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The Center for Integration of Medicine and Innovative Technology (CIMIT), is a consortium of nonprofit Massachusetts-based institutions led by Massachusetts General Hospital and includes Brigham and Women's Hospital, Massachusetts Institute of Technology and Draper Laboratory. The primary aim of the Center is to develop technologies that will advance the capability of modern medicine to diagnose and treat patients using minimally invasive and less costly approaches. CIMIT will coordinate and implement research programs in cardiovascular disease, cancer, stroke, trauma and critical care, that are supported by basic science and engineering development in biomaterials, endoscopic tools, energy delivery, intelligent decision systems, medical imaging, micro-sensors, outcomes, robotics and simulation. A unique military/civilian partnership fostered by CIMIT will allow DOD technologies to be evaluated by CIMIT investigators and facilitate the transfer to the military of successful minimally invasive approaches developed at CIMIT. An educational program, which includes coursework, seminars, and on-site training opportunities, will serve the shared needs of academic and military physicians and scientists. The overall goal of CIMIT is to create a national program that combines clinical and technological excellence in order to generate, develop, and reduce-to-practice innovative and high-impact concepts in minimally invasive therapy.

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INTRODUCTION

The Center for Integration of Medicine and Innovative Technology (CIMIT) has completed the first year of DoD support under Cooperative Agreement Number DAMD17-02-2-0006. CIMIT is a non-profit consortium of world-leading academic and research institutions founded by Partners HealthCare System, Massachusetts General Hospital, Brigham and Women's Hospital, Massachusetts Institute of Technology, Charles Stark Draper Laboratory and Beth Israel Deaconess Medical Center. The overall goal of the program has evolved beyond minimally invasive therapy to include other aspects of acute care using high technology approaches.

CIMIT's mission is to improve patient care by bringing together scientists, engineers, and clinicians to catalyze development of innovative technology, emphasizing minimally invasive diagnosis and therapy.

Key Accomplishments by Program - *Project – Principal Investigator*

Operating Room of the Future

Learning Predictive Rules from Medical Data
Principal Investigators: David Rattner, M.D., MGH and Leslie Kaebling, Ph.D., MIT
The CIMIT team has examined the domain of OR scheduling and evaluated the performance of machine learning approaches to solve the problem of surgical length prediction. The team has shown that with careful parameter tuning, these algorithms are more accurate than the existing case length prediction by a few minutes on average.

ORF Outcomes
Principal Investigator: James Stahl, M.D., MGH
The handheld data gathering tool using IPAQ hardware and SQL database software (ABCDb™) developed by James Stahl has been cross validated across data-gatherers. These data have been used to examine the standard surgery scheduling system (DSS) for staff enter, start and stop times and to validate the Radianse indoor positioning system.

Patient Safety Project
Principal Investigator: Keith Isaacson, M.D., MGH and Newton-Wellesley
The CIMIT team has collaborated to put together a schema for the patient database. Working together the investigators have identified the key information that must be stored for each patient. This was performed by doing a walk through of the flow of needed information from admitting to discharge for a patient. The CIMIT investigators provided all the needed information that should be stored for the patient, when it would be stored and when it would be retrieved.

Simulation

Medical Simulation
Principal Investigator: Steven L. Dawson, M.D., MGH
In response to an Army request for a smallpox inoculation training system, we successfully proposed and delivered SITU, a smallpox inoculation training system. With the assistance of LT COL Mary Parker, MD, we delivered a number of the SITU units to the Preventive Medical team at the Army's 2nd Infantry Division in Camp Casey, Dongduchon, Korea. Over the last four months of the fiscal year, Army personnel in Korea were instructed in proper inoculation technique and personnel care using the SITU system.

Tissue Engineering

Tissue Engineering: Microfabrication
Principal Investigators: Joseph Vacanti, M.D., MGH and Jeffrey Borenstein, Ph.D., Draper Laboratory
Our key accomplishments over the past year include: the next generation design model has produced physiological values for shear in capillary networks; rapid, repeatable process for three-dimensional scaffold construction has been developed and prototype processing equipment built; numerous PLGA microvascular networks with as many as 10 layers and no leakage have been built and delivered to the laboratory for cell culture and testing; and a novel method for the separation of endothelial and organ-specific cellular layers in microdevices has been invented and is currently being demonstrated.

Polymeric Nanoparticles for Localized High Efficiency Gene Transfer
Principal Investigator: Robert Langer, ScD, MIT
The CIMIT team has synthesized and screened 2350 poly(β-amino ester)s for their ability to deliver DNA *in vitro*. Using high throughput methods we have identified over 40 polymers capable of delivering DNA as better than the current state of the art polymeric gene delivery systems. Careful study of select hits has provided a new level of structure/function information. In addition, we have developed microsphere formulations that consistently exhibit 3-4 orders of magnitude increase in transfection efficiency over microparticles composed of PLGA alone. Furthermore, the microparticle formulations induce surface upregulation of activation markers in dendritic cells while PLGA formulations fail to generate signs of maturation. The CIMIT team is actively preparing for both *in vivo* experimentation and commercialization.

Nanofibrous scaffolds for cartilage regeneration
Principal Investigator: Sonya Shortkroff, Ph.D., BWH
The goal of this project is to examine the effects of varying fiber diameters of scaffolds for cartilage tissue engineering on maintenance of phenotypic attributes of the chondrocyte. It was of prime importance that the electrospun scaffolds have distinct fiber size ranges. By manipulating the various parameters the CIMIT team was able to produce electrospun PCL scaffolds with uniform fiber diameters in three size ranges (450 nm, 2 μm and 7 μm). Our next challenge was to assure adequate seeding of the cells onto the fibrous scaffolds. To this end, we have identified cell-seeding techniques that provide uniform distribution and 90-95% effective adhesion of the cells.

Image-Guided Therapy

Laparoscopic Ultrasound
Principal Investigator: James Ellsmere, M.D., MGH
The CIMIT team continues the preclinical studies to make the navigation system more robust for clinical evaluation. We have implemented manual registration functionality to the system to allow the user to finely tune registration. Also, the CIMIT team has acquired new 3DUS volumes using the Volusion 930 from GE Medical Imaging. The plan is to use these volumes to further develop investigations in registering intraoperative 3DUS with preoperative CT and segmenting abdominal vascular structures for surgical landmarks.

Minimally Invasive Approach to Reconstruction of the Midfacial Skeleton
Principal Investigator: Maria J. Troulis D.D.S., MGH
In collaboration with the Harvard Medical School Department of Continuing Education, we conducted an international workshop entitled: Endoscopy for Mandibular Reconstruction and Salivary Disease. This was the first such workshop in the field of maxillofacial surgery and was fully subscribed and attended by leaders in the field of OMFS from the United States and Europe.

This course was the direct result of 5 years of partially CIMIT sponsored pioneering work in minimally invasive surgery of the mandible. The course received high ratings from the participants, many of who are now incorporating these techniques in their practices and teaching programs.

Biodefense

Real-Time Assay for the Detection and Patho-typing of Escherichia coli O157:H7 in Processed Bovine Meat
Principal Investigator: Stephen B. Calderwood, M.D., MGH
The CIMIT team has made good progress on improving the signal-to-noise ratio for the μCANARY device, calibrating the sensitivity of the μCANARY sensor to determine minimum detection limits, and optimizing coating of anti-O157 antibody for binding of organism to the sensor. We have also identified several DNA sequences unique to pathogenic strains of *E. coli* O157 for use in strain typing.

Characterization of a Pyrolysis High Field Asymmetric Waveform Ion Mobility Spectrometer for the Detection of Bacillus Spores
Principal Investigator: Cristina E. Davis, Ph.D., Draper Laboratory
The CIMIT team has made significant progress with the optimization of the pyrolysis-FAIMS system, and the ability to detect spore biomarkers has been verified. Data was taken for *B. subtilis* spores suspended in water and was compared to data taken for water alone. This comparison shows extremely promising results, as at least three distinct peaks were visually observed in the spectra of the spore samples that were not in the water-only samples. Correlogic Systems, Inc. found at least seven major biomarker peaks using their pattern discovery and recognition algorithms. This indicates that the pyrolysis-FAIMS system is capable of detecting specific spore biomarkers.

Detection of Pentane in Patient Breath using Planar FAIMS
Principal Investigator: Cristina E. Davis, Ph.D., Draper Laboratory
This year the CIMIT team has made solid scientific advances, and we have publicly presented our work several times. Members of our team have worked to continue attracting extramural funding for our FAIMS projects. Draper submitted a FAIMS proposal to NASA entitled "FAIMS for Multi-use space applications including environmental and health monitoring" for $1.4M for 3 years. The goal of this work would be develop a flight-ready, low power, low mass device for chemical and microbial environmental monitoring of the human crew compartments of the International Space Station and the Space Shuttles. This proposal has leveraged results generated by CIMIT-funded work, and would be directly related to our CIMIT-funded research in that it will help to build our focus on non-invasive health diagnostic applications for the FAIMS.

Networked Sensor Systems

Patient Centric Networking and Applications
Principal Investigator: John Guttag, Ph.D., MIT
The CIMIT team has developed new methods and algorithms for screening for mitral valve prolapse (for which a patent application was filed) and detecting the onset of epileptic seizures. This work was tested on de-identified data provided by physicians at MGH and Children's Hospital. Preliminary results suggest that our methods are highly effective. Over the next year we will be submitting IRBs to test our tools in clinical settings.

Diagnostics

Electrostrictive Polymer Artificial Muscle (EPAM) Devices for Magnetic Resonance Imaging (MRI)
Principal Investigator: Steven Dubowsky, Ph.D., MIT
The development of potentially useful EPAM actuators has progressed significantly this year. Improvements in design, materials selection, and assembly processes have improved the reliability and performance characteristics of the actuators. Several alternative design concepts have been proposed and evaluated experimentally for the adjustable RF receiving coil. Such designs offer solutions that eliminate potential problems with the original design concept, including limited image quality and resizing capabilities. Design concepts for the Focused Ultrasound System have been generated and evaluated. One such device has been fabricated. This aspect of the work will be major direction for the coming year.

A Method and Device for Performing Bladder Mapping
Principal Investigator: W. Scott McDougal, M.D., MGH
The CIMIT team has acquired all necessary instrumentation for this project. Also, we have developed a phantom bladder, have successfully photographed segments of the phantom and have determined that six individual photographs can be compositely overlaid to create a bladder map.

Radio Frequency Impedance Mapping for Medical Imaging
Principal Investigators: Aaron K. Grant, Ph.D., and Daniel K. Sodickson, Ph.D. Beth Israel Deaconess Medical Center
The CIMIT team has made the following specific achievements over the past year:

- Acquisition of a cluster of 10 linux computers for use in electromagnetic modeling and image reconstruction for RFIM
- Development of parallel computer programs for electromagnetic modeling
- Implementation of algorithms for image reconstruction
- Construction of a set of coil arrays for use in RFIM
- Acquisition of RF test equipment for performing measurements of coil array properties
- Demonstrations that the aforementioned hardware and software can be used to measure the conductivity and permittivity of homogeneous imaging phantom with sufficient accuracy to be of clinical interest
- Demonstrations that linear arrays of RF coils can encode spatial information about the distribution of conductivity in inhomogeneous imaging phantoms, and
- Construction and testing of an array for experiments in fully three-dimensional imaging.

Robust Elastography for High-Resolution Strain Imaging in the Vulnerable Atherosclerotic Plaque
Principal Investigator: Raymond Chan, Ph.D., MGH
Over the past year our experiments with vessel phantoms and diseased coronary arteries demonstrated that with conventional OCT imaging and motion region-of-interest constrained optical flow estimation, strain estimates from within the vessel wall appeared to be more blurred than expected. In the current quarter, we have sought to address this problem by first identifying the root cause, and then by making improvements to the image acquisition system and to the processing algorithms used for strain estimation.

In Vivo Detection of Inflamed Plaques in Rabbits Using FDG and a Novel Beta-Detecting Catheter
Principal Investigator: Ahmed Tawakol, M.D., MGH
Approval to begin the experiment was granted by DoD in Spring of 2003. Since approval was received in the Spring of 2003, the initial investment of effort in this project was to produce the atherosclerotic animals that are needed for this investigation. Because of the several-month delay

in starting the protocol, a 1-yr no-cost extension was requested (and has been granted) to continue the experiments.

Project: Diagnosis of Pancreatic Cysts
Principal Investigator: Brett Bouma, Ph.D., MGH
An OCT microscope was developed and focal parameters were optimized for imaging morphologic and microscopic features of pancreatic cysts. Sufficient resolution was obtained to allow the identification cyst epithelia. Morphologic features, also diagnostic of cyst type, were observed and correlated with histology.

Spectrally Encoded Confocal Microscopy
Principal Investigator: Brett Bouma, Ph.D., MGH
The CIMIT team has developed a system for acquiring SECM images at a rate of 30 frames per second, more than three-orders of magnitude faster than our prototype system and sufficient for real-time, cellular resolution imaging in living subjects.

Early Diagnosis of Osteoarthritis by Polarization Sensitive Optical Coherence Tomography (PS-OCT)
Principal Investigator: Johannes F. deBoer, PhD., MGH
Joint specimens have been collected following total knee replacement surgeries and measurements have been made on osteoarthritic cartilage using PS-OCT. Preliminary results demonstrate that PS-OCT can visualize clear and distinct differences between healthy cartilage and osteoarthritic cartilage *in-situ*.

Photochemical tissue bonding: enabling studies and application to microsurgical reconstruction of peripheral nerves
Principal Investigator: Robert Redmond, Ph.D., MGH
The CIMIT team has screened more than 20 dyes for photochemical activity and crosslinking ability in an *ex vivo* tendon bonding model. These were all compared to the currently used dye, rose bengal. Of these, toluidine blue showed an almost equal efficiency in bonding tendon as rose bengal. It has the advantage of absorbing red light that penetrated deeper into tissue.

Speckle Imaging for Plaque Characterization
Principal Investigator: Guillermo Tearney, M.D., Ph.D., MGH
The CIMIT team has developed a method to identify and characterize atherosclerotic plaque types by the analysis of time-varying speckle fluctuations and have shown that the decorrelation time constant of speckle fluctuations provides a measure of the intrinsic biomechanical properties of atherosclerotic plaque under *in vitro* static conditions. In our study of over 30 aortic plaques, we demonstrated that compliant lipid plaques had a significantly lower decorrelation time constant than fibrous and calcific plaque types. We have extended this method to investigate the identification of plaque types during tissue translation and deformation and have demonstrated that speckle decorrelation decreases with increasing deformation rates. Hence, additional information on the biomechanical properties of atherosclerotic plaque may be obtained by measuring speckle decorrelation at different stages of the ECG cycle. We have also investigated the use of optical fiber bundles and have been successful in obtaining speckle images of phantom materials using a single mode fiber bundle.

Real-time intraoperative functional imaging for the assessment of myocardial injury and graft patency during simulated off-pump coronary artery bypass surgery.
Principal Investigator: Tomislav Mihajlevic, M.D. Brigham and Women's Hospital
In addition to testing the accuracy of real-time NIF vascular imaging techniques with the fluorophore mentioned (IR-786), the CIMIT team has been using the FDA-approved agent

indocyanines green (ICG) as well as testing other similar heptamine indocyanines which have varying hydophobicities. The team has successfully tested the NIF imaging system in open-chest porcine models using various fluorophores and different concentrations. We have further confirmed our results with fluorescent microspheres. Tests have also been completed in a cardiopulmonary bypass model to assess both vascular anatomy and cardioplegia delivery.

