. The MIR device also receives and process the electromagnetic pulses reflected by these objects. This technology permits the device to be manufactured into an inexpensive, compact (cell phone size) device that is powered by a standard 9-volt battery.

A prototype micropower impulse radar has been assembled and is being evaluated for detecting the presence of intracranial hematomas (blood pooling inside the skull). Experiments using numerical models and biological phantom models have yielded promising results and will be presented. Human subject studies are currently being planned.

The handheld MIR device will be operated by touching the signal emitting aperture with the subject's head. The scanning process involves simply of moving the detection device over the subject's head in a systematic fashion.

The emitted electromagnetic radiation have both peak and average power levels that are orders of magnitude lower than that of a hand-held cellular phone and well below the level of existing safety standards for non-ionizing radiation.

The availability of a small, hand-held device for the detection of intracrannial hematomas would be useful for triage decisions in the field, in the emergency department of small hospitals, and even in the emergency department and operating room of trauma centers where critical decision making about therapeutic prioritization are necessary. Such a device would aid, for instance, in the decision making process about whether or not a patient should undergo surgical treatment for head injuries at the same time that necessary operations on the abdomen or chest are being done. Informed decision-making in such circumstances can be life-saving. This study will additionally provide unique insight into the complex interaction between the human body and non-ionizing, low power, impulse electromagnetic radiation.

Principal Investigator: J. E. Delmore, D. A. Dahl, A. D. Appelhans

Institution: Idaho National Engineering and Environmental Laboratory

Research Title: SIMS Technology for The Study of Micro Surface Chemistry

Abstract

J. E. Delmore, D. A. Dahl and A. D. Appelhans
Idaho National Engineering and Environmental Laboratory

The INEEL's development of ion trap secondary ion mass spectrometry (SIMS) technology is focused on analyzing the surface of "natural" samples directly, that is, without subjecting them to pre-treatment or chemical extraction. The goal is to develop the key technologies required to elucidate the complex chemical features (molecular, not simply elemental) of unmodified, heterogeneous surfaces in order to understand the chemical composition at the surface and how this effects the interaction of the surface chemistry with its environment. With self-stabilizing charge control techniques and a non-imaging ion trap-based SIMS, we can now take natural samples such as polymers, soils, vegetation, and bio-organism colonies, and put them directly into the mass spectrometer with no preparation to obtain a chemically specific analysis of the top most monolayer of the surface. This has enabled investigation of speciation, surface reactivity, adsorbate-surface interactions, and of the cell membrane composition of microorganisms. Future directions will focus on methods to enable analysis of a broader range of samples under conditions representative of their natural environment.

Principal Investigator: S. G. Demos, M. Staggs, H. B. Radousky, and R. R. Alfano

Institution: Lawrence Livermore National Laboratory and City College of the City University of New York

Research Title: Deep Subsurface Imaging in Tissues Using the SPDI Technique

Abstract

The spectral polarization difference imaging technique (SPDI) is proposed as a method that can provide deep subsurface imaging in tissues. This technique uses the wavelength dependence of the mean visit depth of photons inside a tissue sample before they emerge in the backscattered direction. Polarization filtering is also used to discriminate against reflected photons from the superficial tissue layers.

The SPDI imaging technique requires acquisition of cross-polarized images under different illumination wavelengths. The exposure time of the CCD camera to record the image for each illumination wavelength must be appropriately adjusted so that the image information arising from the outer tissue layers are approximately the same for both images. The image recorded using a shorter illumination wavelength is then subtracted from another image recorded using a longer illumination wavelength to obtain a set of SPDI-based image.

In this work, imaging depths of the order of 1 cm are demonstrated using the SPDI technique. Results also indicate that 1-mm size objects located more than 5 mm below the surface can be imaged with a resolution that degrades with increasing imaging depths.

The improvement of the contrast in the images obtained using the SPDI technique is the result of the removal of a large segment of the image information that is not relevant to the target. This is achieved by subtraction of the two images obtained at different wavelengths to cancel out the image information arising from photons that were backscattered before reaching the depth where the object of interest is located. In an ordinary imaging arrangement, photons that are backscattered at the surface and just below the surface dominate an image. The information regarding an object located below the surface (which is transported by photons that have reached this depth) is hidden in a strong "background" making its identification difficult. Using NIR illumination, a sufficient portion of the backscattered photons can reach large photon penetration depths and reveal the image information of an object located underneath the surface. The advantage of this technique is that it allows for large imaging depths. This is achieved at the expense of the limited spatial resolution that this technique can provide.

The research is supported by the Department of Energy. This work was performed under the auspices of the U.S. Department of Energy by University of California Lawrence Livermore National Laboratory, through the Institute for Laser Science and Applications and the Materials Research Institute, under contract No. W-7405-Eng-48.

Principal Investigator: Benjamin F. Edwards, Ph.D.

Co-Investigators- Susan A. Autry-Conwell, James E. Boggan, M.D., Bruce Madewell, Ph.D.

Institution: University of California, Davis, Neurological Surgery

Research Title: Photodynamic Therapy

Abstract

Photodynamic therapy (PDT) involves the use of a chemical photosensitizing agent that is taken up and retained in living cells. The photosensitizer is then activated by a specific wavelength of light, usually from a laser, matching the absorption characteristics that are unique to that specific photosensitizer. Tissue destruction results when the light activated photosensitizer interacts with cellular molecular oxygen to generate cytotoxic oxygen radicals.

In our lab a variety of in vitro and in vivo model systems are used to evaluate and optimize the efficacy of novel photosensitizing compounds. The goal is to increase the efficacy and broaden the application of PDT for the treatment of localized cancers and non-cancerous hyperproliferative diseases. Three in house light sources are used in these studies: a variable intensity blue lamp system (DUSA Pharmaceuticals) with peak output at 417 nm, a broad spectrum red light source (Lumenetics, Inc.) covering 600 - 700 nm, and an argon pumped dye laser (Spectraphysics, Inc.) tunable over the 620 - 690 nm range.

In vitro studies include:
(1) Screening of new porphyrin-based photoactive agents synthesized by collaborators at UCD Department of Chemistry. Drug uptake, efflux, intracellular localization and phototoxicity are determined using a panel of human and rodent cell lines.
(2) A phototoxicity bio-assay to test the efficacy of newly developed multi-wavelength light sources for the activation of 5-aminolevulinic acid (ALA) generated protoporphyrin IX (PpIX).
(3) Evaluation of first and second generation photosensitizers for phototoxic activity against antibiotic resistant Gram- negative and Gram- positive bacteria (S. aureus, E. coli, P. aeruginosa) commonly found in infected wounds.

In vivo pre-clinical studies include:
(1) The Fisher 344 rat / 9L gliosarcoma model is being used to evaluate endogenous (e.g., ALA / PpIX) and exogenous (e.g., Lutetium Texaphyrin) photosensitizers for use in localizing and treating malignant brain tumors.
(2) A chick embryo chorioallantoic membrane (CAM) tumor xenograft system is being developed to allow continuous real time monitoring of laser-tissue interaction during PDT. One goal is to develop a non-invasive monitoring system to evaluate the progress of PDT mediated cellular/tissue damage during treatment.

In vivo clinical studies:
In collaboration with oncologists and dermatologists at the UCD School of Veterinary Medicine, a variety of spontaneous tumors and non-malignant hyperproliferative disorders in cats and dogs have been treated with PDT. In addition, low intensity laser light (LIL) has been used to enhance the wound healing process in a variety of canine surgical patients.

Principal Investigator: A.D.A. Hansen and J.M. Jaklevic

Institution: Lawrence Berkeley National Laboratory

Research Title: Bio-Instrumentation at the Lawrence Berkeley National Laboratory

Abstract

The Bio-Instrumentation Group of the Lawrence Berkeley National Laboratory is a unit of LBNL's Engineering Division specializing in the design, fabrication and implementation of instrumentation modules and systems for use in Life Sciences research projects. Some items are custom designed and fabricated in-house: others may be adapted from commercial equipment. The Group was founded in 1988 to support the nascent Human Genome Project (HGP) at LBNL. Early instrumentation accomplishments included colony pickers; robotics systems for microtiter plate handling; agarose gel loading, running and image analysis stations; rapid thermal cyclers and PCR setup systems; oligonucleotide synthesizers; and considerable developments on thin-gel and capillary electrophoresis systems, including advanced base-calling software. The last major instrumentation system constructed before the LBNL HGP transferred to the JGI was the 'Prep-Track' modular workstation system for high-throughput conveyor processing of microtiter plates.

In the last few years, the LBNL Bio-Instrumentation Group has constructed a number of systems for other Life Sciences projects, both at LBNL, at other academic institutions, and also under WFO agreements with the private sector. These include several capillary-based microdot arrayers, a simultaneous dual-color array fluorescence scanner, and a multi-year collaboration with a major pharmaceutical company requiring hardware development for combinatorial chemistry systems, HTS, etc.

Current work includes development of the second-generation capillary microdot arrayer, high-throughput cell growth pattern morphology analysis, and considerable work on instrumentation systems for automating various aspects of protein crystal growth and x-ray diffraction setups at the LBNL ALS.

The poster presentation will illustrate a selection of some of the past accomplishments of the LBNL Bio-Instrumentation Group, its current projects, and its capabilities that are available as an engineering, robotics, and instrumentation resource for the research community.

Principal Investigator: Robert C. Hughes

Institution: Sandia National Laboratories

Research Title: Implantable MEMS Sensors

Abstract

The miniaturization of sensors using silicon based microelectronics and MEMS (Micro-Electro-Mechanical Systems) is leading to a generation of sensors that are small enough and rugged enough to be implanted in living systems. In this poster we will discuss two technologies being developed at Sandia: The Radiation Sensing Field Effect Transistor (RadFET) for measuring radiation dose inside the body and a miniature pressure sensor with telemetry to monitor cerebrospinal fluid (CSF) pressure from inside the cranial cavity.

The RadFET chip is only one square mm and is inexpensive to manufacture in large numbers by standard silicon wafer processing. It integrates ionizing radiation flux giving total dose for a wide variety of photon energies and energetic particles. Doses from less than one Rad to 100,000 Rads are easily recorded. The RadFET can be inserted in a medical catheter for in vivo measurements of cancer therapy radiation doses eliminating reliance on imprecise computer-calculated dose estimates. The RadFET provides an immediate readout to determine if the accurate dose is being administered or whether nearby bones or other body parts have affected distribution of the radiation dose. It is especially well suited for use in brachytherapy—the cancer treatment where radiation sources are either placed close to the tumor or actually implanted within the lesion to emit doses of radiation over a period of time. The RadFET readout circuit is low voltage, and doses are recorded even when the power is off.

The Sandia pressure sensor is fabricated using bulk micromachining techniques and consists of a single-crystalline silicon diaphragm over a reference pressure cavity. The semiconductor processing techniques used to produce these sensors are the same as those used to produce computer chips and therefore provide the capability of extremely small size. The long-term goal of this research is to develop a miniature sensor with telemetry to monitor cerebrospinal fluid (CSF) pressure from inside the cranial cavity and relay this information to a nearby-reader. Such an in vivo system would enhance clinical monitoring of cranial pressure and enable at-home monitoring. This would allow clinical intervention to prevent damage caused by elevated CSF pressures resulting from certain pathological conditions. Sandia's expertise in small, low power telemetry systems and pressure sensor fabrication are keys to the success of this project.

Principal Investigator: Robert H. Kraus, Jr., Ph.D.

Institution: Los Alamos National Laboratory

Research Title:

Abstract

We report on the progress toward developing novel technologies to enable significant advances in magnetoencephalography, MEG, a noninvasive functional neuroimaging technique that directly measures the electrophysiological consequences of neural activity with better than millisecond temporal resolution. MEG, in conjunction with structural information, provides researchers with a unique tool to study neuronal activity and the evolution of that activity in the human brain associated with function and cognition. MEG data is acquired with better than millisecond temporal resolution allowing one to directly observe the evolution of neural activity. Other functional brain imaging modalities such as fMRI and PET indirectly observe neural activity through the hemodynamic response and are also limited by the comparatively sluggish response of the hemodynamic system. Wide clinical application of MEG has largely been limited by the small number of systems available with which to conduct research studies and clinical trials, the lack of readily accessible MEG data and analysis algorithms, the lack of integration with other functional neuroimaging modalities (such as fMRI and PET) and the expense of these systems. The specific focus of this work will advance the sensor technology, and the modeling and computational tools that provide the technological foundation for higher quality, more reliable, faster, and cost effective neuroimaging of human brain function using MEG. We will build on several years of DOE/OBER supported innovation that has been directly responsible for two filed patents and two more in process (see below) and a large number of publications, and international conference and workshop presentations and papers. The technologies and tools developed under this grant will contribute directly and significantly to multimodal neuroimaging methods that integrate MEG for the study of basic, clinical, and diagnostic neuroscience. This work will benefit neuroscience efforts that implement and integrate MEG by providing the tools to enable researchers and clinicians to acquire higher quality data and perform more reliable analyses.

Our vision is to combine the successes resulting from this work with those from other related efforts funded by NIH, DOE/DP, NFFBI (the National Foundation for Functional Brain Imaging), and Los Alamos internal research funds to build a “national resource” devoted to advancing the state-of-the-art of instrumentation, techniques, computational tools, and basic methodologies for multimodal noninvasive neuroimaging of human brain function. This resource will not only provide instrumentation, analysis tools, and methodologies but also establish a national repository of functional neuroimaging data, computational tools (such as forward and inverse solvers, etc.), and expertise devoted to educational and collaborative efforts.

Principal Investigator: Steve Lane

Institution: Lawrence Livermore National Laboratory

Research Title: Continuous Glucose Sensor for the Treatment of Diabetes

Abstract

Department of Energy researchers at Lawrence Livermore National Laboratory have teamed with MiniMed, Inc. to develop a chemical glucose sensor as part of a biomechanical pancreas. In 1998, Diabetes was responsible for the deaths of 200,000 Americans. An estimated 16 million Americans suffer from diabetes in the U.S. alone, where diabetes is the third leading cause of death by disease. Direct costs to the U.S. health-care system resulting from diabetes care are over $92 billion annually. Diabetes is a metabolic disease in which the body does not produce or use insulin properly. The cells of the body use glucose as their energy source. Insulin is a hormone that allows glucose to enter the body's cells so they can have energy for life. Careful stabilization of glucose levels is crucial to minimizing such life-threatening diabetes complications as kidney disease, nervous system disorders, amputations, blindness, heart disease, and stroke.

Current methods of measuring blood glucose levels, often involving a finger stick, are painful, inconvenient, and prone to error. Additionally, it is virtually impossible to test frequently enough with current technologies to maintain relatively stable glucose levels. However, a team of scientists at LLNL and MiniMed are developing a minimally invasive device to monitor glucose levels; it will be fully implantable in the body and able to measure glucose levels continuously.