Trauma Management

Untethered Monitoring
Principal Investigator: Nathaniel Sims, M.D.
This past year, all tasks and deliverables were completed on schedule, on budget. The complete system prototype with final documentation was delivered to the Life Signs Detection Program Manager at Natick Labs on September 30th, 2003. The prototype includes a basic sensor array (for measuring heart rate, temperature, and motion), an "alive/dead" health state algorithm, and a wireless communication network. The sensor array is packaged in a thoracic textile belt. A stretch sensor for monitoring respiration is incorporated into the design of the belt. Inclusion of this respiration sensor in the prototype, goes beyond the required demonstration as a separate proof-of-concept milestone, and reflects the team's dedication to exceeding the requirements of the original agreement.

Core Programs

Industry Liaison Program
Program Director: Janice E. Crosby, R.N., M.B.A., MGH
The CIMIT team has continued expansion of CIMIT's network of Industry partners. The Industry Liaison Program (ILP) continues to be a vital link between industry and CIMIT's programs and investigator community. Currently, CIMIT is working with over 45 companies at various stages of membership. Three new companies joined the ILP with 12-15 additional companies in the introductory stage.

Office of Technology Implementation Program
Program Director: Jonathan Rosen, Ph.D., MGH
Between August and November 2002, the OTI interviewed each of the 43 recipients of CIMIT Awards for FY03. Based on these interviews, the OTI prepared detailed reports for each of the institutional technology transfer offices describing which investigators at that center were funded by CIMIT, were likely to produce new invention disclosures, would need Material Transfer Agreements, and would present potential technology transfer opportunities during the coming year. As a result of this activity, several institutions assigned case managers in advance to high potential investigators to facilitate their patent and licensing activities.

Regulatory Affairs Program
Program Director: John J. Smith, M.D., J.D., MGH
During the past year, the CIMIT Regulatory Affairs Program continued to work with stakeholders to make the existing regulatory and coverage/payment system more efficient, transparent and predictable. A major focus on conflict of interest in medical research culminated in a CIMIT/Harvard Medical School/Stanford University Forum on Conflict of Interest, held in Boston in October 2002. Three forum-related white papers have been release to warm receptions from the stakeholder community, with multiple scholarly articles based on this research either published, accepted for publication or submitted for publication.

Technology Assessment
Program Director: G. Scott Gazelle, M.D., Ph.D., MGH
The CIMIT team continues to support the entire CIMIT scientific and administrative community, as well as the two Technology Assessment and Outcomes Analysis Program Research Projects. The team also assists CIMIT to focus resource allocation for the development of innovative medical technologies that can result in improved patient care; provide advice on and perform studies to assess the effectiveness, cost and cost-effectiveness of new technologies under development; and demonstrate the value of these new technologies to the public, physicians, payers, industry, and legislators so as to facilitate their appropriate dissemination and implementation.

Operating Room of the Future

Learning Predictive Rules from Medical Data
Principal Investigators: David Rattner, M.D., MGH and Leslie Kaebling, Ph.D., MIT

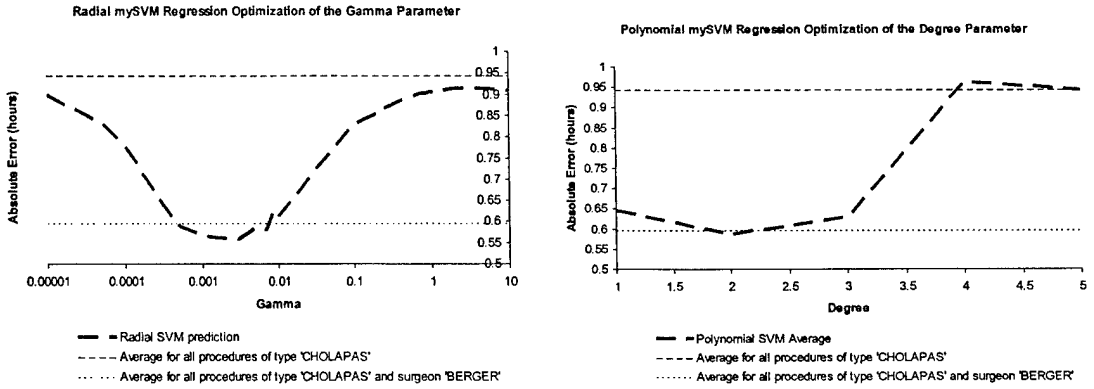
Executive Summary

Accurate operating room scheduling improves patient and staff satisfaction, and streamlines the utilization of costly hospital resources. OR directors from 200 hospitals nationwide agree that accurate estimation of surgery duration is among the most essential tools for successful operating room management.

We are creating a set of computational tools to improve operating room scheduling. In particular, we would like to provide OR administrators at MGH with accurate and timely information about the expected utilization, and suggestions for beneficial schedule changes. The most crucial function of these tools is accurately estimating the duration of surgeries.

Key Results

While funding for the past year was delayed to this year, we spent that time familiarizing ourselves with the domain of OR scheduling and evaluating the performance of machine learning approaches to solve the problem of surgical length prediction. We have shown that with careful parameter tuning, these algorithms are more accurate than the existing case length prediction by a few minutes on average.



Specific Aims

Specific Aim 1: Improve the accuracy of surgical length prediction.
Specific Aim 2: Present the information acquired through the first aim in a way that will help OR administrators make educated decisions daily.

Progress

Specific Aim 1: Improve the accuracy of surgical length prediction.
Experimentation with a range of standard machine learning algorithms has already created some degree of improvement in prediction accuracy.

Progress

Specific Aim 2: Present the information acquired through the first aim in a way that will help OR administrators make educated decisions daily.

The tool should use the expected surgical length predictions along with the variance of this prediction to create a probabilistic model of the ways an operating room schedule may be actualized. This tool should give accurate predictions of OR utilization, overtime, and delay before

the day begins, and it should be constantly updated as the day unfolds. Furthermore, the tool should allow for visualization and manipulation of OR schedules to improve patient and staff satisfaction, and to increase utilization.

Future Plans

Given that surgical lengths are highly variable, we propose two avenues attack to this problem:

- First, we hypothesize that the error of our predictions could be reduced if we can collect more relevant data that do not currently reside in the surgical scheduling database. For example, we are creating a system to allow surgeons to incorporate their estimate of case complexity and duration into our current prediction system.
- Second, we plan to quantify the variability of surgical procedures. This will be useful for calculating the expected utilization of operating rooms on a daily basis. Probabilistic models expose a richer depiction of the distribution of possible times, rather than a fixed estimate, which is inherently error-prone.

Metrics

Personnel working on this project:
Leslie Pack Kaelbling, Professor, MIT
Dr. David Rattner, M.D., MGH
Sam Davies, Masters Degree Candidate May 2004, MIT

This work is being done in collaboration with the CIMIT Outcomes project and the Operating Room of the Future group.

This work will be incorporated into an MIT master's thesis, and may be published in a journal of artificial intelligence or hospital management.

Publications and Presentations

Diane Matteo and Steven Breslawski. "Operating Room Scheduling: Factors to Consider" *AORN Journal* 59:3, March 1994.

ORF Outcomes

Principal Investigator: James Stahl, M.D., MGH

Executive Summary

The Technology Assessment and Outcomes Analysis Program began its collaboration with the ORF project team in December of 2000. A computer simulation model was developed to analyze the ORF using process flow and financial data from the current operating room environment. The results of this analysis were presented to the executive committee of the MGH Department of Surgery in January 2001 and to the national meeting for the Society for Medical Decision Making, October 21-24, San Diego CA 2001. The paper on this work has been resubmitted and is under review at Medical Decision Making. Based on this work a collaborative SBIR (# R43 RRO18076-01) with Radianse, Inc (formerly, Sentinel Wireless) was submitted and accepted by the NCRR.

Key Results

Prospective data collection for ORF process outcomes completed June 2003. 124 patients were consented and enrolled.
Phase 2 of ORF satisfaction survey completed at end of July 2003
Phase 1 of SBIR (# R43 RRO18076-01) completed. Validation of IPS in OR environment completed 7/29/2003
Phase 1 report and submission for Phase 2 moneys in process – due December 2003
Project progress summary

Specific Aim

Measurement of ORF outcomes.

Progress

The handheld data gathering tool using IPAQ hardware and SQL database software (ABCDb™) developed by James Stahl has been cross validated across data-gatherers. These data have been used to examine the standard surgery scheduling system (DSS) for staff enter, start and stop times and to validate the Radianse indoor positioning system.

Phase 2 of the survey of staff satisfaction and stress has been completed. This survey is aimed to assess the effect of introducing new technology into the OR. This survey is designed to poll both ORF staff and persons in similar jobs across the OR quarterly. These latter serve as controls for exposure to the intervention specifically the ORF and its technologies. The rationale for conducting this survey every quarter to control for secular trends and to look for adaptation

Radianse data and handheld data now regularly feed into project database site. However, further progress on the ORF project database is slow. Though staff has been assigned to develop linkages between vendor databases and the project database, vendors have been slow to share the requisite information.

Cost-effectiveness analysis

The finance department and James Stahl have initiated and are midway in completing a complete financial analysis of the ORF. This has required setting up a unique cost center for the ORF to do microcosting and extensive literature review and analysis for the top down analysis. This is expected to be completed at the end of October 2003

Future Plans

The Radianse indoor positioning system is slowly being expanded in the MGH OR to provide automatic process data collection.

Metrics
Personnel working on this project:
James Stahl, M.D.
Warren Goldman, M.D.
Marie Egan, R.N.

Publications and presentations
Stahl JE. Identifying and characterizing how Anesthesia personnel learn and adapt to a new technology in the OR – being presented SMDM 10/2003.

Stahl JE, Sandberg W, Goldman JM, Wiklund RA, Rattner D. A Living Laboratory: The Center for Integration of Medicine and Innovative Technology OR of the Future Project– being presented ASA 10/2003.

Sandberg W, Stahl J, Goldman J, Rattner D. Redesigning Anesthesia Care for an Operating Room of the Future: Implementation and Preliminary Results – being presented ASA 10/2003.

Patient Safety Project
Principal Investigator: Keith Isaacson, M.D., MGH/NWH

Executive Summary
CIMIT and Mobile Aspects are working together to tag and track patients utilizing Mobile Aspects RFID technology as they go into hospital operating rooms. This advance is expected to increase the level of patient safety by instantly alerting all clinicians to the identity of the patient, the procedure to be done, and any health risks. The goal of the first phase is to prove the concept of tagging an inanimate object as it goes through a hospital doorway and display information about the patient on to a monitor in the room.

In addition, the two groups are working together to establish a method for storing pertinent information about the patient on to his / her tag so that it can be displayed. The deliverables for this project include building the patient database and showing a feasibility trial of passively identifying a patient in the ORF at Massachusetts General Hospital in order to demonstrate the systems abilities.

Key Results
The investigators have collaborated to put together a schema for the patient database. Working together the investigators have identified the key information that must be stored for each patient. This was performed by doing a walk through of the flow of needed information from admitting to discharge for a patient. The CIMIT investigators provided all the needed information that should be stored for the patient, when it would be stored and when it would be retrieved.

Mobile Aspects has also been able to develop a system for automatically identifying a patient as s/he goes through an operating room door. Working with the patient information database developed, the system automatically picks up the patient data and displays the pertinent information on a computer monitor.

The system has now been readied for integration with the Karl Storz OR1 system utilized in Massachusetts General Hospital's Operating Room of the Future. The integration will be tested during a proof of concept in the ORF to occur in mid-October, 2003.

Specific Aims
Specific Aim 1: Develop a patient information database which can be accessed in real time to display pertinent information about a patient on a screen.
Specific Aim 2: Perform a proof of concept of passively identifying a patient as they pass on a gurney through an operating room doorway and displaying information about that patient on a screen.

Progress
Specific Aim 1: Develop a patient information database which can be accessed in real time to display pertinent information about a patient on a screen.

The patient information database has already been developed with the input of CIMIT investigators. The database contains rows for information such as name, surgery, laterality, physician, allergies and blood type. It also contains a row for a picture of the patient for positive patient identification protocols. In addition a standard is currently being develop to efficiently house the basic patient information on the RFID tag to be placed on the patient. The rest of the information required for the patient will be pulled from the database with a unique identifier.

Ninety percent of the database has been developed and can be accessed in real time. In addition, the patient picture can also be accessed and displayed in real time. It must now be tested how fast the information will be displayed with an integration with the Karl Storz OR1 system.

Progress

Specific Aim 2: Perform a proof of concept of passively identifying a patient as they pass on a gurney through an operating room doorway and displaying information about that patient on a screen.

The investigators have already proved the concept of passively identifying an inanimate object through a doorway at Mobile Aspects R&D labs. The effect of doing the same operation in an operating room setting must now be studied.

Future Plans

The software and hardware will be tested in a proof of concept at the ORF at Massachusetts General Hospital. The system will be integrated with the OR1 system of the Karl Storz system being used in the ORF. In addition the RFID hardware will be placed in the ORF and the tag will be placed on a real gurney with a CPR dummy. The feasibility demonstration will be videotaped and recorded. The usability and other environmental effects of being tested in a real operating room will be noted to make improvements to the system. This could be from complex radio frequency effects to simple user interface changes.

Metrics

Personnel working on this project:
Keith Isaacson, M.D.

Publications and Presentations

In preparation.

Simulation Program

Medical Simulation
Principal Investigator: Steven L. Dawson, M.D., MGH

Executive Summary
The Simulation Group had an eventful FY '03. Three new projects began-EVE, SITU and vocal cord tissue measurement. As a direct response to an urgent government request, one new project was proposed, conceived, designed, and built within a ten week period, and subsequently field-tested in Korea, on time and on budget (SITU). Significant new scientific information was created through the EVE endovascular project and that work will become the basis for separate NIH and NSF grant proposals in the first quarter of FY '04. The group added two new members to supplement expertise in mathematical modeling and programming, while at the same time adjusting to the reduced funds for FY '04 in our CIMIT research support, due to changes in the CIMIT research emphasis. Thus our major challenge in FY'04 will be to secure sufficient funds to continue our existing research and team structure and, ideally, to grow sufficiently to allow consistent effort to be devoted to each research project.

Key Results
- In response to an Army request for a smallpox inoculation training system, we successfully proposed and delivered SITU, a smallpox inoculation training system.

Specific Aim
To develop procedural medical simulation strategies and devices.

Progress
- With the assistance of LT COL Mary Parker, MD, we delivered a number of the SITU units to the Preventive Medical team at the Army's 2nd Infantry Division in Camp Casey, Dongduchon, Korea. Over the last four months of the fiscal year, Army personnel in Korea were instructed in proper inoculation technique and personnel care using the SITU system.
- We also began a new collaboration with the Massachusetts Eye and Ear Infirmary, to design instruments to measure the tissue properties of the human vocal cords and then to perform those measurements in conjunction with Dr Stephen Zeitels, world renowned laryngologist at the MEEI, as a method of restoring normal speech to the thousands of patients who have lost the ability to speak normally. Although this work is supported by funds outside the TATRC grant to CIMIT, our ability to step up and perform this work is a direct result of the existing research base which the TATRC funds enable;
- We began a major effort to create a new state-of the art in medical simulation using flexible surgical instruments, such as catheters, balloons, and stents. For this project, called "EVE", we will create an anatomic test bed mimicking the vascular system of the human brain, with the goal of teaching medical personnel how to quickly and safely treat stroke within the "Golden Hour" for initiation of therapy. As a secondary result of this work, our new flexible instrument models will allow even more realistic simulation of scenarios in other anatomic areas;
- We demonstrated the CELTS Surgical Skills Training System to the members of the SAGES community (Society of American Gastrointestinal Endoscopic Surgeons), the leading American laparoscopic surgical forum as a part of the Learning Center at the SAGES annual meeting;
- We began the CELTS validation studies at the Shapiro Learning Center at Beth-Israel Deaconess Medical Center in Boston, MA.
- During the last 12 months, we added Dr Xunlei Wu to our team as a full-time member with expertise in mathematical models and programming;

- We also supported Mr. Vincent Pegoraro, a French Master's level student for his Master's thesis in visualization and graphics ("*Simulation of X-ray and Fluoroscopic Images In Real-Time*", Polytech'Lille);
- We published seven peer-reviewed papers;
- We filed two provisional patents and one invention disclosure;
- We presented peer-reviewed and invited lectures at numerous regional, national and international meetings, including
    - Medicine Meets Virtual Reality 11, Newport Beach, CA.
    - IEEE Ultrasonics, Ferroelectrics and Frequency Control Symposium, Honolulu, HI
    - ASME Summer Bioengineering Conference, Key Biscayne, FL
    - Symposium on Soft-Tissue Modeling and Surgical Simulation, Nice, France, and
    - ATACCC 2003, St. Pete Beach, FL

We thus completed two of the three deliverables projected in our FY '02 annual report- a surgical skills training system, and endoluminal tracking device.

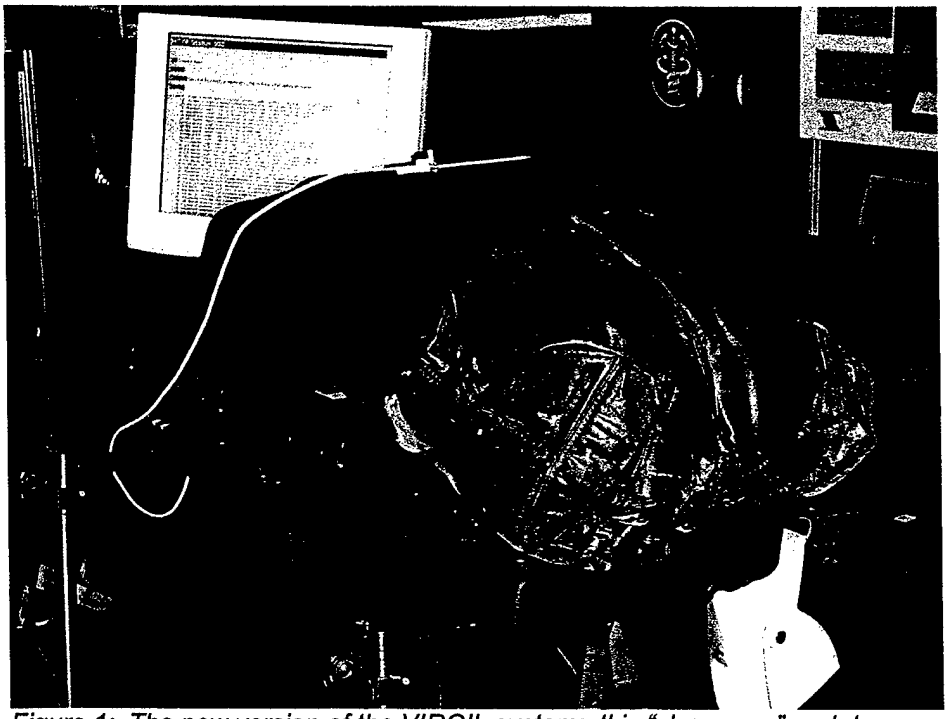


Figure 1: The new version of the VIRGIL system: this "classroom" prototype retains the full functionality of the original full mannequin VIRGIL system but eliminates the head, arms and legs. Significant improvements incorporated into the smaller version are improved collision detection, jsp-based GUI, wireless data transmission and data retrieval capabilities for validation, metrics and assessment of skills.

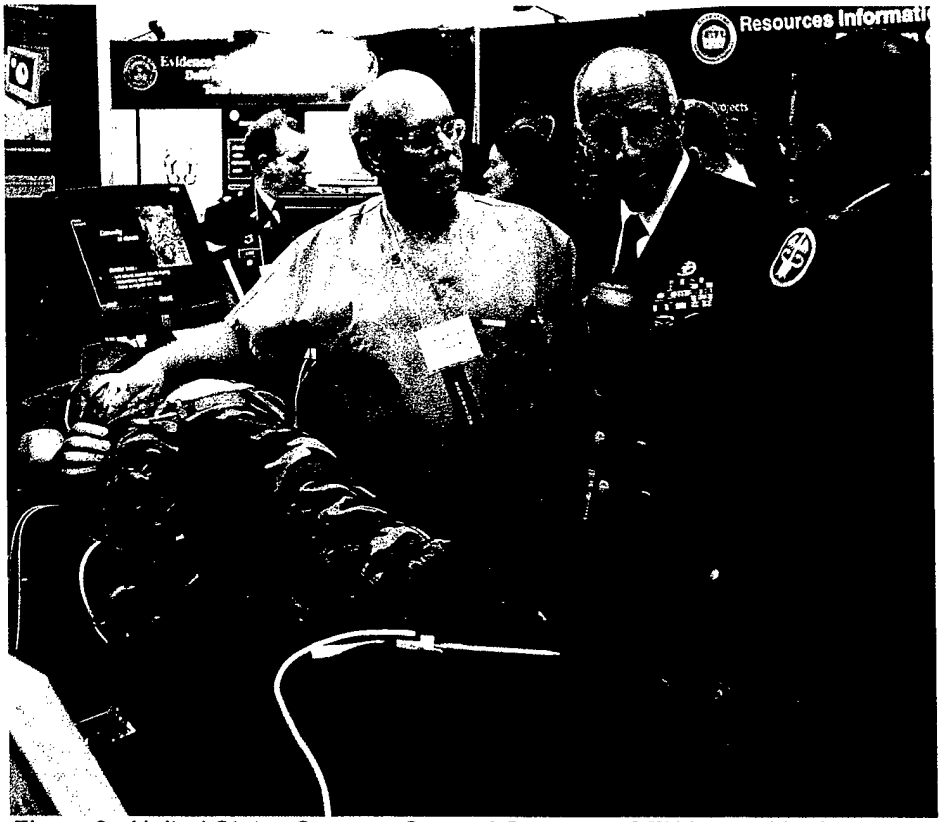


Figure 2: United States Surgeon General Carmona, GEN Lester Martinez—Lopez, Commanding Officer, USAMRMC, and Dr. Dawson discussing medical training using VIRGIL (background) and the new smaller VIRGIL system (foreground) at the 2002 AMSUS meeting, Louisville, KY, November 12, 2002.

Figure3: From left, LTG James Peake, United States Army Surgeon General, Admiral Richard Carmona, United States Surgeon General, Dr Dawson , and SGT Ray Anspach, USAF, reviewing the SITU system at the 2003 American Telemedicine Meeting in Orlando, FL, 26 April, 2003.

2nd Lt. Simon Strating, C Company, 702nd MSB and division environmental science officer, demonstrates proper smallpox vaccination procedure to medics of 1st Battalion, 506th Infantry Regiment. The medics practiced injection technique on a unique training arm that accurately simulates human anatomy.

Photo and caption from "Indianhead"- For the 2ID Community Volume 40, Number 18, September 5, 2003.

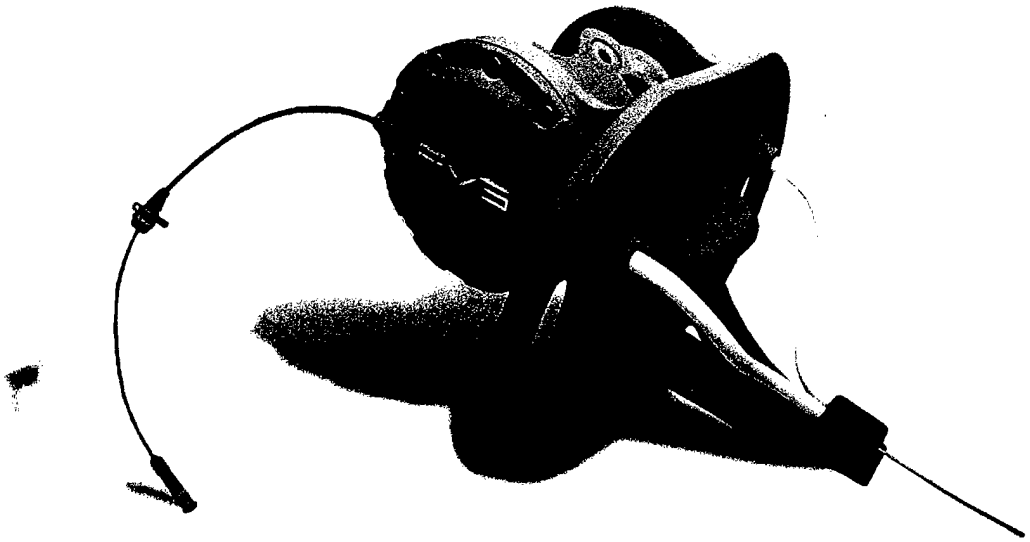
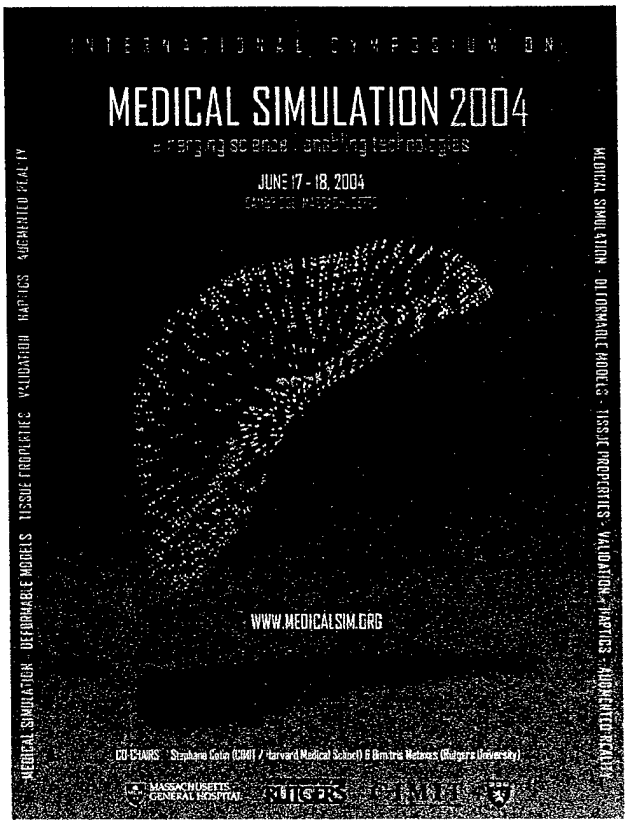


Figure 4: The EVE Tracking Device was developed as an elegant, simple solution to the problem of tracking flexible instruments in simulations. The system has no moving parts and permits both left and right-sided interactions with a mannequin. The design is undergoing testing in The Simulation Group. An Invention Disclosure has been filed on the system.



Future Plans

To continue collaborations and development of medical simulation strategies, systems and devices as above in Progress section of this report. International Symposium on Medical Simulation to be held in Cambridge, MA on June 17-18, 2004 (see flyer above).

Metrics

The following personnel are working on this project:
Steven L. Dawson, M.D.
Stephane Cotin, Ph.D.
Mark Ottensmeyer, Ph.D.
Paul Neumann, Ph.D.
Ryan Bardsley
Robert Waddington

Publications and Presentations

Master's Thesis, Mr. Vincent Pegoraro
Simulation of X-ray and Fluoroscopic Images in Real-Time,
Ecole Universitaire de Lille,
September, 2003.

Dawson, SL. A critical approach to medical simulation. Bulletin of the American College of

Surgeons, 2002; 87(11): 12-18.

Konofagou EE, Ottensmeyer MP, Agabian S, Dawson SL, Hynynen K. "Estimating localized oscillatory tissue motion for assessment of the underlying mechanical modulus," IEEE Ultrasonics, Ferroelectrics and Frequency Control Symposium, Honolulu, HI, Oct. 5-9, 2003, in press.

Kerdok A, Cotin SM, Ottensmeyer MP, Galea AM, Howe RD, Dawson SL. "Truth Cube: Establishing Physical Standards for Real Time Soft Tissue Simulation," Medical Image Analysis, vol. 7, pp. 283-291, 2003.

Kalanovic D, Ottensmeyer MP, Gross J, Buess G, Dawson SL. Independent testing of soft tissue visco-elasticity using indentation and rotary shear deformations. Proceedings of 11th Annual Meeting, Medicine Meets Virtual Reality, Westwood JD, Hoffman HM, Mogel GT, *et al* eds. IOS Press, 137-143, 2003

Stylopoulos N, Cotin S, Dawson S, Ottensmeyer M, Neumann P, Bardsley R, Russell M, Jackson P, Rattner D. CELTS: A clinically-based computer enhanced laparoscopic training system. Proceedings of 11th Annual Meeting, Medicine Meets Virtual Reality, Westwood JD, Hoffman HM, Mogel GT, *et al* eds. IOS Press 336-342, 2003

Manivannan M, Cotin S, Srinivasan M, Dawson S. Real-Time PC based X-ray Simulation for Interventional Radiology Training. Proceedings of 11th Annual Meeting, Medicine Meets Virtual Reality, Westwood JD, Hoffman HM, Mogel GT, *et al* eds. IOS Press, 233-239, 2003

E.E. Konofagou, M.P. Ottensmeyer, S. Agabian, S.L. Dawson, K. Hynynen. "Estimating localized oscillatory tissue motion for assessment of the underlying mechanical modulus," IEEE Ultrasonics, Ferroelectrics and Frequency Control Symposium, Honolulu, HI, Oct. 5-9, 2003, in press

Intellectual Property
United States Provisional Patent Application, 60/453,170
Stephane Cotin, et al.,
"A Software Based Implementation for Evaluating Surgical Performance Using Kinematic Analysis"
March 10, 2003

United States Patent Application, 60/462,674,
Steven L. Dawson, et al
"Inoculation Kit"
April 14, 2003

Massachusetts General Hospital Invention Disclosure, "An Optical Tracking and Haptics Device for Medical Simulation"

Tissue Engineering Program

Tissue Engineering: Microfabrication

Principal Investigators: Joseph Vacanti, M.D., MGH and Jeffrey Borenstein, Ph.D., Draper Laboratory

Executive Summary

Tissue engineering as a field is now emerging as a promising potential solution to the ever-worsening problem of the shortage of donor organs available for transplantation. This project is aimed at the development of a technology capable of producing replacement tissues and organs in the laboratory through the use of microfabrication processes. In the past year, we have developed and demonstrated microfabrication techniques capable of producing three-dimensional microvascular network scaffolds in biodegradable polymers for applications in renal and hepatic assist and replacement devices.

Major milestones in the design and fabrication of microvascular network structures have been achieved in the past year. In the area of design, models capable of providing uniform lining of cells along channel walls have been generated, leading to a new generation of vascular network designs with characteristics mimicking physiological systems in all key respects. In the area of microfabrication, the focus has been on the development of reproducible methods and procedures for the construction of three-dimensional microfluidic networks made using the biodegradable polymer PLGA. These new processes control temperature, pressure and alignment so that devices are produced more rapidly and without flaws such as leakage and occlusion during the bonding process. Finally, novel methods for control of fluid and metabolite flow between cell-containing chambers have been invented and demonstrated.