This new device is a fluorescent chemical sensor that consists of carefully engineered molecules embedded within a biocompatible polymer. In the absence of glucose, these molecules are non-fluorescent. However, glucose alters the electron configuration of these molecules in such a way that they become fluorescent and emit light of a specific color. It is the intensity or brightness of this emitted light that allows for the determination of the body's glucose level. A more intense light emission corresponds to a higher glucose level.

It is the goal of the LLNL-MiniMed team to develop a continuous long-lived glucose sensor that will enable the realization of this biomechanical pancreas. This novel system would function as follows: (1) the sensor would measure the glucose level and communicate that information directly to the insulin pump; (2) the pump would, if necessary, automatically deliver the appropriate insulin dose to the individual in order to lower the glucose level. The biomechanical pancreas would virtually mimic the functions of a healthy pancreas by constantly monitoring glucose levels in the body and making the appropriate adjustments in insulin levels based on sensor readings.

The insulin pump developed by MiniMed is the most advanced method for administering insulin; it eliminates the need for diabetics to self-administer numerous daily insulin injections. An insulin pump is composed of a small battery-operated pump with an insulin reservoir and a computer chip that allows the user to control insulin delivery. Insulin is delivered into the body from the external pump via a plastic tube. MiniMed also manufactures an implantable insulin pump that is currently being tested in Europe. By combining an insulin pump with a continuous glucose sensor, it is possible to produce a biomechnical pancreas.

Chemical sensors developed at LLNL are also being investigated for use as accurate, miniaturized, stockpile inspection tools and as a means for detecting chemical and biological warfare agents, which are key technologies within the Department of Energy's mission.

Principal Investigator: L.E. Larsen, M.D.

Institution: Sandia National Laboratory/NM

Research Title: Transuretheral Leaky-Wave Applicator for Hyperthermic Treatment of Benign Prostatic Hyperplasia

Abstract

Benign prostatic hyperplasia (BPH) is a condition of extraordinary prevalence. By age 65, fully half the male population will has BPH. By age 85 the prevalence raises to 90% of the male population. BPH is not always symptomatic in the early stages, but urinary tract infections or stasis or sufficient prostate enlargement can lead to urinary obstruction.

The first line of treatment is usually medical. When this tactic becomes ineffective, the next treatment offered is usually surgical. Surgery can have serious side effects such as infection, impotence, and incontenence. Minimally invasive methods based on radiofrequency hyperthermia to shrink periuretheral tissues offer a middle ground in terms of lower rates of complication than surgery, but the improvement in urodynamics may be less than satisfactory or transient.

The device developed under LDRD funding at Sandia National Laboratories makes use of a novel electromagnetic structure known as a leaky-wave antenna (U.S. Patent 6,051,018) to improve uniformity of heating in periuretheral tissues. The benefit of this technology is to avoid unncessary destruction of tissue due to excessive temperature elevation in hot spots while regrowth of tissues is reduced in regions of insufficient temperature elevation.

The performance of the leaky-wave transuretheral applicator was tested in prostate equivalent tissue phantoms by means of scanning, differential infrared radiometry. High specific abosrption rates and uniform periurethral heating were demonstated with use of the applicator at the ISM frequency of 915 MHz.

Principal Investigator: Richard London

Institution: Lawrence Livermore National Laboratory

Research Title: Imaging Biological Tissue with Optical Coherence Tomography

Abstract

*Imaging biological tissue with optical coherence tomography

R. A. London, P. Amendt, B. W. Colston, Jr., and L. B. Da Silva

Lawrence Livermore National Laboratory, University of California, CA 94550

Optical coherence tomography (OCT) is a non-destructive 3-D imaging technique that has been proven to work well in transparent media such as the eye. It can also be used to image several mm into highly scattering tissue. We describe recent research to design and test OCT systems for several biomedical applications. The research focuses on methods to improve the sensitivity of OCT in highly scattering media and includes both experiment and computational modeling. The experiments explore several concepts for signal enhancement including the use of multiple wavelengths, doppler shifts, and polarization. For computational modeling, the Monte Carlo method incorporated into the LATIS laser-tissue interaction code is used. Computational work includes a study of the role of multiple scattering in determining the signal/noise ratio of an OCT system, and a study of several methods to increase the signal such optimizing the size and acceptance angle of the light collection optic and the use of polarization discrimination. Medical applications including dental imaging for detection of caries and peridontal disease and intravascular imaging are discussed.

*This work was performed under the auspices of the U.S. Department of Energy by the University of California Lawrence Livermore National Laboratory under contract No. W-7405-Eng-48.

Principal Investigator: Anthony Makarewicz

Institution: LLNL

Research Title: *Acoustic Focusing of Optically-Generated Shock Waves in the Treatment of Kidney Stones

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Abstract

One half million people suffer the debilitating pain of kidney stones in the United States each year. Of these, approximately 60% can not be successfully treated with medication and dietary restrictions and must be treated more aggressively, either with surgery or one of many modalities of lithotripsy. These aggressive treatments cost between $5,000 to $10,000 per occurrence, for an annual national cost of up to $3 billion. High costs limit the availability of these aggressive treatments to large medical centers.

We are developing a novel medical technology for destroying kidney stones (lithotripsy) via intracorporeal application of an optically-generated focused shockwave. This technique will be an efficacious, safer, and lower-cost alternative to the currently available technologies for kidney stone destruction. The device will be introduced through the urethra and bladder, utilizing a flexible optical fiber to deliver laser energy. The tip of the fiber will be capped with an opto-acoustic transducer and an acoustic lens to focus the generated shock wave on the kidney stone. Our new device combines the beneficial characteristics of current technologies used for kidney stone destruction (localized application of energy, maneuverable fiber optic delivery system, relative safety of an acoustic shock wave) while eliminating the potential dangers (perforation of soft tissue by the direct application of laser energy and the cumulative effects of multiple high-energy shock waves on soft tissue far from the stone).

Device development requires the investigation of several parameters including: optical fiber tip shape, absorber properties, lens shape, and acoustic waveform shape, which is controlled by the lens shape and the laser pulse duration. We have undertaken the design using computational techniques. The numerical results of acoustic pulse focusing will be compared to experiments of system mock ups. Plans for reduction of the system size and shock wave characteristics for kidney stone destruction will also be discussed.

*This work was performed under the auspices of the U.S. Department of Energy by the University of California Lawrence Livermore National Laboratory under contract No. W-7405-Eng-48.

Principal Investigator: Surya K. Mallapragada

Institution: Ames Laboratory

Research Title: Resorbable Polymers for Drug Delivery and Tissue Engineering Applications

Abstract

Biomedical research in our laboratory focuses on the development and use of resorbable polymers for drug delivery and for tissue engineering applications. This poster will focus on projects that include mammary tissue regeneration using porous biodegradable polymer scaffolds and the development of pH and temperature sensitive smart polymer gels for drug delivery. The mammary tissue project pioneers the development of replacement tissue for breast reconstruction using tissue engineering principles and biodegradable polymer scaffolds. The goal of this project is to engineer breast tissue replacement in vitro and develop an overall strategy to design efficient, biocompatible, resorbable scaffolds and optimize conditions for mammary tissue regeneration with properties comparable to those of native breast tissue. The three dimensional scaffolds serve as a physical support and also as an adhesive substrate for the cells, mimicking the action of the extracellular matrices of the body. Mouse mammary epithelial cells (HC11) and fibroblasts are isolated and co-cultured in various ratios on three-dimensional biodegradable and soluble polymer scaffolds. Estradiol and progesterone are incorporated into the scaffolds during the fabrication process. The structure and properties of the regenerated mammary tissue are evaluated using microscopy, collagen, cytokeratin, glycosaminoglycan, laminin, and casein content determinations, mRNA expression patterns by cDNA microarray analysis, mechanical property measurements, and histological studies and the properties compared to those of native tissue.