Key Results

Our key accomplishments over the past year include: the next generation design model has produced physiological values for shear in capillary networks; rapid, repeatable process for three-dimensional scaffold construction has been developed and prototype processing equipment built; numerous PLGA microvascular networks with as many as 10 layers and no leakage have been built and delivered to the laboratory for cell culture and testing; and a novel method for the separation of endothelial and organ-specific cellular layers in microdevices has been invented and is currently being demonstrated

Specific Aims

Specific Aim 1: Develop computational methods for the design of three-dimensional vascular networks, utilizing fluid dynamic models described in the Vacanti report.

Progress

A fluidic network can only be considered appropriate for use as a tissue-supporting vasculature if the network satisfies a variety of criteria. The two most important criteria are that the network distribute blood throughout the organ, and that the shear force applied by the blood to the wall of the vessels remain constant throughout the network. Deviations in the shear will inhibit cell growth (low shear rate) or cause cell death and inhibit adhesion (high shear rate). The literature contains many instances where groups have attempted to design constant-shear networks, either with no success or with success only in trivially small networks. In the past year, we have developed a novel iterative algorithm capable of designing the organ-scale constant-shear networks necessary for implantation. This algorithm has been used to design a two-dimensional network which we have fabricated and are now testing.

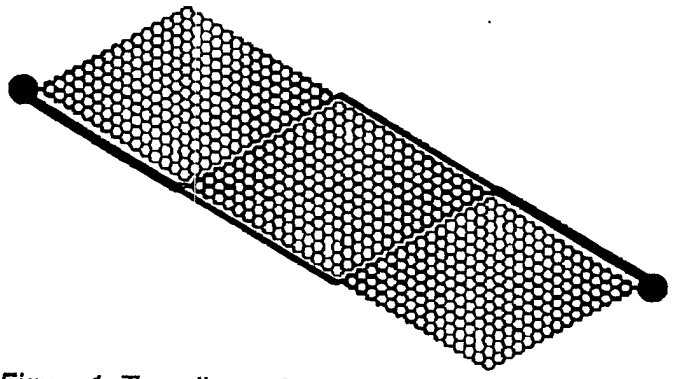


Figure 1. Two-dimensional constant-shear network

The aim of the testing is to verify that the theoretical model's predictions are accurate. Measurements are made in the network using Dr. Johannes de Boer's Optical Coherence Tomograph (OCT). This device can measure flow velocities, flowrates, and shears within the network without disturbing flow.

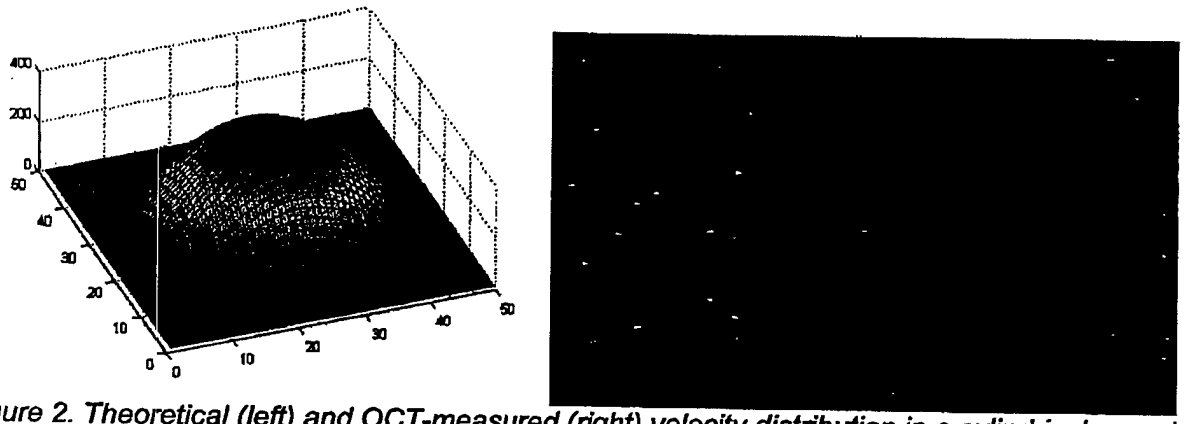


Figure 2. Theoretical (left) and OCT-measured (right) velocity distribution in a cylindrical vessel

We are currently using the new algorithm to design full three-dimensional networks. We are first using the model to create networks that mimic all aspect of natural vasculature.

Figure 3. Theoretical network mimicking physiological flow and geometry characteristics

Once networks that match physiology to a sufficient degree are generated, we can modify the networks so that they can be constructed by MEMS. The modified networks have the same flow, shear, and connectivity characteristics as natural vasculature, but the vessels are constrained to directions (either existing in the x-y plane or in the z-direction) that can be produced by replica molding .

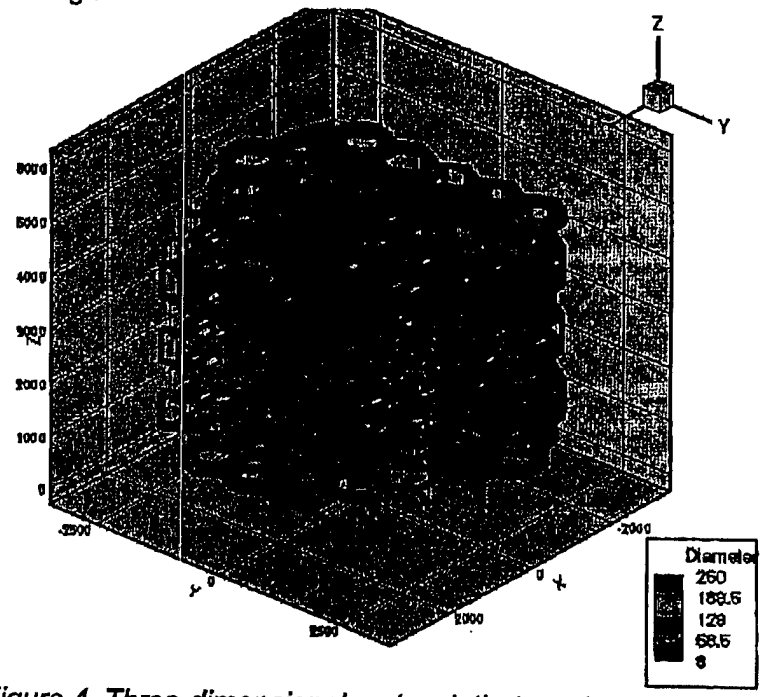


Figure 4. Three-dimensional network that can be fabricated using MEMS technology

Specific Aim 2: Transfer the microfabrication processes developed for Specific Aim 1 to biocompatible and biodegradable materials through the use of micromachined masters, compression molding and other techniques.

Progress

One of the most critical and challenging features of tissue-engineered scaffolds is the development of a mechanism capable of controlling transport between the various cell-containing compartments. For instance, endothelialized capillary beds will transport oxygen and nutrients to the sinusoid constructs in an engineered liver device, but larger blood components such as platelets and erythrocytes must be contained within the blood vessels. In the past year, a new and promising method for controlling transport across these chambers has been invented. This method, referred to as the "vertical pore" technique, builds the porous semi-permeable capability directly into the vascular layer, avoiding the requirement for insertion of a membrane layer between the vascular layers. This vertical pore technique represents a nanofabrication approach to the construction of the scaffolds, since the minimum feature size is on the order of 200 nanometers or less. Figure 5 below shows an SEM of a silicon master mold machined with the vertical pore geometry. This method will ultimately lead to scaffolds with much higher cell densities and greatly reduced quantities of polymer within the growing tissue.

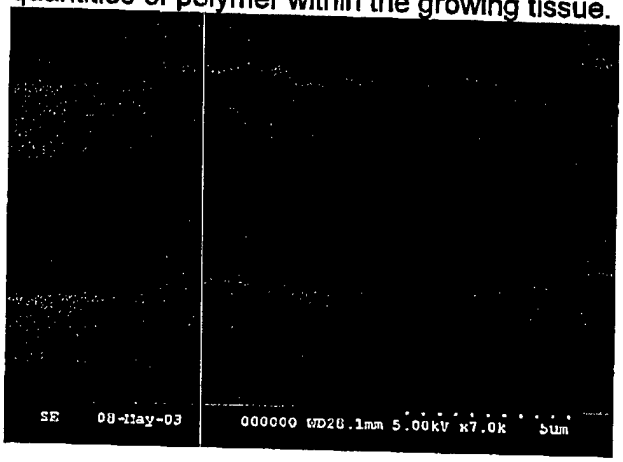


Figure 5. Silicon micromachined vertical pore master mold. Vertical step height is 200 nm.

Specific Aim 3: Scale microfabrication technology to enable manufacturable methods for producing three-dimensional constructs.

Progress

In the past year, previously demonstrated capabilities in the machining of micron-scale features in the biodegradable polymer PLGA have been further advanced, and a rapid and well-controlled process for the construction of multi-layer PLGA devices without leaks or occlusions in the channels has been demonstrated. Earlier work reported by K.R. King revealed that there is a well-defined process window for PLGA processing in which fusion bonding between layers can occur without suffering significant deformation of channels and other features. When scaling up to large numbers of layers, however, factors such as temperature uniformity become critical, and flaws in these larger devices are often observed. Brian Orrick and Mert Prince of Draper Laboratory have designed and constructed a process station for multilayer PLGA device builds, shown in Figures 6 and 7 below. This device has produced dozens of sealed PLGA microvascular networks, some of which contain as many as 10 layers, which have been tested and shown to be free of leaks and occlusions in the channels. This represents a major step towards the development of a manufacturable process for 3D scaffold production.

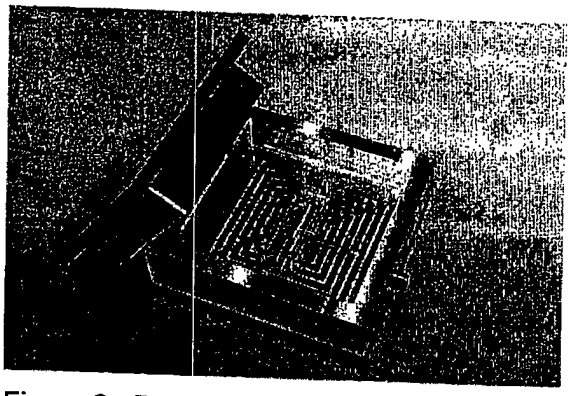


Figure 6. Demonstration of nanoporous filter.

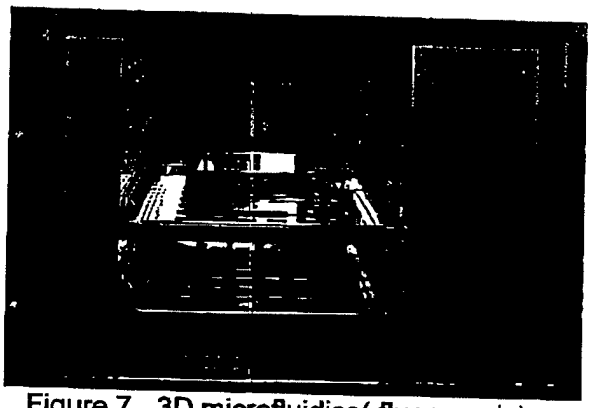


Figure 7. 3D microfluidics(fluorescein)

Future Plans

- In the next year, three-dimensional scaffolds built using PLGA will be constructed with the vertical pore technique, and suitable filtration for organ assist applications will be demonstrated.
- In the next year, the new models for capillary networks will be translated into vascular designs and used to construct multilayer devices for testing. The vertical pore method discussed below will be incorporated to create a design that includes both a vasculature and parenchymal network, mimicking the overall structure of a liver.
- In the coming year, three-dimensional devices suitable for renal filtration with and without cells will be constructed and tested.

Metrics

Personnel working on project:
Dr. Jeffrey T. Borenstein, Principal Investigator, Director, Biomedical Engineering Center, Draper Laboratory
Brian K. Orrick, BS, MBA, Microfabrication, Draper MEMS Fabrication Manager
Ernest Kim, MS, Mechanical Engineering and Biomechanics, Draper Laboratory Fellow
Mert Prince, Microfabrication Specialist
Isaac R. Costa, BS, Interdepartmental Science, Draper Research Technician
Eli J. Weinberg, BS, MIT Mechanical Engineering MS Student, Draper Fellow
Jennifer Blundo, BS, MIT Mechanical Engineering MS Student, Draper Fellow
Edward Barnard, MIT Materials Science Undergraduate, Draper Research Intern
Eleonore Pritchard, MIT Biology Undergraduate, Draper Research Intern

Degrees received during project
Brian K. Orrick, MBA, Boston College, 2002.

Publications and Presentations

Living Three-dimensional Microfabricated Constructs For The Replacement Of Vital Organ Function, J.T Borenstein, W. Cheung, L. Hartman, M.R. Kaazempur-Mofrad, K.R. King, A. Sevy, M. Shin, E.J. Weinberg, and J.P. Vacanti, Technical Digest for the Transducers 2003 Conference, 2003.

Microfabricated Microfluidic Biodegradable Systems For Vascularized Tissue Engineering Of Vital Organs: Design, Modeling, And Functional Testing , M.R. Kaazempur-Mofrad, J.T. Borenstein, W.S. Cheung, L.M. Hartman, E.J. Weinberg, M.Y. Shin, and J.P. Vacanti, BioNanoMicrosystems Conference.

Hepatocyte and Endothelial Cell Survival in a Tissue Engineered Human Liver Device with its own Vascular Network, Wing S. Cheung, Jeffrey Borenstein, Mohammed Kaazempur-Mofrad, Michael Shin, Alec Sevy, Katherine Kulig, Joseph P. Vacanti, American College of Surgeons.

Vascularized Tissue Engineering Of Vital Organs: Design, Computational Modeling And Functional Testing, M.R. Kaazempur-Mofrad, J.T. Borenstein, L.M. Hartman, W.S. Cheung, E.J. Weinberg, M. Shin, A. Sevy, and J.P. Vacanti, Engineering in Biology and Medicine Conference.

Development of an Implantable Tissue-Engineered Liver Device with a Vascular Network of Channels Co-cultured with Human Hepatocytes and Human Microvascular Endothelial Cells, Wing S. Cheung, Jeffrey Borenstein, Mohammed Kaazempur-Mofrad, Michael Shin, Alec Sevy, Katherine Kulig, Joseph P. Vacanti, American Society for Transplant Surgery.

Artificial Vasculature through a Microfabricated Biodegradable Elastomer, Yadong Wang, Christina Wilbert, M. R. Kaazempur-Mofrad, Kevin King, Jeffery T. Borenstein, Joseph P. Vacanti, Robert Langer, Engineered Tissue Growth Conference.

Design of a Single Capillary-Parenchymal Co-culture Bioreactor Using a Self-Assembling Peptide Membrane, E.S. Kim, M.R. Kaazempur-Mofrad, J.T. Borenstein, J.P. Vacanti, and R.D. Kamm, 2nd MIT Conference.

Numerical Model of Flow in Distensible Microfluidic Network, E.J. Weinberg, M.R. Kaazempur-Mofrad, J.T. Borenstein, 2nd MIT Conference,

Vascularized Tissue Engineering of Vital Organs: Integration of Endothelialized Beds with Parenchymal Tissues, Kaazempur-Mofrad MR, Borenstein JT, Cheung WS, Hartman LH, Weinberg EJ, Shin MY, and Vacanti JP. To appear in Proc. BMES Annual Fall Meeting.

A Novel Microfabricated Device for Microvascular Hemofiltration: Toward a Tissue Engineered Renal Replacement System, Kaazempur-Mofrad MR, Borenstein JT, Hartman L, Sevy A, Shin M, Weinberg EJ, and Vacanti JP, To appear in Proc. 6th Annual Meeting of the Tissue Engineering Society.

Tissue Engineering: Multiscaled Representation of Tissue Architecture and Function, Kaazempur-Mofrad MR, Weinberg EJ, Borenstein JT, and Vacanti JP. To appear in Complex Systems Science in BioMedicine, Deisboeck, Kresh, Kepler (Eds.), Kluwer Academic - Plenum Publishers, New York.

Polymeric Nanoparticles for Localized High Efficiency Gene Transfer

Principal Investigator: Robert Langer, ScD, MIT

Executive Summary

The safe and effective delivery of therapeutic genes remains a central challenge in the field of gene therapy. While the majority of current gene therapy protocols employ viral delivery systems, concerns regarding the safety of viral vectors have prompted many to look for synthetic alternatives. The long-term goal of this project has been to create a safe synthetic polymeric gene delivery system with high transfection efficiency for local delivery of plasmid DNA. The work conducted toward Specific Aim 1 in the past year has been directed toward the continued development of new polymeric materials for gene delivery and the development of a mechanistic understanding through which these materials mediate transfection. Using a semi-automated, high throughput system, we have synthesized and screened a 2350 member library of poly(β-amino ester)s for use as gene transfer agents. Polymers of interest have been resynthesized and characterized in great detail, providing new insight into structure/function relationships. The work conducted toward Specific Aim 2 in the past year has been directed toward the development of pH-responsive microspheres for use in DNA vaccine applications. We have developed microsphere formulations that are up to 4 orders of magnitude more effective at delivering DNA to antigen presenting cells (APCs). Both systems are now being optimized in anticipation of *in vivo* experiments.

Key Results

We have synthesized and screened 2350 poly(β-amino ester)s for their ability to deliver DNA in vitro. Using high throughput methods we have identified over 40 polymers capable of delivering DNA as better than the current state of the art polymeric gene delivery systems. Careful study of select hits has provided a new level of structure/function information. In addition, we have developed microsphere formulations that consistently exhibit 3-4 orders of magnitude increase in transfection efficiency over microparticles composed of PLGA alone. Furthermore, the microparticle formulations induce surface upregulation of activation markers in dendritic cells while PLGA formulations fail to generate signs of maturation. We are actively preparing for both *in vivo* experimentation and commercialization.

Specific Aims

Specific Aim 1: To synthesize a library of structurally-related poly(β-amino ester)s and apply the library to high-throughput screening assays to more rapidly identify degradable, DNA-complexing materials and efficient transfection vectors.
Specific Aim 2: To encapsulate DNA within pH-sensitive microspheres formed from poly(□-amino ester)s.

Progress

Specific Aim 1: To synthesize a library of structurally-related poly(β-amino ester)s and apply the library to high-throughput screening assays to more rapidly identify degradable, DNA-complexing materials and efficient transfection vectors.

We have developed a large library of degradable polymers for gene delivery using semi-automated, robotic means. Synthesis is straightforward (Figure 1), and a diverse collection of monomers is commercially available (Figure 2). Initial screening was repeated in triplicate under a variety of conditions. These high throughput screens have revealed a number of highly efficient gene delivery polymers (Figure 3). Resynthesis of two key polymers C28 and C36, at multiple molecular weights has revealed new insight into how length and end termination effects transfection (Figure 4), and cytotoxicity (Figure 5). These have been synthesized under conditions

that allow us to control polymer length and have all been characterized using GPC to determine their molecular weight.

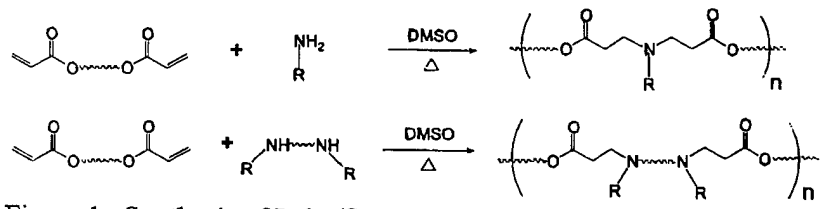


Figure 1. Synthesis of Poly (β-amino ester)s. Poly (β-amino ester)s are synthesized by the conjugate addition of primary (equation 1) or bis(secondary amines) (equation 2) to diacrylates.

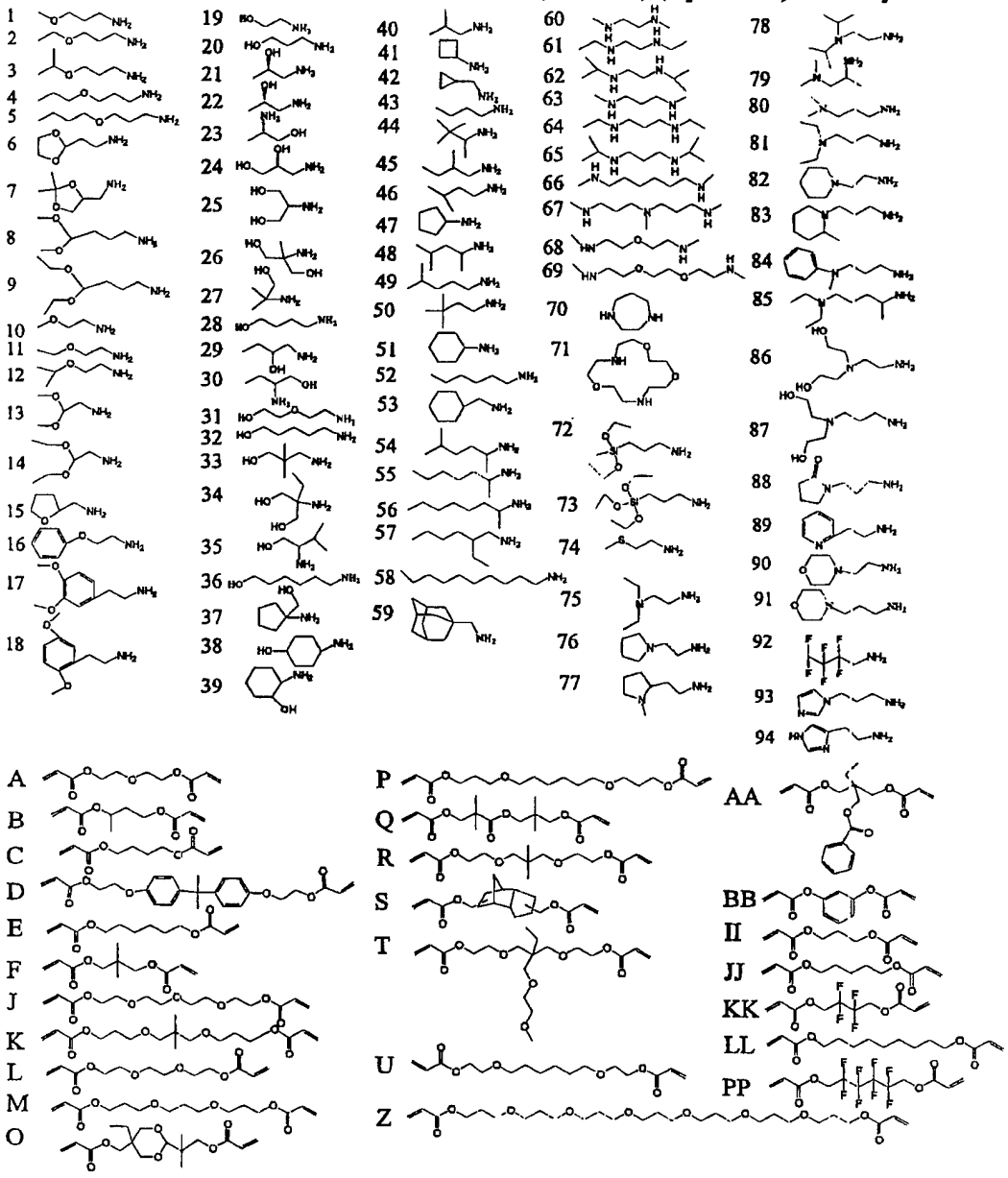


Figure 2. Amino (A) and diacrylate (B) monomers.

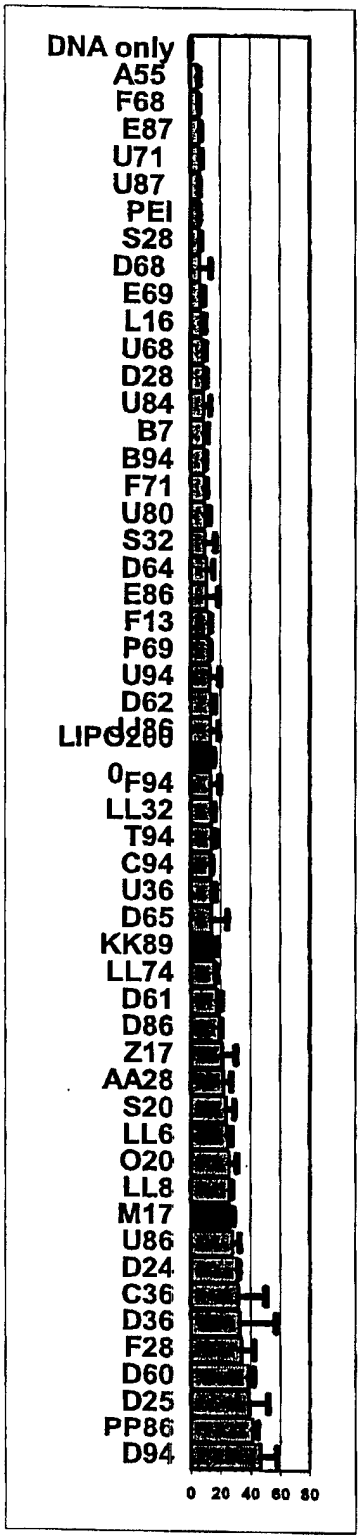


Figure 3. Optimized transfection efficiency of the top 50 polymers relative to PEI and lipofectamine2000. Polymers were tested as described in experimental protocols. In the first

broad screen N:P ratios of 40:1, 20:1 and 10:1 were tested. The top 93 were rescreened at six different N:P ratios equal to: (the optimal N:P ratio from the first screen) x 0.5, 0.75, 1.0, 1.25, 1.5, and 1.75 in triplicate. Control reactions are labeled in Red, and polymers that did not bind DNA in a gel electrophoresis assay are shown in black.

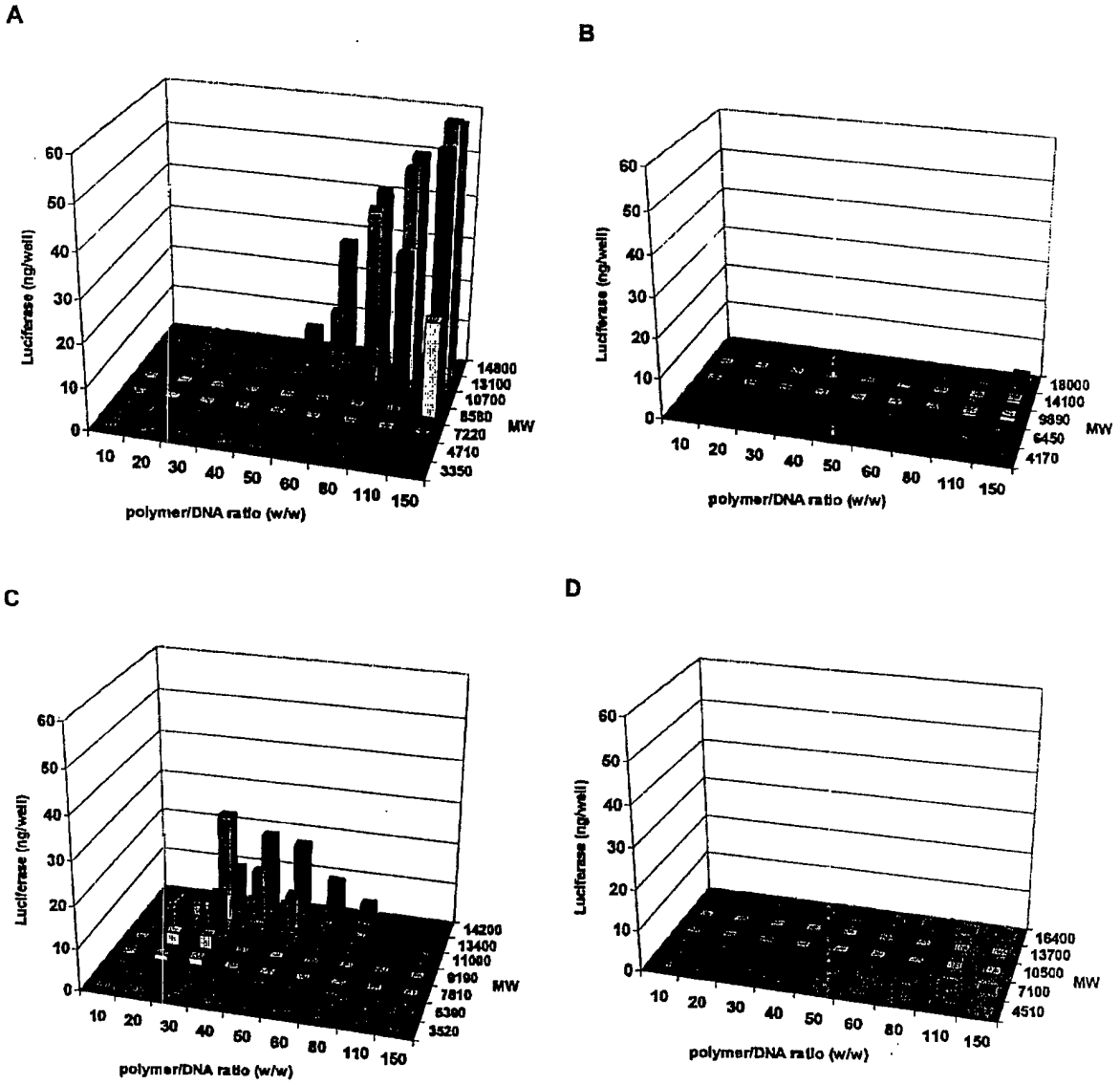


Figure 4. Luciferase transfection results for C28 and C36 as a function of polymer molecular weight, polymer/DNA ratio (w/w), and polymer end-group. (A) Poly-1, amine-terminated chains; (B) Poly-1, acrylate-terminated chains; (C) Poly-2, amine-terminated chains; (D) Poly-2, acrylate-terminated chains