The drug delivery project seeks to develop novel strategies for adaptive smart biomimetic hydrogels that respond to changes in the physiological environment such as pH and temperature. The overall goal of this project is to develop better minimally invasive smart therapeutic systems for improving the stability of drugs and delivering drugs on demand. An injectable poloxamer gel, grafted or blended with a pH sensitive polymer and appropriately modified to alter release rates, can be injected as a liquid and can deliver drugs slowly and in response to environmental stimuli over the desired period. This would eliminate the need for implanting a controlled release device. Another objective is to model the pH and temperature sensitivity of these smart polymers to optimize the design of smart polymers under physiologically meaningful conditions. A model system to release insulin will be designed by making these systems glucose sensitive by incorporation of glucose oxidase.

Principal Investigator: Judith R. Mourant

Institution: Los Alamos National Laboratory

Research Title: Development of a Technique for Cancer Diagnosis/Detection by Noninvasive Assessment of Epithelial Tissue Morphology

Abstract

Early detection of cancerous and precancerous changes has the potential to decrease cancer mortality. Non- and minimally- invasive techniques would be ideal for screening patient populations. However, many of the non-invasive methods currently available for diagnosing and locating pre-malignant changes are not very accurate. The most accurate technique for cancer diagnosis is histopathological analysis of tissue specimens--obviously a very invasive technique for the patient. Histopathology is a poor technique for determining whether a lesion is present or for finding an abnormality in a large area. However, pathology works well when a cancer or precancerous change is suspected in a localized area. Pathologists can detect early changes in tissue morphology. For example, many of the early lesions of the cervix that are detected will regress on their own and never become an invasive cancer. We would like to develop a noninvasive method of detecting many of the same structural changes that are detected by pathologists. Pre-cancers are characterized by increased nuclear size, increased rate of proliferation, changes in chromatin organization and an increase in number and/or size of nucleoli, etc. As part of an NIH-funded project we have been determining whether light scattering methods are sensitive to these changes. We have shown that light scattering is sensitive to changes in proliferation and there is growing evidence that light scattering is sensitive to nuclear structures. Therefore, the challenge is to design an inexpensive, accurate and easy to use system that can detect pre-cancerous changes in epithelial tissue where most cancers originate. Recently we have demonstrated that light scattering using polarized excitation and light collection can detect very small changes in the size distribution of scatterers in a turbid media. Here we present data demonstrating that polarized light scattering can measure the average size and concentration of scatterers in dense medium. Data showing a strong sensitivity to cell proliferation rate will also be presented. All measurements are made using a geometry amenable to non-invasive measurement of tissue. Furthermore, calculations to be presented indicate that the technique can be used to only interrogate the epithelium where most cancers originate and not the underlying stroma.

Principal Investigator: David W. Nigg

Institution: Idaho National Engineering and Environmental Laboratory

Research Title: SERA - Simulation Environment for Radiotherapy Applications

Abstract

In the early 1990s the Idaho National Engineering and Environmental Laboratory (INEEL) and Montana State University (MSU) developed a Monte Carlo treatment planning system for Boron Neutron Capture Therapy known as BNCT_rtpe (BNCT Radiation Therapy Planning Environment). Although BNCT_rtpe has been a useful and relatively efficient tool that has received world-wide recognition and use, it exhibits execution times (2-4 hours per field) that are longer than ideal. Accordingly, INEEL and MSU undertook some studies in the late 1990s that were focused on achieving a significant breakthrough in execution speed for this type of software via a total reformulation of the mathematical algorithms. This developmental effort has led to the recent introduction of the completely new SERA (Simulation Environment for Radiotherapy Applications) treatment planning software.

The SERA treatment planning system incorporates a novel method for reconstructing patient geometry from medical images and for subsequently tracking particles through this geometry during a Monte Carlo radiation transport simulation. The method, in contrast to coarse-voxel reconstruction methods and the Non Uniform Rational B-Spline (NURBS) method used in BNCT_rtpe, is based on a pixel-by pixel uniform volume element ("univel") reconstruction of the patient geometry. Fast scan-line rasterization methods, implemented largely with integer arithmetic, are used to allow rapid particle tracking through the univel geometry. Univels along the particle track are investigated and precise intersection points ("distance to boundary" in Monte Carlo terminology) can be rapidly calculated as the particle moves from one anatomical region to the next. By scaling the univels to match the resolution of the original image data the very high geometric fidelity of the NURBS reconstruction method used in BNCT_rtpe is retained. Furthermore, the computed fluxes and doses have the same statistical accuracy as with a NURBS model, but the execution time for the transport computations is reduced by a factor of between five and ten. This speedup factor holds even though the new univel model may consist of several million elements. Single-CPU execution times for SERA, with current desktop scientific computing hardware (e.g. 400 MHz Pentium III systems running under Linux), are in the range of 10-15 minutes per field.

SERA also features some much-improved image handling tools and display interfaces as well as several new three-dimensional geometry and dose distribution display interfaces. It may also be noted that the basic physics modules of SERA will allow incident neutron energies up to 100 MeV, with an explicit treatment of recoil proton transport. This expands the utility of the SERA system into the field of fast-neutron radiotherapy, with or without BNCT augmentation. Efforts are also currently underway to upgrade the photon transport algorithm in SERA to accommodate external beam photon therapy as well as brachytherapy.

This work was sponsored by the United States Department of Energy, Office of Science, under DOE Idaho Operations Office Contract Number DE-AC07-99ID13727.

Principal Investigator: Karen Reiser, MD, and Kenneth Trauner, MD

Institution: University of California, Davis

Research Title: Laser Activated Tissue Welding

Abstract

This project consisted of development of a novel approach to tissue welding using photochemistry and organic reagents. Photo-oxidizer initiated welding offers a number of advantages over other kinds of closure techniques. First, covalent bonds serve as the "closure device" thus eliminating the need for exogenous mechanical devices. Second, the reaction pathways being used occur under normal conditions in vivo, thus minimizing the likelihood of unexpected tissue response. Third, these covalent bonding reactions do not require the presence of either cells or vasculature; thus, the reactions can proceed under conditions associated with delayed or impaired wound healing.

Significant work has been accomplished in two areas. First, using organic chemical-based crosslinking, we have been able to "weld" both human and bovine tendon. The tendons were bisected, compressed then covalently bonded. Maximum strength is achievable within 1 day. Welded human tendons were tested on an Instron machine, and yielded strengths ranging from 20-120 newtons. Second, we have developed a reproducible in vitro system that allowed us to rapidly screen reaction variables, and, further, to document that reaction products that form under physiological conditions are the same as those found in normal tissues. Highly purified soluble type I collagen solutions placed in microtiter plates are used for investigating such variables as tissue preparation modalities, time, temperature, chemical reagant, and photooxidizer. Using this system we measured rates of polymerization of various initiators of the reactions. Since oxidation steps are obligatory in generating the crosslinks, timing of the reaction is controlled with a "photochemical trigger" that generates reactive oxygen species when activated by laser energy at a specific wavelength. Multiple photosensitizer candidates are under investigation. Promising tensile strengths in bonded tendons suggest numerous potential surgical and tissue engineering applications for this new technology.

Principal Investigator: David Schlyer

Institution: Brookhaven National Laboratory

Research Title: Beta Microprobe for Radiotracer Kinetics in Freely Moving Animals

Abstract

A scintillation microprobe has been developed to directly measure positron decays in living tissue. The probe consists of a small LSO crystal coupled to an optical fiber which is read out with a photomultiplier tube operated to a single photon counting mode. Positron conversions in the crystal are detected with high efficiency due to the excellent stopping power and high light output of LSO, and allows for the direct determination of the positron decay activity in a highly localized region of tissue. The probe can be used in the study of chemical kinetics and the development of new radiotracers in awake and freely moving animals.

Principal Investigator: Christine L. Hartmann Siantar

Institution: Lawrence Livermore National Laboratory

Research Title: Using PEREGRINE for Treatment Verification in Radiation Therapy

Abstract

The PEREGRINE dose calculation system provides 3D Monte Carlo transport calculations fast enough for day-to-day radiation therapy planning. It operates on low-cost, commodity hardware , enables real time visualization of dose as it is simulated, and completes a full treatment simulation in minutes. The initial version of this system, which calculates radiation dose distributions for photon therapy, has been licensed will soon be available for commercial distribution to the radiation therapy community.

The work described here extends PEREGRINE's capabilities to serve a critical need in the verification of dose delivered to the patient. This year, we have developed online portal image-simulation tools that will enable the physician to verify that the correct dose distribution was delivered to the patient for each treatmen and the patient is in same position every day. We have used these tools to investigate how to improve portal image quality and verify dose delivered. This presentation describes the prototype, experimental/simulation results, and our plans for the future.

Principal Investigator: Luiz Da Silva

Institution: Lawrence Livermore National Laboratory

Research Title: Stroke Treatment System

Abstract

Department of Energy researchers at the Lawrence Livermore National Laboratory are attacking the problem of stroke with new tools to rapidly restore blood flow. Stroke is the third leading cause of death (150,000/year) and the leading cause of disability in the United States. Approximately 500,000 strokes occur annually in the U.S., accounting for costs of over $26 billion/year for treatment and rehabilitation. Worldwide, 4.5 million deaths per year are attributed to stroke. Ischemic, or vascular occlusion, strokes account for approximately 80% of strokes; hemorrhage makes up the remainder.

It is imperative that a patient experiencing a stroke seek medical attention immediately as there is roughly a three to six hour window in which to resolve the clot before permanent neurological impairment may result. Current treatment modalities include mechanical intervention or pharmacologic thrombolytic (drug) therapy to disrupt or dissolve thrombus (blood clots). Current mechanical interventions can be relatively invasive and are limited in their accessibility to larger vessels, for example carotid arteries. However, most occlusions occur in smaller, more deeply-seated vessels such as the middle cerebral artery. Thrombolytic therapy may be effective but thrombolytics are not indicated for all stroke victims, are not effective on all thrombus, and have associated risks, some of which may have severe consequences, particularly hemorrhage. Successful development of a new treatment modality could have significant benefits to the outcomes of stroke patients, ultimately improving mortality rates and decreasing morbidity, thereby decreasing the cost of rehabilitation and improving the quality of life in stroke patients.

Researchers at LLNL have developed unique technologies to aid in the disruption of thrombus occlusions. This minimally invasive technique, Endovascular Photo-Acoustic Recanalization (EPAR), involves guiding a catheter to the site of the occlusion and introducing an optical fiber delivery system into the catheter. Laser light is coupled into the optical fiber and delivered to the occlusion, causing mechanical disruption of the occlusion and re-establishing blood flow to the brain. The mechanism of interaction involves depositing laser energy into blood or blood clot, creating an acoustic wave, which is transmitted into the clot and, finally, formation of a vapor bubble which aids in the emulsification of the clot.

The size of the fiber and catheter allow for treatment of occlusions in small diameter cerebral arteries, less than 1 mm. The limited amount of power required and the specific nature of laser-interaction have thus far proven to be atraumatic to blood vessels and surrounding tissues. Additionally, the duration of the entire procedure should be significantly shorter than thrombolytic therapy. Initial development of the laser and delivery system were performed at LLNL, incorporating computer modeling and experimentation. Computer models effectively aided in optimizing irradiation parameters and predicted thrombus-material failure modes. Parametric laboratory experiments were performed to determine optimal laser irradiation parameters for safe and effective clot emulsification. Experiments ranged from studying the pressure and temperature effects of single laser events to testing the feasibility of laser-assisted thrombolysis in vivo. In vitro studies indicated that clots could be emulsified into particles that should pass unobstructed through the vasculature.

The EPAR concept is a derivative of laser and optical technologies developed within the DOE core defense mission. Additionally, laser-tissue interaction models, originally developed as laser-matter simulations for the stockpile stewardship mission, were crucial in optimizing the laser paramters for optimal acoustic wave effectiveness. Technology and models developed during the course of this work continue to contribute to the stockpile stewardship mission.

Principal Investigator:	Gerald J. Small
Institution:	Ames Laboratory
Research Title:	Monoclonal Antibody-Gold Biosensor Chips for Detection of Depurinating Carcinogen-DNA Adducts by Fluorescence Line-Narrowing Spectroscopy

Abstract

Gerald J. Small, Jeremy R. Kenseth, George P. Casale, Scott D. Duhachek, Marc D. Porter, and Ryszard Jankowiak
Ames Laboratory-USDOE, Iowa State University, Ames, IA 50011

A new direct readout methodology for detection and quantification of fluorescent carcinogen-DNA adducts is described. It combines the binding specificity of an immobilized monoclonal antibody (MAb) with high resolution, low temperature fluorescence spectroscopy. The MAb, which is covalently bound to a gold surface via a chemisorbed disulfide coupling agent, binds the adduct of interest in an aqueous sample. Laser-induced fluorescence under non-line narrowing (FNLN) and line-narrowing (FLN) conditions was used to detect (benzo[a]pyren-6-yl)guanine (BP-6-N7Gua) bound to immobilized MAb. At room temperature the BP-6-N7Gua fluorescence was not detected, most likely because of quenching by the gold surface and/or efficient dynamic quenching. However, fluorescence was observed at room temperature when the surface was covered with a thin layer of glycerol. Possible reasons for the fluorescence enhancement are considered. Lowering of the temperature to 77 K led to approximately an order of magnitude further increase in fluorescence intensity. Highly structured FLN spectra obtained at 4.2 K allowed for definitive adduct identification. The potential of the above methodology for risk assessment studies of individuals exposed to polycyclic aromatic hydrocarbons is considered.

Principal Investigator: Suresh C. Srivastava

Institution: Brookhaven National Laboratory

Research Title: Effect of Molecular Size on the In-Vivo Natural Binding to CAR of in-111 and I-131 Labeled Adenoviral Sub-Unit Proteins

Abstract

S.C. Srivastava, G.E. Meinken, P. Freimuth
Brookhaven National Laboratory, Upton, NY, U.S.A.