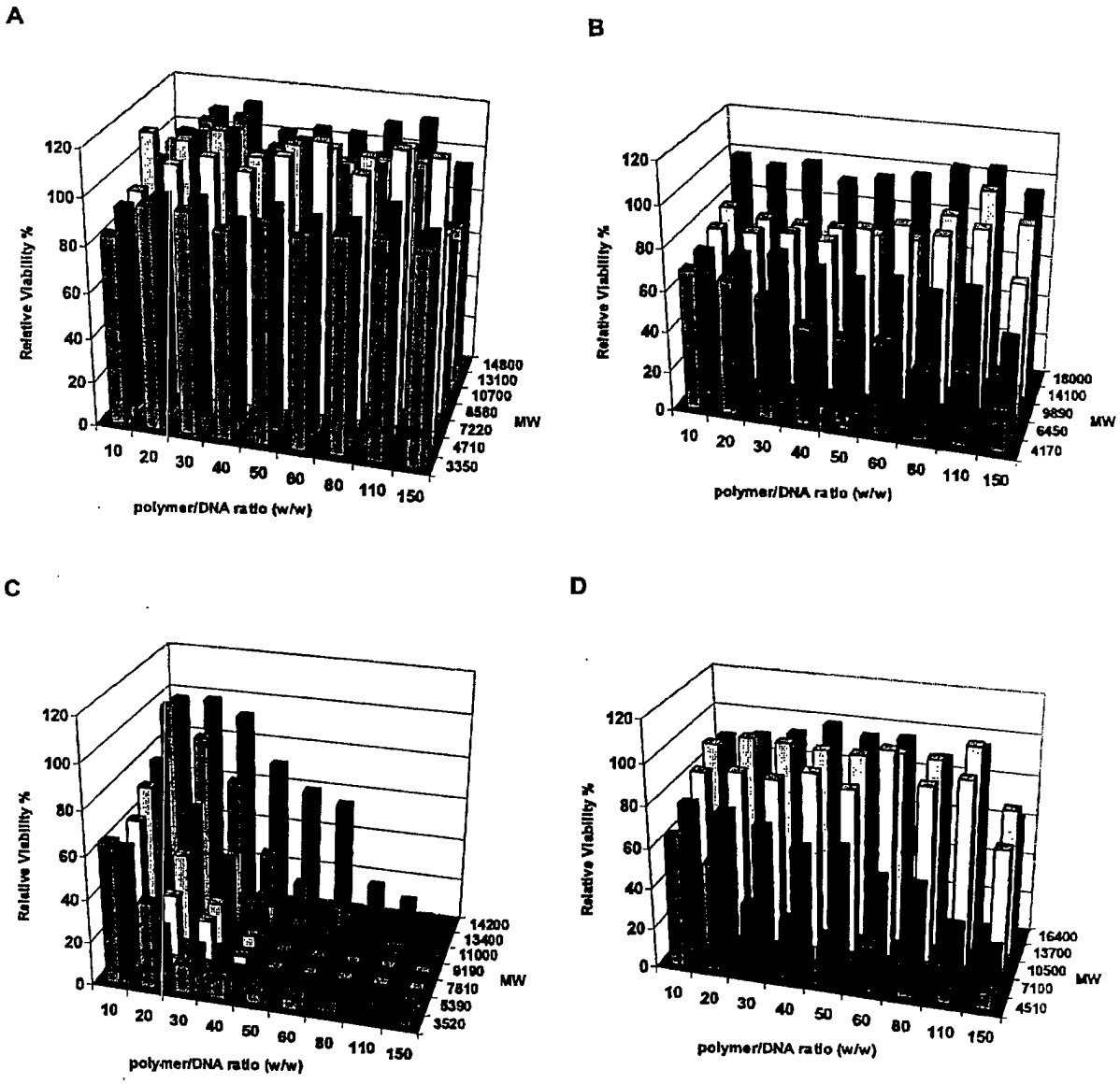
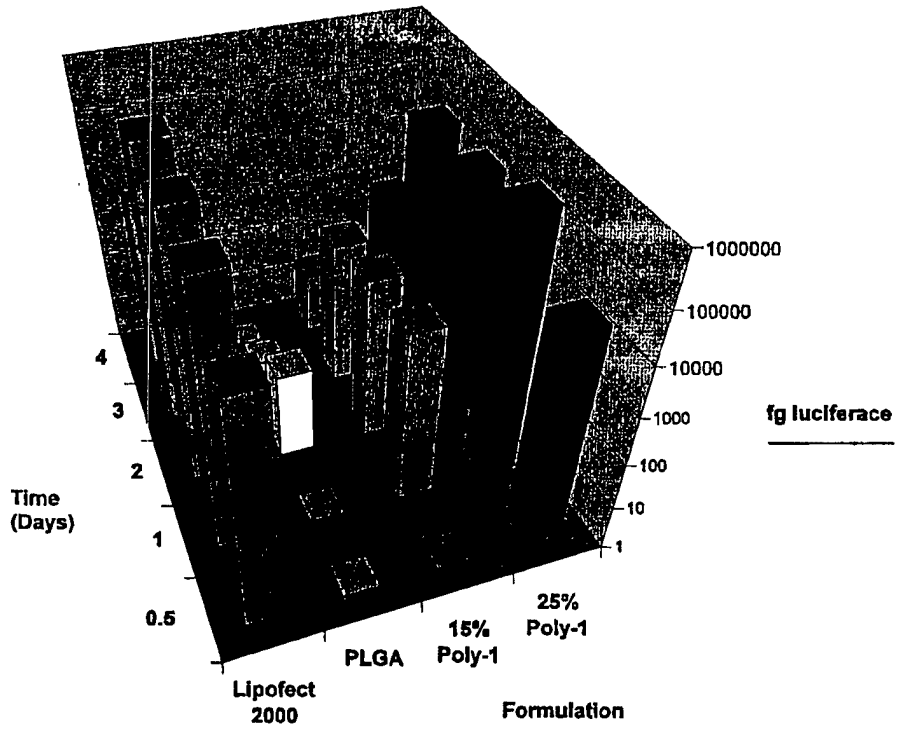


Figure 5. Cytotoxicity of polymer/DNA complexes prepared using C28 and C36 as a function of polymer molecular weight, polymer/DNA ratio (w/w), and polymer end-group. (A) Poly-1, amine-terminated chains; (B) Poly-1, acrylate-terminated chains; (C) Poly-2, amine-terminated chains; (D) Poly-2, acrylate-terminated chains.

Progress

Specific Aim 2: To encapsulate DNA within pH-sensitive microspheres formed from poly(β-amino ester)s.

This past year the team used a pH sensitive poly(β-amino ester), poly-1, to encapsulate DNA for use in genetic vaccines. We have developed microsphere formulations that consistently exhibit 3-4 orders of magnitude increase in transfection efficiency over microparticles composed of PLGA alone. Furthermore, the microparticle formulations induce surface upregulation of activation markers in dendritic cells while PLGA formulations fail to generate signs of maturation. We have completed in vitro studies and are preparing for *in vivo* efficacy testing.



B

Figure 6: Transfection of firefly luciferace into P388D1 macrophages using Poly-1/PLGA pCMV-Luc plasmid microspheres. Results are displayed as femptograms of luciferace (determined by luminescence assay) per mg of total protein (determined by BCA colorimetric assay) on the Z-axis vs. time (Y-axis) and formulation (X-axis). Concentrations of microspheres incubated with the cells were B. 50(µg/ml). An optimal formulation of Lipofectamine 2000 (0.8:1 Lipofectamine:DNA) is displayed in blue as a positive control in each plot. 25% Poly-1 formulations (red) consistently performed at par with the Lipofectamine positive controls while 15% Poly-1 formulations (pink), although lower than 25% formulations, consistently performed at a higher level than PLGA microparticles (white) at luciferace transfection.

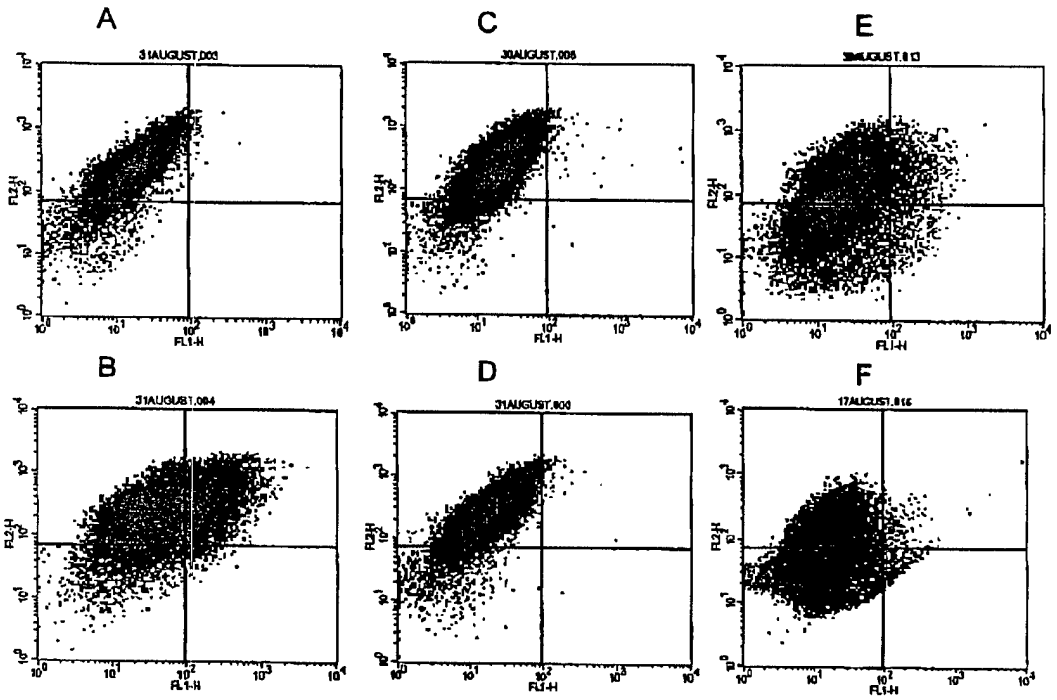


Figure 7: Activation of antigen presenting cells by incubation with Poly-1 microsphere formulations as indicated by cell surface expression of maturation markers. Expression of F4/80-R-Phycoetherin is shown on the y-axis log scale and expression of MHC-Class II-FITC on the x-axis log scale after incubation of Jaws II dendritic cells with microspheres for 1 day (A,C, E) and 3 days (B, D, F). Untreated control exhibited an immature phenotype indicated by low levels of MHC-Class II and high levels of F4/80 (A). Cells incubated with a cocktail of cytokines demonstrated a phenotype typical of matured cells with a higher surface expression of MHC Class II and a lower expression of F4-80 (B). PLGA microsphere treated (50µg/ml) cells appear to have an immature phenotype after 1 and 3 days of incubation (C & D), while cells incubated with 25% Poly-1 / 75% PLGA(50µg/ml) microsphere formulations are activated as indicated by downregulation of F4-80 and upregulation of MHC class II at both time points (E, F).

Future Plans

1) Continued resynthesis and analysis of hit polymers in gram scale in preparation for *in vivo* experimentation and commerclalization, and
2) The next step in assessing the efficacy of the pH-sensitive microsphere systems as a genetic vaccine is to assay the efficiency *in vivo*

Metrics

Personnel working on project:
Akin Akinc, received pHD in 2003, now staff researcher at Al Nylum
Daniel Anderson, Research Associate
Jason Fuller, Graduate Student
Ali Khademhosseini, Graduate Student
Steven Little, Graduate student
David Lynn, Assistant Professor, University of Wisconsin

Publications and Presentations

Akinc, A. B., Anderson D. G., Lynn D. M., and Langer R. Synthesis of Poly(β-amino esters) Optimized for Highly Effective Gene Delivery. (*Bioconjugate Chemistry*, in press)

Jon S. Y., Anderson D. G., and Langer R. Poly(aminoalcohol esters) As Potential DNA Vectors with Low Cytotoxicity (*Biomacromolecules,* in press).

Anderson, D. G., Lynn D. M., and Langer R. (2003) Semi-automated synthesis and screening of a large library of degradable cationic polymers for gene delivery. (*Angewandte Chemie,* 42, 3153-3158).

Akinc, A. B., Lynn D. M., Anderson D. G., and Langer R. (2003) Parallel Synthesis and Biophysical Characterization of a Degradable Polymer Library for Gene Delivery. (*JACS*, 125(18), 5316-5323).

Nanofibrous scaffolds for cartilage regeneration
Principal Investigator: Sonya Shortkroff, Ph.D., BWH

Executive Summary
Nanotechnology has promoted investigations into the use of nano-particles for biomedical applications such as drug delivery, biosensors and coatings or surfaces for implantable biomaterials. Nanofibrous materials have been investigated for their usefulness to the textile industry and for wound dressings in the biomedical field. This project seeks to investigate nanofibrous biomaterials as cell seeded scaffolds for tissue engineering applications based on the hypothesis that nanofiber sized scaffolds will simulate the extracellular environment and therefore will be conducive to cell homeostasis and phenotypic expression and synthesis of extracellular matrix components.

Nanofibrous meshes have been produced by electrical spinning of a polymer onto a surface. By altering certain parameters in the electrospinning process, three dimensional polymeric scaffolds can be produced with defined fiber diameters in the nanometer or the micrometer range. Using electrospinning technology, this project tests the hypothesis that nanofibrous scaffolds provide optimal structures for tissue engineering. The potential use of cell-seeded nanofibrous scaffolds for tissue or organ repair and regeneration has widespread application. To test the hypothesis, chondrocyte seeded nano- and micro-sized fibrous scaffolds for cartilage regeneration will be investigated *in vitro* and by *in vivo* implantation in an animal model system.

Key Results
As our goal was to consider the effects of varying fiber diameters of scaffolds for cartilage tissue engineering on maintenance of phenotypic attributes of the chondrocyte, it was of prime importance that the electrospun scaffolds have distinct fiber size ranges. By manipulating the various parameters we were able to produce electrospun PCL scaffolds with uniform fiber diameters in three size ranges (450 nm, 2 □m and 7 □m). Our next challenge was to assure adequate seeding of the cells onto the fibrous scaffolds. To this end, we have identified cell-seeding techniques that provide uniform distribution and 90-95% effective adhesion of the cells.

Specific Aims
Specific Aim 1: To determine the effects of fiber diameter on chondrocyte adherence and cell morphology and was contingent on production of scaffolds with uniform fiber diameters.
Specific aim 2: To examine the effects of fiber diameter on chondrocyte proliferation and matrix production *in vitro* in 2-6 week culture.

Progress
Specific Aim 1: To determine the effects of fiber diameter on chondrocyte adherence and cell morphology and was contingent on production of scaffolds with uniform fiber diameters.
Scaffolds: Polycaprolactone electrospun scaffolds were produced under the direction of Professor Greg Rutledge at MIT. By altering the spinning parameters, scaffolds were prepared with mean

fiber 0.1-0.8μm 1-3μm 7-10μm diameters of 0.45, 2.0 and 7.0 μm, as determined by scanning electron microscopy image analysis.

Cell Adhesion

Bovine articular chondrocytes were placed in Dulbecco's Modified Eagle/Ham's F-12 Medium containing 10% fetal bovine serum, 1% penicillin/streptomycin solution and 50μg/ml ascorbic acid. At a concentration of $1x10^7$ cells/ml, 20 μl of cells were seeded with a micropipettor onto the electrospun polycaprolactone scaffolds and the percent of cell adhesion was determined by image analysis. Because of the great variability between samples, fiber size had no significant effect on the number of cells adherent to the scaffolds (Fig. 1). By extrapolation, the total number of cells accounted for 25-40% of the seeding density.