Biodistribution of In-111 and I-131 labeled adenoviral sub-unit proteins in mice has been studied to determine the effects of radiolabeling and the molecular size of viral vectors on their natural binding to the coxsackievirus and adenovirus receptor (CAR)-expressing tissues. Methods: Intact adenovirus (Ad, ~80nm diam.), the trimeric native fiber protein, AdFP (180kD), and the fiber knob protein, AdFKP (60kD) were labeled with I-131 using the Iodogen method. AdFKP, conjugated to DTPA (2X and 10X), was also labeled with I-131 and In-111. AdFP was purified from infected human cultured cells, and the recombinant AdFKP was synthesized in E. coli. Binding activity of all preparations was determined using reaction with biotinylated CAR followed by chemiluminescent detection. Biodistribution was studied following i.v. injection into mice. Results: I-131 labeled Ad and AdFP accumulated (%ID g-1 at 6h) in many organs as expected (e.g., muscle, bone, kidneys, <2%) but more preferentially in the liver and lungs (>5%), indicating higher specificity of binding to CAR. I-131 AdFKP showed the same trend; however, its distribution was more widespread among other tissues reflecting its smaller size and/or some loss of specificity or affinity. In-vitro assays showed that the binding specificity to CAR was maintained only if the 6-Histidine extension (used for purification) on the AdFKP was not removed prior to conjugation with DTPA. In-111-6-His-AdFKP-DTPA was preferentially taken up (%IDg-1 at 6h) into lungs (6.0%) and liver (12.8%) and much less in other tissues (<2%), indicating specific binding to CAR expressing organs. I-131-6-His-AdFK-DTPA gave essentially similar distribution. Results with the 2X and 10X DTPA preparations were not statistically different. Conclusions: All three Ad ligands accumulate preferentially in CAR expressing tissues, liver, and lung, with minor accumulations elsewhere. CAR binding of iodinated AdFP and AdFKP is generally maintained but the smaller AdFKP appears more sensitive to radioiodination. Our results also indicate that I-131- and In-111-6-His-AdFKP-DTPA, both retain specificity of binding to CAR and that there is a protective effect of histidine without which this binding specificity is compromised. Work supported by USDOE, Office of Biological and Environmental Research, under Contract No. DE-AC02-98CH1088.

Principal Investigator: Richard E. Swaja

Institution: National Institutes of Health

Research Title: Biomedical Engineering: Status and Directions

Abstract

A recent study by the National Academy of Sciences identified biomedicine as one of only two science and technology fields where the Federal budget can be expected to increase over the next ten years. One of the important growth areas associated with this field is biomedical engineering which involves the application of physical, engineering, and computational science principles and techniques to solve biomedical problems. Despite significant contributions and advances that can be attributed to bioengineering, issues still exist with regard to how to most effectively foster trans-disciplinary training, communication, and research collaborations between the science/engineering and biomedical communities which tradiationally have different educational and occupational environments. At the National Institutes of Health, the Bioengineering Consortium (BECON) has provided a focus for identifying and addressing issues associated with biomedical engineering both inside NIH and with other Federal agencies since its establishment in 1997. BECON programs aimed at coordinating research funding opportunities, providing trans-disciplinary training, and facilitating communication among the biomedical and allied disciplines will be described. At the national level, bioengineering research and training have been identified as future areas of focus and support at several Federal agencies, multi-agency committees including academic and business representatives have been formed to identify and address issues associated with biomedical engineering, and local bioengineering centers and cosortia consisting of academic and research organizations have been formed to facilitate training and sharing of resources. This presentation will describe results of these efforts, new initiatives and directions related to bioengineering, and problems which will need to be addressed so that the full benefits of applying engineering/science principles to solve biomedical problems can be realized.

Principal Investigator: Jan J. Stokosa, C.P.

Institution: Stokosa Prosthetic Clinic

Research Title: Amputation and Prosthetic Rehabilitation in the Lower-extremity: Where We're at and Where We'd like to Be

Abstract

Few experiences may be more profoundly shocking to the human body than amputation. This loss is irretrievable. At first, the impact of its finality is difficult to comprehend or believe - losing a treasured part of the body is not fully appreciated until its loss. The missing part was a major component of the body's functioning capability, without conscious effort, in the established pattern of daily living.

The anatomy of the remaining portion of the limb after amputation is quantitatively and qualitatively different than the anatomy of the intact limb. The vast differences in physology, weight-bearing capability, motor and sensory function, and pain, usually manifest several months after surgery. Conventional amputation techniques render the greatest physiologic disturbance. Amputation techniques emphasizing a biological approach, such as the Ertl technique, result in a superior physiologic and biologic end-organ.

In the design, fabrication, and fitting of any extremity prosthesis, comfort to the wearer must be an overriding concern. Other elements of the prosthesis and the fitting process are subordinate to and dependent on proper socket fit. Discomfort will result in rejection or improper use of the prosthesis, thwarting other benefits. The most sophisticated component part with the most accurate biomechanical alignment is of little value if walking causes pain or skin breakdown, or both.

The goal of amputee rehabilitation is to aid the amputee in reentering and regaining his or her place in society: working, playing, and engaging in a full range of human relationships. Progress in this endeavor will be marked by the amputee's placing a diminishing emphasis on the amputation and prosthesis. Ideally, amputaton and prosthesis will move outside the inner circle of the patient's life concerns. The prosthetist's role in this process, in the broadest terms, is to enhance the amputee's mobility and appearance, with maximum comfort.

State-of-the-art amputation surgery, prosthesis design, and discussion of areas for improvement will be discussed.

Principal Investigator: C. A. Thompson, D. Lande, S. S. Olivier, M. W. Kartz

Institution: Lwarence Livermore National Laboratory

Research Title: Adaptive Optical Correction for Vision Science Applications

Abstract

The human eye suffers from significant high-order aberrations that limit human visual acuity. These aberrations also limit the ability to image structures within the eye. Previous work in this field has shown the benefit of employing an adaptive optical (AO) system, using a modest 37-actuator deformable mirror, to retinal imaging and visual acuity enhancement. We have developed an adaptive optical test-bed in our laboratory, based on a high-resolution liquid crystal spatial light modulator (SLM). The SLM device allows control of over 200,000 phase points resulting in wavefront correction at resolutions several orders of magnitude greater than previously achievable. Modification of this AO test-bed for human vision measurements, would enable us to analyze the phenomenon of hyper-acuity, determine the ultimate resolution of the human eye and the ideal correction to eye optics based on both aberrations and neurological factors. Beside the contribution to fundamental vision research, this work would be important for the corrective vision community since it can provide the tools for next-generation LASIK and contact lenses to go beyond the "20/20" standard. We will present results from our SLM-based AO system and describe techniques for performing high-resolution correction of human vision.

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Principal Investigator: Kenneth Trauner, MD

Co-PI Rich London, Ph.D., Graça Vicente, Ph.D., Jessica Salter, SRA

Institution: University of California, Davis, Department of Orthopaedic Surgery

Research Title: Photodynamic Treatment of Arthritis

Abstract

The long term goal of this project has been the development of photochemical techniques for the treatment of arthritis. Studies have targeted the disease processes of both rheumatoid and osteoarthritis. Initial rheumatoid studies focussed on transcutaneously and percutaneously destroying the inflamed synovium of rheumatoid animal models. The affinity of T lymphocytes and activated macrophages for photosensitizers, and the reported transdermal systemic anti-inflammatory effects of PDT suggest that low level PDT treatments delivered transcutaneously should have the ability to induce an anti-inflammatory effect within the joint by selectively targeting activated T lymphocytes, macrophages, and synoviocytes. Later studies with a rat model have attempted to modify the inflammatory response in the rat arthritis model using low level transcutaneous photodynamic techniques and circumferential light activation of joints.

For osteoarthritis, our laboratory is investigating the use of PDT as a potential chondroprotective modality. Cellular studies with both human and bovine chondrocytes have demonstrated photochemical modulation of chondrocyte production of metalloproteinase enzymes. A reduction in degradative enzyme production without reduction in cellular viability suggests PDT as a potential chondroprotective agent. Current studies are assessing several new synthetic photosensitizers to optimize the desired effect while minimizing chondrocyte toxicity.

Development of light delivery techniques also remains an area of active investigation. The importance of optimizing light delivery for PDT synovectomy effects was established in early pilot studies that compared treatment efficacy using two different optical fiber delivery systems. Large differences in treatment effects may be achieved by varying light distribution, timing, and dosage. As a CLAM collaboration, we are currently developing a three dimensional optical model of the human knee joint, to provide information to optimize light distribution within the geometrically complex diarthrodial joints.