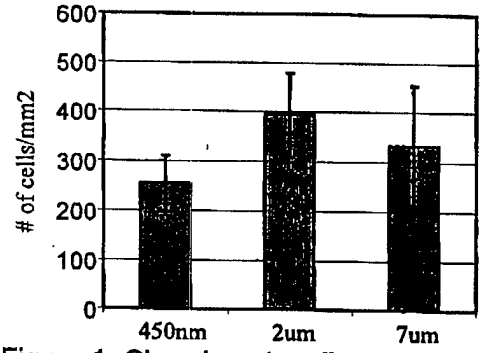


Figure 1: Chondrocyte adherence to varied PCL fiber sizes after 1 hour

At one hour, there was no difference in cell morphology as cells on all three fiber-diameter scaffolds presented a rounded shape. However, at 24 hours a morphologic difference was observed between the three fiber sized scaffolds. Cells on the nm fibers had a polygonal shape with multiple fiber attachments, while the cells on the 2 micron fibers retained more of a rounded to polygonal shape and the cells on the 7 micron fibers were elongated to polygonal and tended to attach and encircle a single fiber or attach at the intersection of several fibers with multiple attachments (Fig.2).

Figure 2: Chondrocytes seeded in medium onto PCL scaffolds

Optimization of Seeding Technique

Because the number of cells adherent to the scaffolds accounted for less than 50% of the total seeding volume, we embarked on a study to improve the static seeding technique. Rather than seeding the cells in traditional culture medium, we investigated placing the cells in a more viscous solution that also would facilitate adherence. Utilizing various concentrations of fibronectin in culture medium, we placed cells on 7 μm scaffolds and incubated the adherent cells in the presence of tritiated thymidine. There was a significant increase in the number of adherent cells when fibronectin was used as the seeding agent (fig. 3).

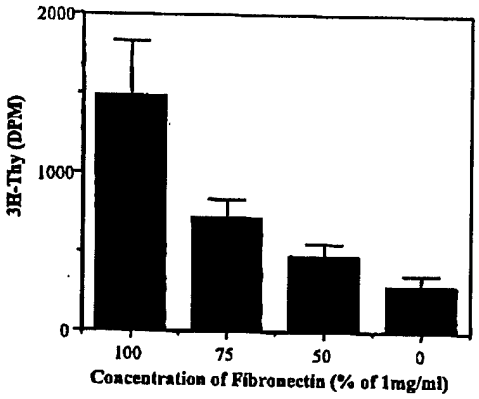


Figure 3.

When seeded using fibronectin, the number of cells adherent on all three types of scaffold increased to 500-1000 cells/mm^2 and accounted for up to 90% of the seeding density (Fig.4). However, there was a distinct preference for the 2□m fiber scaffolds. Morphology of these cells also was demonstrably different from the chondrocytes seeded with media.

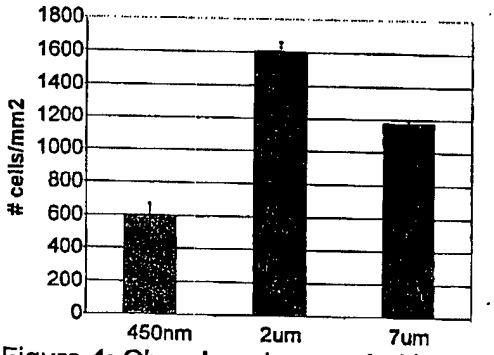


Figure 4: Chondrocytes seeded in FN onto PCL scaffolds

Cells on the 450nm scaffolds had both round and elongated cells while the cells on the 2□m and the 7μm scaffolds displayed a rounded shape (Fig. 5). The significantly lower cell number on the 450nm scaffolds could be attributed to difficulty in manipulation of these scaffolds. Production of the nanometer sized scaffolds yielded meshes with thicknesses of 50-100 microns, which tended to fold on seeding and interrupted the contact angle of the cell-loaded FN droplet. Fibronectin also coated the fibers and was observed as gray areas associated with the cells in all cases.

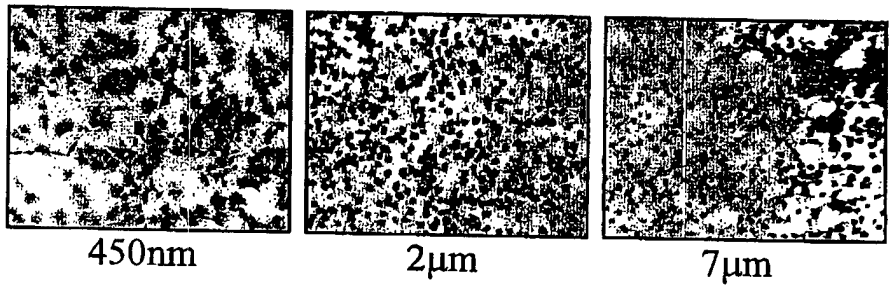


Figure 5: Chondrocytes seeded with FN onto varied PCL fiber scaffolds after 1 hour

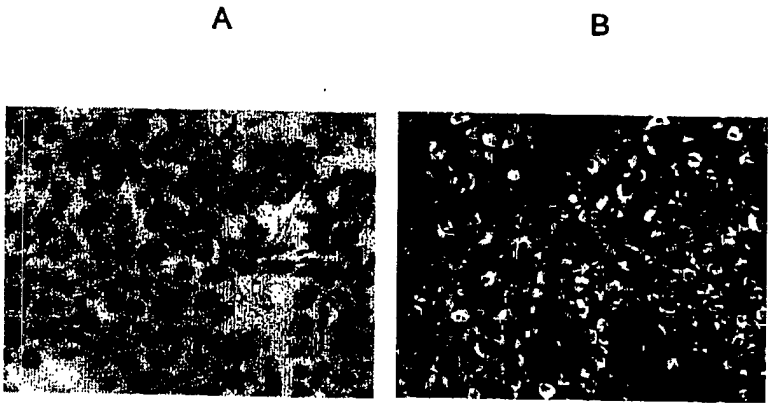


Figure 6: Chondrocytes seeded with FN and incubated for 3 days on 7μm scaffolds. A) cells stained with giemsa and viewed by light microscopy and B) cells stained with fluorescent labeled antibody to vimentin and viewed by confocal microscopy.

By confocal microscopy of the 7μm scaffolds, it was evident that the chondrocytes penetrated a distance of 30-40microns but cells were rarely observed in the deeper region of the 300-500μm thick scaffold.

To achieve better seeding control and more uniform adhesion of cells throughout the scaffold, an alternative seeding technique and larger pore sizes for the scaffolds were needed. With the use of a macro-dialysis chamber, we were able to seed the chondrocytes in cell culture medium equally on all three fiber-diameter meshes with approximately 95% of the seeding density (Fig. 7). From this information, it is clear that fiber diameter in the ranges examined has no effect on cell adhesion.

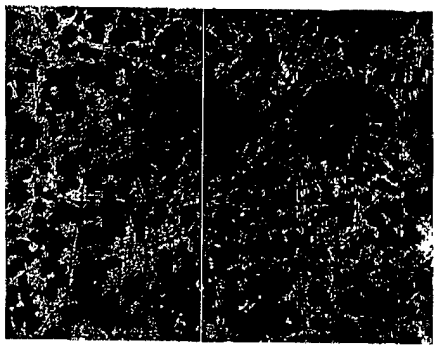


Figure 7: Chondrocytes adherent to a 2μm PCL scaffold using the macro-dialysis chamber for seeding.

Progress

Specific Aim 2: To examine the effects of fiber diameter on chondrocyte proliferation and matrix production *in vitro* in 2-6 week culture.
These studies have not yet been performed.

Future Plans

For Specific Aim 1, adhesion of cells to the different fiber diameters has been fully addressed and can be controlled by use of the macro-dialysis chamber. However, the effect of this seeding technique on cell morphology has not been established. A second experiment is planned to investigate the effect of fiber diameter on cell shape at 24 and 72 hours after seeding with the macro-dialysis chamber.

For Specific Aim 2, we are continuing to enhance the scaffold properties by increasing the interfibrillar distances to allow cell deposition through the entire thickness of the scaffold. We expect to initiate the long term *in vitro* studies in early October.

Metrics

- Jasmin Garcia has worked on this project for 4 months and is currently enrolled at University of Pittsburgh Dental School. Her replacement will work part-time on this project to its completion.
- Prof. Gregory Rutledge, PhD is our collaborator at MIT and is Director of the Program in Polymer Science and Technology
- Jian Yu is a graduate student in the Dept of Chemical Engineering
- Joseph Lowery is a graduate student in the Dept. of Chemical Engineering
- Thomas S. Thornhill, MD is the Chairman of Orthopedic surgery at Brigham and Women's Hospital and a consultant on this project.

Publications and Presentations

Abstracts have been submitted to the Orthopedic Research Society Mtg 2004 and to the International Society of Biomaterials Mtg. 2004.

Electrospun PCL Scaffolds for Tissue Engineering of Cartilage CIMIT Forum presentation 6/10/03.

Image-Guided Therapy Program

Laparoscopic Ultrasound
Principal Investigator: James Ellsmere, M.D., MGH

Executive Summary
Laparoscopic ultrasound has been shown to improve the staging of pancreatic cancer. The adoption of laparoscopic ultrasound by physicians, though, has been hampered by the difficulty they have in understanding the spatial orientation of the imaging plane. We are developing a system to overcome this visualization problem. During the last year, we established a test plan to prospectively evaluate the utility of a novel surgical navigation system, investigated two new image based approaches for registering intraoperative volumes, and devised a new visualization method based entirely on 3DUS that builds on our earlier findings using CT angiogram but is potentially easier to integrate with existing clinical workflow.

The aim of this project is to enable physicians to use laparoscopic ultrasound to improve the staging of pancreatic cancer. Over the last decade several groups have described how laparoscopic ultrasound can be used to improve the staging of pancreatic cancer and reduce the number of patients who undergo non-therapeutic laparotomies. Despite these reports, only select centers are currently using this modality. Most gastrointestinal specialists have had not adopted laparoscopic ultrasound in their practice because they have difficultly understanding the spatial orientation of the 2D ultrasound images. Our goal has been to develop a surgical navigation system that enables surgeons overcome this visualization problem. We believe that such a system will improve the care of patients with pancreatic cancer by improving a surgeon's ability to identify those patients who will not benefit from surgery prior to undergoing a laparotomy.

Key Results
Preclinical validation of navigation system. We are continuing our preclinical work to make the navigation system more robust for clinical evaluation. We have implemented manual registration functionality to the system to allow the user to finely tune registration.

Registered 3D US & CT volumes of pig aorta. We acquired new 3DUS volumes using the Volusion 930 from GE Medical Imaging. Our plan is to use these volumes to further our investigations in registering intraoperative 3DUS with preoperative CT and segmenting abdominal vascular structures for surgical landmarks.

Specific Aims
Specific Aim 1: Laparoscopic Ultrasound Field-Of-View Orientation System

Progress
We have developed a surgical navigation system that enables physicians with limited ultrasound experience to effectively use laparoscopic ultrasound (Fig. 1). We presented our initial experience with the system at the 2003 Meeting for the Society of the American Gastrointestinal Endoscopic Surgeons and have published results validating its performance.

We have designed new software that objectively records a physician's ability to identify retroperitoneal structures in laparoscopic ultrasound images with or without using the 3D orientation feedback.

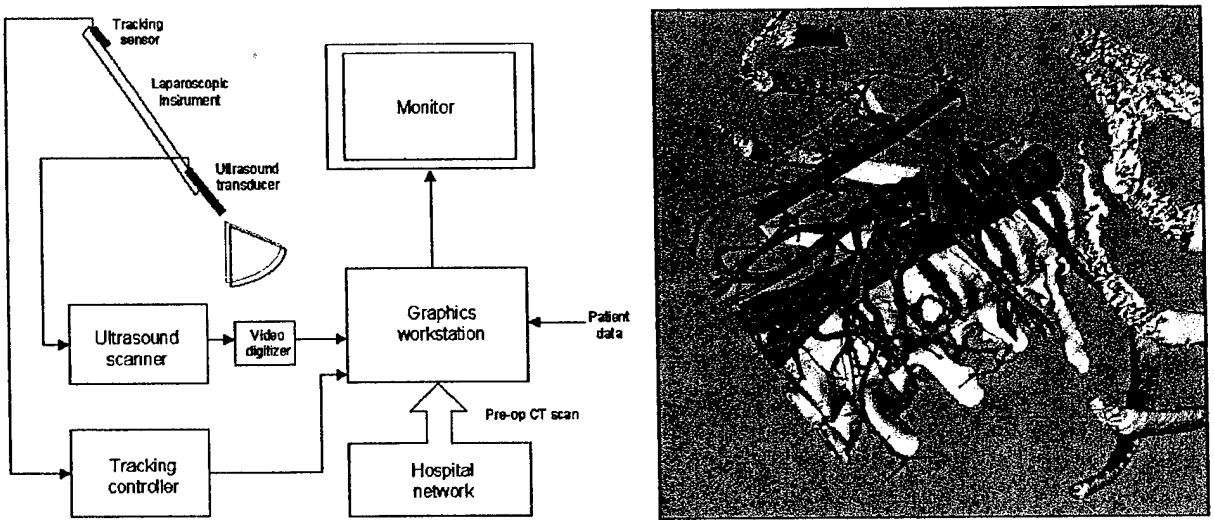


Fig. 1. The system shows the laparoscopic surgeon the ultrasound's field of view overlaid on a 3D model of the arterial anatomy.

Preclinical validation of navigation system
To assess the utility of the navigation system, we performed off line testing. During a pig exam, video from the laparoscopic camera, laparoscopic US and navigation system was simultaneously digitized. From the recordings, twelve different synchronized clips of intra-abdominal anatomy were prepared. Two laparoscopic ultrasonographers reviewed the clips and established by consensus whether any of nine vessels were present. Twenty surgeons then independently reviewed the clips and were asked to identify whether any of the nine vessels were present. For all the clips, they were shown the laparoscopic view and the laparoscopic US. For half of the clips, they were also shown the orientation display. Whether the orientation display was shown for a particular clip was alternated for each successive surgeon. Accuracy was compared using the odds ratios (with 95% confidence intervals) from 2x2 tables. For all vessels, the orientation display improved the odds ratio for correctly identifying structures from 3.7 (2.7 - 5.2) to 8.9 (6.2 - 12.8). For arteries, the orientation display improved the odds ratio from 2.4 (1.4 - 4.3) to 9.6 (6.2 - 12.8). For veins, the orientation display improved the odds ratio from 4.4 (2.8 - 6.8) to 13.6 (7.2-25.7) There was no significant difference in the odds ratio if the tip of the probe was visible in the laparoscopic video clip. However, if the tip of the probe was not visible in the laparoscopic video clip (e.g., imaging the retroperitoneum), the orientation display improved the odds ratio from 2.3 (1.4 - 3.8) to 12.4 (7.2 - 21.4).

Registered 3D US & CT volumes of pig aorta
It would be preferable if the model of the aorta in our system could be generated using transabdominal 3D US. The focus of our work todate has been assessing the feasibility and utility of tracking a laparoscopic transducer and displaying the position and orientation of the US plane relative to a model of the aorta. Part of our ongoing work is assessing whether a model of the aorta generated from transabdominal 3D US could be an alternative approach for providing spatial cues that help physicians orient laparoscopic US images. The 3dUS volumes are used for algorthim development and the CT volumes are used for validation.

Specific Aim 2: Image-based registration

Progress
The current implementation of the navigation system uses fiducial-based registration. In an attempt

to improve the system accuracy and to make registration less user dependent, we have been investigating image-based registration. We are currently evaluating two different approaches. One approach is to register 3DUS and CT volumes based on centerlines extracted from the major systemic and portal vessels. The other approach is to filter US images to accentuate the distinct texture of the vascular structures and then merge the volumes based on a more generalized form of the mutual information.