Principal Investigator: James Trebes

Institution: Lawrence Livermore National Laboartory

Research Title: X-ray Catheter for the Treatment of Restenosis

Abstract

An x-ray catheter system is being developed to address a key element of heart disease treatment. Heart disease caused by blockage of a coronary artery is a common medical problem, affecting over 1,000,000 Americans annually. The catheter works in conjunction with conventional balloon angioplasty to prevent the common problem of reclogging of the effected artery after angioplasty. The x-ray catheter delivers a large dose of x-rays to the internal walls of the artery. The x-ray dose acts to interrupt the body's response to the angioplasty injury that often leads to re-clogging.

When partial or complete closure of a coronary artery occurs, the patient can experience significant pain, loss of mobility, degradation of quality of life, and even death. Commonly a balloon angioplasty is performed to re-open the artery. In this procedure, a catheter is introduced into the coronary artery by access through a small opening in the patient's femoral artery above the thigh. The tip of the catheter has a cylindrical balloon, which is inflated at the site of the blockage and expands the artery, usually resulting in a substantial increase in blood flow. In many cases, scar tissue forms along the inside of the artery during the natural healing process following angioplasty, which partially or completely blocks the artery. Known as restenosis, this clogging requires repeated angioplasty or other more invasive procedures. Restenosis affects about 250,000 patients in the United States annually, with medical costs for treatment now running $2.5 billion. Research performed at the Washington Heart Center, Emory University, and the Scripps Clinic has shown that treatment of the arterial wall with ionizing radiation immediately after angioplasty can prevent restenosis and help insure full recovery for the patient. The x-ray catheter is a safe, cost-effective means of delivering this ionizing radiation in the form of x-rays.

A prototype miniature x-ray tube attached to the end of a shielded electrical cable has been demonstrated and several prototypes have been developed. The x-ray tube can be inserted into an artery allowing an x-ray dose to be delivered directly to the arterial wall in a controlled manner. Both the x-ray tube and the cable connection are electrically shielded to prevent electrical hazards. The x-ray catheter is not intrinsically radioactive; it is activated by a low-level electrical current and produces no radioactive waste. A main feature of this breakthrough is that the x-ray catheter emits its x-rays only during the time it is energized inside of the artery. This makes handling much easier than conventional radioactive sources. In Mayo Clinic trials, soft x-rays produced by these x-ray tubes have been shown to be effective in treating restenosis in tissue tests. Progress to date on the development of a practical x-ray catheter includes: (1) measurements confirming that the thermal load produced by the x-ray catheter is biologically acceptable, (2) production and operation of x-ray catheter prototypes, and (3) experimental demonstration that therapeutic x-ray doses can be generated by prototypes. In order to be small enough to navigate the arterial path to the important coronary arteries, the x-ray tube portion of the catheter must be < 1.5 mm in diameter; current focus is on reducing the size of these devices from the present 3 mm diameter to a small size. The x-ray catheter was derived from the core competence in x-ray imaging and diagnostics for the stockpile stewardship program. The miniaturized x-ray source has several potential applications for inspection and radiography applications in the continuing stockpile stewardship program.

Principal Investigator: Dr. Tuan Vo-Dinh

Institution: Oak Ridge National Laboratory

Research Title: Advamced Fluorescence Techniques for In-Vivo Cancer Diagnosis

Abstract

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An optical diagnostic procedure based on laser-induced fluorescence (LIF) has been developed for direct in-vivo cancer diagnosis without requiring biopsy. Endogenous fluorescence of normal and malignant tissues were measured directly using a fiberoptic probe inserted through an endoscope. A nitrogen dye laser tuned to 410 nm was used as the excitation source. The fiberoptic probe was inserted into the biopsy channel of an endoscope and lightly touched the surface of the tissue being monitored. Each measurement was completed in approximately 0.6 second for each tissue site. We have developed a technique using the differential normalized fluorescence (DNF) to enhance small but consistent spectral differences between the normal and malignant tissues. This technique greatly improves the accuracy of diagnosis for malignant tissue. The LIF methodology has been applied in a clinical study involving over 200 patients in order to differentiate normal tissue from malignant tumors of the esophagus. The results of this DNF approach were compared with histopathology results of the biopsy samples and indicated excellent agreement in the classification of normal tissue and malignant tumors for the samples investigated. The effect of inflammation on the diagnosis was also investigated.

Advanced techniques such as synchronous fluorescence and time-resolved detection are currently being developed to further improve the optical diagnostic method. These techniques are aimed at developing an improved and novel system to diagnose esophageal cancer and high-grade dysplasia as well as low-grade dysplasia in Barrett's esophagus. A technical innovation of this project is the development of a unique real-time synchronous luminescence (SL) monitor for detecting small differences in fluorescence profiles of tissues. Molecular fluorescence is a sensitive technique that can be used to measure endogenous fluorescence spectra of biological samples. However, fixed-excitation fluorescence spectra tend to be similar for normal and dysplastic tissues. A methodology that is capable of improving the specificity of the fluorescence technique is the synchronous scanning method, often referred to SL. The proposed SL monitor could lead to significant advances in rapid and effective detection of cancer and dysplasia of the esophagus.

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Principal Investigator: Maria da Graça Henriques Vicente, Ph.D.

Co-PI Benjamin F. Edwards, Ph.D.

Institution: University of California Davis, Department of Neurological Surgery

Research Title: Synthetic Porphyrin Systems for Tumor Detection and Destruction

Abstract

Porphyrin-like macrocycles have been shown to selectively localize in a wide variety of neoplastic tissues, and this property provides the basis for their use in the photodynamic therapy (PDT) of tumors. PDT relies on the selective uptake of a photosensitizer in tumor tissues, followed by generation of singlet oxygen and other cytotoxic species upon irradiation with red light. The only FDA-approved PDT drug is a porphyrin derivative (Photofrin®), which has to date been used to treat over ten thousand cancer patients world-wide. In addition to necrosis (as the result of oxidative damage) it has been recently shown that some porphyrins also induce apoptosis (programmed cell death). Active research in the area of development of highly efficient PDT photosensitizers is currently underway, since Photofrin® presents the disadvantages of being a complex mixture of compounds of variable composition, with only a weak absorption at 630 nm. All the promising new PDT photosensitizers currently in human clinical trials are porphyrin-based compounds with enhanced absorptions in the red region (chlorins, benzoporphyrins, and phthalocyanines).

Another therapeutic modality for cancer treatment, the Boron Neutron Capture Therapy (BNCT) is based on the 10B(n,4He)7Li nuclear reaction which occurs when a 10B nucleus captures a reactor-generated low-energy neutron to produce cytotoxic high linear energy transfer particles (4He2+, 7Li3+). Due to their tendency to selectively accumulate in neoplastic tissue, porphyrins are attractive boron carriers for BNCT. Our research program is aimed at the development of new porphyrin-based capture agents and photosensitizers for application in both BNCT and PDT. The correlation of the chemical structure and biological activity of these compounds is studied in order to establish metrics for the successful design of effective sensitizers for cancer treatment.

Porphyrins and their diamagnetic metal complexes are highly fluorescent thus providing a means for the detection of tumor cells by confocal fluorescence microscopy, and an effective treatment planning. Furthermore, tumor-selective paramagnetic metal complexes of porphyrins [for example Mn(III) complexes] are effective contrast agents for MRI. Radiolabeled derivatives of porphyrins with 3H, 14C, and 125I are useful radiodiagnostic agents. Porphyrin complexes bearing radioisotopic metals have also been shown to retain their in vitro and in vivo localization properties in tumor cells and to be highly promising radiopharmaceuticals for tumor detection and antibody labelling. Some porphyrins have also been shown to be active radiosensitizers, and to display sensitizer enhancement ratios up to 2.4. Other non-cancerous therapeutic applications of porphyrins include treatment of atherosclerosis, vascular restenosis, age-related macular regeneration, rheumatoid arthritis and blood sterilization.

Principal Investigator: Drew Weisenberger

Institution: Jefferson Laboratory

Research Title: Bio-Medical Detector Development at Thomas Jefferson National Accelerator Facility

Abstract

The Detector Group at the DOE's Thomas Jefferson National Accelerator Facility (Jefferson Lab) has been involved in the development of nuclear particle detectors for two general areas of application: (1) in the basic research effort of the laboratory in experimental nuclear physics, and (2) for biomedical applications. This poster presentation will enlist and highlight some of the key research and technology transfer projects in which the Jefferson Lab Detector Group is involved, with potential applications in cancer detection and treatment, and in small animal based molecular biology research. The present nuclear medicine gamma imager applications include: dedicated scintimammography and positron emission mammography in breast cancer diagnosis, beta/gamma intra-operative surgical probes, and compact imagers for stereotactic breast biopsy. The small animal functional single gamma imagers were developed for in vivo molecular imaging in mice. The Detector Group has been able to inject its detector technology expertise to these areas of application through collaboration with academia, medical centers and industry. The key in-house element s of the successful implementation were the resource base of the DOE facility and the active technology transfer program.

Principal Investigator: Robert A. Wind

Institution: Pacific Northwest National Laboratory

Research Title: Magnetic Resonance Microscopy at Pacific Northwest National Laboratory

Abstract

A review will be presented about the current magnetic resonance microscopy (MRM) capabilities at PNNL, as well as biological applications of this technique. These MRM capabilities include respiratory-triggered in vivo MRM of small animals (mice) in external fields of 7 and 11.7 Tesla, and in vitro MRM of live single cells and small cell systems at 7, 11.7, and 17.6 Tesla. The field dependence of the MRM sensitivity for different sizes of biological samples will be discussed, and the results will be compared with measurements obtained with newly developed microcoils. Also, first results will be presented obtained on a combined optical (confocal) and magnetic resonance microscope, which was recently developed at PNNL, and which makes it possible to obtain images of large single cells and monolayers of mammalian cells simultaneously. Finally, the prospects for cellular research will be discussed for another development, to be undertaken at PNNL in the near future, namely the combination of MRM and dynamic nuclear polarization (DNP). This technique can be applied after doping the sample with a suitable radical, and can be used for MRM sensitivity enhancements and oximetry measurements on a cellular level.

Principal Investigator: William O. Wray and Arminas Ragauskas

Institution: Los Alamos National Laboratory & Telematics Science Laboratory/Lithuania

Research Title: Noninvasive Intracranial Pressure Measurement & Non-contact Intraocular Pressure Measurement

Abstract

Normal intracranial pressure (ICP) in humans is about 15 mmHg. Abnormally elevated intracranial pressure occurs in 50-75% of patients who have suffered severe head trauma (Miller et. al., 1992). For those cases in which the ICP rises above 20 mmHg, a 95% mortality rate has been observed. Thus, it is apparent that secondary brain injury due to head trauma could be greatly reduced if elevated ICP could be detected quickly so that appropriate treatment could be initiated without delay.

At present, ICP measurement techniques are highly invasive requiring placement of a catheter tipped strain guage or a fluid filled catheter into the brain tissue or a cerebral ventrical. Placement of these catheters damages brain tissue and entails the risks of causing intercerebral bleeding and/or infection. There is a 27 % incidence of infections associated with catheters left in place for 48 hours or more in a clinical setting and the risks of infection in a non-clinical setting are prohibitive. Due to these risks, ICP is usually monitored only in severely head injured patients, in a clinical setting and only for periods of 48 hours or less. All of these restrictions could be relaxed, resulting in vastly improved care for the patient, if a noninvasive ICP measurement system were to be made available.

The Bioscience Division at Los Alamos National Laboratory is developing a noninvasive ICP measurement system based on a patent-approved vibrational resonance technique proposed by Dr. Dipen Sinha in the Material Science Division at Los Alamos. This system seeks to associate shifts in the vibrational resonance spectrum of the skull with variations in ICP. The only physical contact with the patient is through two small (about the size of a dime) piezoelectric transducers that are held in place by an elastic band with a velcro fastener. This system is quite compact and nonintrusive and would be appropriate for long-term, continuous monitoring of ICP in an intensive care scenario. Tests were conducted on ten healthy human subjects at Los Alamos during FY99 and well defined, repeatable, individualistic, vibrational resonance spectra were found to exist over the frequency range from 40 to 100 kHz. Furthermore, frequency shifts of spectral peaks were observed in connection with postural changes and activities that are known to induce changes in ICP; the association of frequency shifts with ICP changes demonstates the feasibility of the vibrational resonance technique.

A means for calibrating the vibrational resonance system and thereby facilitating noninvasive determination of absolute ICP values is provided by an second ICP instrument that is under development by Arminas Ragauskas DSc, Head of Telematics Science Laboratory at Kaunas University of Technology in Lithuania. We have entered into a collaboration with Dr. Ragauskas to jointly develop our respective instruments in a manner that takes maximum advantage of the natural synergy of the two devices. Dr. Ragauskas' system is based on the simultaneous ultrasonic measurement of the blood flow parameters in the intracranial and the extracranial segments of the eye artery. He has determined experimentally that when ICP is equal to the pressure on the extracranial segment of the eye artery, the blood flow parameters within the two segments are aproximately equal. Therefore, it is possible to determine ICP by raising the extracranial pressure in the region of the eye by means of a pneumatic face mask until the blood flow parameters in the two segments have equilibrated; when equilibration is achieved, the ICP is given by the induced extracranial pressure, which is equal to the easily measured pressure within the face mask. This system could be used for periodic measurements of ICP in an intensive care scenario, but it is not appropriate for continuous monitoring. The truly unique aspects of Dr. Ragauskas design are that it provides the only currently available method for measuring absolute ICP noninvasively and that it does so via an extracorporal pressure measurement that can be made with high accuracy. As such, it could ultimately provide a "gold standard" calibration tool for the calibration of other noninvasive ICP devices that are more appropriate for continuous use in an intensive care unit. We intend to use Dr. Ragauskas device for calibration of the vibrational resonance system under development at Los Alamos.

In a second closely related project, the Bioscience Division is developing a non-contact intraocular pressure measurement system that would relate vibrational resonance shifts in the cornea to variations in intraocular pressure. In this case, vibrations would be excited through the air from a stand-off distance of about a centimeter and corneal response would be monitored with an LED optical vibration sensor or a laser interferometer. The advantage of this system is that, since there is no contact with the cornea, local anesthesia is not required and a glaucoma patient could conceivably monitor his own IOP at home rather than having to return to his doctor's office for each measurement.

Principal Investigator: Tom Zawodzinski

Institution: Los Alamos National Laboratory

Research Title: Systems Based on Artificial Muscles for Prosthetics Applications

Abstract

Artificial muscles are devices that allow the development of mechanical contractile or tensile forces from electrical or chemical stimulation. Substantial effort has been devoted to the use of ‘soft’ or compliant materials, especially polymer electrolytes, for this purpose. We will report on electrochemical characterization and transport modeling to enhance our understanding of the function of the performance of these materials. We will discuss conclusions from our recently developed first-principles models of ion and water transport in polymer electrolytes. We will also discuss elements of some proposed work aimed at extending the artificial muscle materials into integrated systems that can serve as "smart prosthetics." All of this work exploits our extensive experience with polymer electrolyte physical chemistry, processing, and applications in devices.