Both techniques are based on rigid registration algorithms. They have been designed to provide acceptable registration accuracy over the operative volume of interest as well to perform fast enough so repeated intraoperative updates are feasible.

The registration experiments to date have been conducted on images of an upper abdomen radiological phantom (Fig 2).

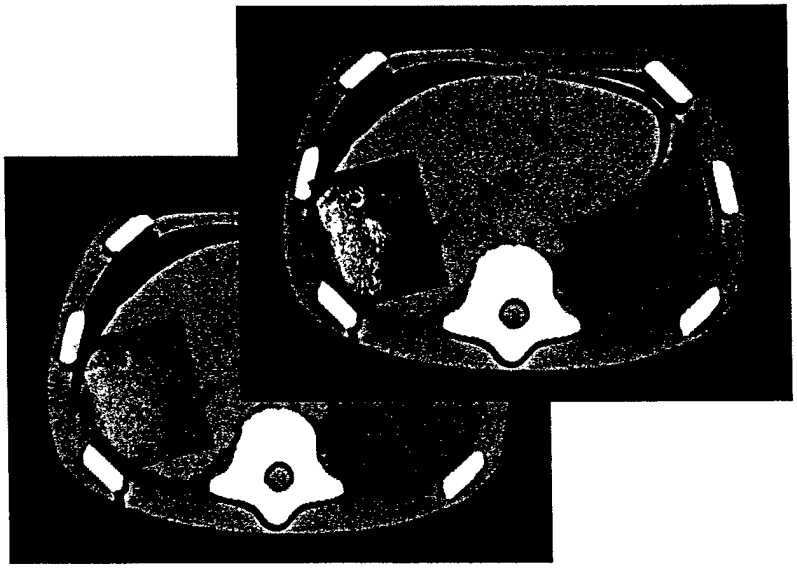


Figure 2. An axial plane through both the 3DUS and CT of the upper GI phantom with different 3DUS transparency levels

Improved 3D US calibration process
In collaboration, with the Department of Mechanical Engineering at Boston University we developed a new US collaboration process. The advantage of the new plane-based technique compared to our earlier point based technique was is that time to calibrate was reduced from 30 minutes to 10 minutes and the accuracy was improved from 3.5mm to 2.5mm. The major advantage on the new process is that it relies on automated image segmentation. We now process a 20 times as many images in solving the calibration parameters.

Specific Aim 3: Advanced tracking hardware design.

Progress
A major technical challenge to overcome before we use our system in a human trial is reducing the size of the tracked laparoscopic ultrasound instrument. The current prototype has a diameter of 15mm. We need to reduce the diameter so that the instrument can fit through a standard 12mm laparoscopic port. We are working with BK-Medical (laparoscopic ultrasound manufacturer) and

Ascension Technology (tracking equipment manufacturer) to construct a new prototype that meets this specification.

Specific Aim 4: Processing 3D US volumes.

Progress
The essence of our surgical navigation system is how we show physicians the plane of the laparoscopic ultrasound relative to the major abdominal arterial branches. In our current implementation, we generate the 3D model of the arterial system from a preoperative CT angiogram of the pig. We have devised a new method for generating the 3D model of the arterial system from the ultrasound system itself. The main advantage of this new method is that it will remove two key steps, namely: downloading the CT study from the radiology information system and registering the 3D CT angiogram. Removing these steps makes using the system more straightforward. In addition, by removing these steps we make the system self-contained and thus potentially more attractive to an ultrasound manufacturer. There are, however, two disadvantages of this method. One, it assumes the physician can scan the volume of interest and, two, it moves the arterial segmentation from a preoperative step to an intraoperative step.

Future Plans
We have acquired new 3DUS volumes using the Voluson 930 from GE Medical Imaging. Our plan is to use these volumes to further our investigations.

Metrics
Personnel working on this project:
James Ellsmere, M.D.
Kirby Vosburgh, Ph.D.

Publications and Presentations
J. C. Ellsmere, J. A. Stoll, D. W. Rattner, D. C. Brooks, R. A. Kane, W. M. Wells, R. Kikinis, and K. G. Vosburgh, "A navigation system for augmenting laparoscopic ultrasound," to be presented at Medical Image Computing and Computer-Assisted Intervention – MICCAI, 2003.

J. C. Ellsmere, J. A. Stoll, W. M. Wells, 3rd, R. Kikinis, K. G. Vosburgh, R. A. Kane,D. C. Brooks, and D. W. Rattner, "A new visualization technique for laparoscopic ultrasound," presented at Massachusetts General Hospital Clinical Research Day, Boston, MA, 2003.

G. Stippel, J. C. Ellsmere, S. K. Warfield, W. M. Wells, 3rd, W. Philips, and A. Pizurica, "A new technique for the registration of 3-D ultrasound to CT or MR images in image guided surgery," presented at World Congress on Medical Physics and Biomedical Engineering, Sydney AU, 2003.

G. Stippel, J. C. Ellsmere, S. K. Warfield, W. M. Wells, and W. Philips, "A new technique for multi-model 3D image registration," presented at Workshop on Biomedical Image Registration – WBIR, Philadelphia PA, 2003.

[5]K. Krissian, J. C. Ellsmere, K. G. Vosburgh, R. Kikinis, and C. F. Westin, "Multiscale segmentation of the aorta in 3D ultrasound images," to be presented at IEEE Engineering in Medicine and Biology Society – EMBS, Cancun, MX, 2003.

[6]R. S. Jose Estepar, C. Alberola-Lopez, J. C. Ellsmere, R. Kikinis, and C. F. Westin, "Freehand ultrasound reconstruction based on ROI prior model and normalized convolution," to be presented at Medical Image Computing and Computer-Assisted Intervention – MICCAI, Montreal QC, 2003.

Ellsmere, J., Stoll JA, Rattner DW, Wells WM III, Kikinis R, Vosburg KG, *Integrating preoperative CT data with laparosopic ultrasound images facilitates interpretation.* Surg Endosc, 2003(17): p. S296.

Minimally Invasive Approach to Reconstruction of the Midfacial Skeleton
Principal Investigator: Maria J. Troulis D.D.S., MGH

Executive Summary
The long-term goal of our Program is to change the current clinical practice of craniomaxillofacial surgery from one requiring major operations with large incisions, extensive dissection and bone grafts to one practiced with minimally invasive endoscopic techniques. Initial CIMIT funding (CPM Fund # 731-4398-5) supported laboratory studies for the development of the endoscopic approach to the mandibular ramus-condyle unit (RCU) specifically for mandibular reconstruction. This grant resulted in the design, testing and modification of novel exposure techniques in an animal model (Troulis, et al., 1998; Troulis et al., 1999). The minimally invasive approach to the RCU was then taken "bench-to-bedside" with the first clinical series published in May 2001(Troulis and Kaban, 2001). October 5-7, 2001 was a landmark in Continuing Medical Education for the MGH Department of OMFS.

In this project, the research is extended to include the midface skeleton. The rationale is to ultimately achieve minimally invasive access to the entire craniomaxillofacial skeleton. Our hypothesis is that it will be possible to replace standard, open, craniomaxillofacial surgical reconstructive procedures with minimally invasive (endoscopic) approaches to the midface. In this proposal, we plan: To design, develop and refine endoscopic approaches to the midface: orbits, zygoma and maxilla, in an animal model. The endoscopic exposure and surgical techniques developed in this Program are unique to CIMIT and the MGH. If successful, these techniques will allow surgeons to correct acquired and congenital CMF skeletal deformities with minimal morbidity, low cost and minimal hospital stay.

Key Results
In collaboration with the Harvard Medical School Department of Continuing Education, we conducted an international workshop entitled: Endoscopy for Mandibular Reconstruction and Salivary Disease. This was the first such workshop in the field of maxillofacial surgery and was fully subscribed and attended by leaders in the field of OMFS from the United States and Europe. This course was the direct result of 5 years of partially CIMIT sponsored pioneering work in minimally invasive surgery of the mandible. The course received high ratings from the participants, many of who are now incorporating these techniques in their practices and teaching programs. The course was repeated in October 2002. Once again we received high ratings (with a letter from Dr. J. Martin). Furthermore, a live demonstration was performed at the course. The next such course is scheduled for October 10-13, 2003.

Specific Aim
To conduct rigorous, analytic, animal studies to demonstrate that minimally invasive therapies are superior in outcome to standard techniques.

Progress
We have started planning the incisions (access) and dissection for the proposed osteotomies. Cadaveric pig heads have been collected and stored (minus 80 degrees).

Karl Storz USA (Mr. Jay Houser) has donated a large amount of endoscopic equipment for the endoscopic research laboratory. Unfortunately, we had a "space issue" which delayed the set-up of this special laboratory. However, this has been resolved and construction is underway. Finally, Karl Storz USA is collaborating with us to establish a teaching center, to allow for course participants to return and gain additional hands-on experience.

Also, being recognized as leaders in this area (minimally invasive oral and maxillofacial surgery) I (PI) and Leonard Kaban (co-PI) as well as MGH course-participants (S.Eisig and J. McCain)and lecturers (P. Jackson) have been invited by the American Association of Oral and Maxillofacial Surgeons, to head a national taskforce on Minimally Invasive OMFS. Dr. Troulis has selected to serve as chairperson.

Future Plans
To obtain approvals for human studies to continue this project.

Metrics
Personnel working on this project:
Maria Troulis, D.D.S., MGH
Leonard Kaban, D.D.M, MGH

Publications and Presentations
Troulis MJ. Basic Endoscopy. Guest Lecturer (Chicago April0 3 and Chicago June 03)
Troulis MJ. The MGH Experience: Endoscopic reconstruction (Chicago April0 3 and Chicago June 03).

Biodefense Program

Real-Time Assay for the Detection and Patho-typing of *Escherichia coli* O157:H7 in Processed Bovine Meat

Pnincipal Investigator: Stephen B. Calderwood, M.D., MGH

Executive Summary

The focus of this project is to develop the μCANARY sensor for detection of *Escherichia coli* O157:H7, and to characterize DNA sequences unique to *E. coli* O157 utilizing representational difference analysis, for use in developing a patho-typing system for this organism.

Key Results

We have made good progress on improving the signal-to-noise ratio for the μCANARY device, calibrating the sensitivity of the μCANARY sensor to determine minimum detection limits, and optimizing coating of anti-O157 antibody for binding of organism to the sensor. We have also identified several DNA sequences unique to pathogenic strains of *E. coli* O157 for use in strain typing.

Specific Aims

Specific Aim 1: To develop and characterize immunoglobin-receptor coating applications on the μCANARY sensor device for microbial pathogen detection.
Specific Aim 2: To evaluate the μCANARY sensor performance.
Specific Aim 3: To characterize DNA sequences unique to virulent *E. coli* O157, identified using Representational Difference Analysis, and evaluate their use in developing a patho-typing system for the organism.

Progress

The specific topics include: 1) Improvements in device signal-to-noise (S/N) and signal stabilization, 2) Calibration of mass sensitivity of the μCANARY sensor to determine minimum detection limits, and 3) Optimization of coating of anti-O157 antibody.

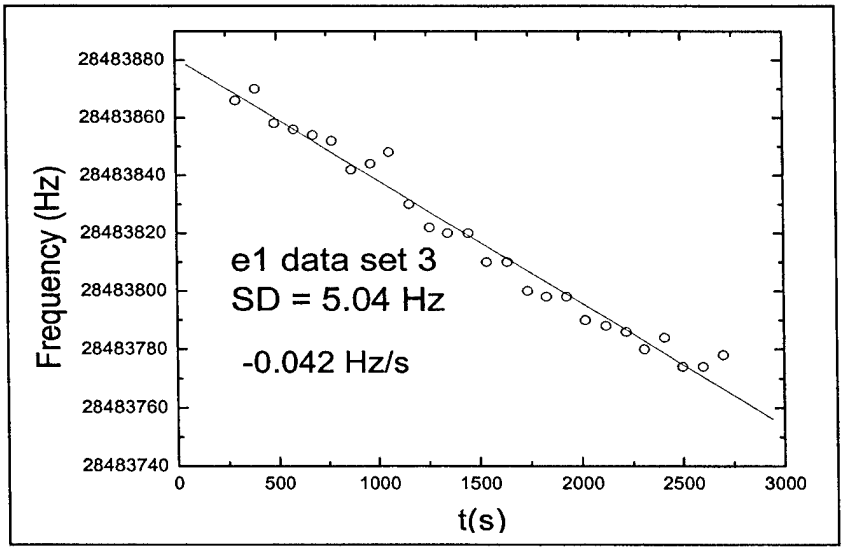


Figure 1. Drift of element one of sensor #204 with time. Active temperature control to 40.00 °C. Signal noise has a standard deviation of 5 Hz.

We have spent much of the past year identifying methods to stabilize the μCANARY sensor over time as well as improve S/N. Inadequate device stability has impacted biotesting with the μCANARY sensor since drift over time has either increased or decreased signal during the course of testing, resulting in frequency shifts that were uncorrelated with the binding of *E. coli* O157. We routinely use optical imaging and data processing of *E. coli* O157 bound to the sensor as an independent measure of bound *E. coli* O157.Our approaches have been to provide active temperature control to the sensor package as well as refine our peak-tracking algorithm.

Temperature control is provided by attachment of a thick-film heater to the sensor package and using a temperature sensor (AD590) mounted next to the μCANARY sensor for closed-loop control. Despite this closed loop control, the frequency of the μCANARY sensor generally drifts downward (Figure 1), at rates of the order of 150-160 Hz/h. This drift is not too problematic if we can calculate for it and correct responses accordingly. The origin of the drift remains a mystery, however. One speculation is that the drift is associated with mechanical relaxation of the packaging material. Experiments are underway to float the sensor off of the packaging material, thus isolating it from thermal mismatch between package material and the silicon μCANARY sensor.

We have also had good results with improving the peak-tracking algorithm in an effort to minimize signal noise. The data in Figure 1 are typical of the recently tested devices, and reflects a standard deviation of the signal of about 5 Hz, or about 0.2 ppm. This improved signal stability greatly improves out S/N, leading to a much lower minimal detectable signal.

One of our final tasks with the sensor technology was to calibrate the mass sensitivity of 'soft' materials, such as polymers and *E. coli*. This is important because our minimal detectable limit is determined by the mass sensitivity of the sensor. Previously we have calibrated the mass response using elastically stiff materials, such as thin film gold. For this calibration work the sensor response (1800 Hz/ng) was about one-half that predicted by theory.

We used an organic material to 'model' mass loading of *E. coli*. The organic material used is dibutylphthalate (DBP) in a fluorinated ether solvent (HFE-7100). Mass loading was done using precise volume (100 nL) delivery of solutions of a known concentration of DBP (10, 50 and 100 ppm) to three elements of sensor #202. The frequency shifts were well behaved over a range of standards tested (1-10 ng). The sensor was regulated at 40 °C with a closed-loop controller using an AD590 sensor mounted next to μCANARY sensor on the PCB. The top of the package was insulated and the sensor test board was mounted on an aluminum block.

A typical measurement involved 100 nL dispensed as 5x20 nL into the middle of the sensor. For the 50 ppm standard, this was 0.100 μL * 50 ng/μL = 5 ng of organic material, dispensed as a thin film over the sensor surface. The results for triplicate measurements are shown in Figure 2.

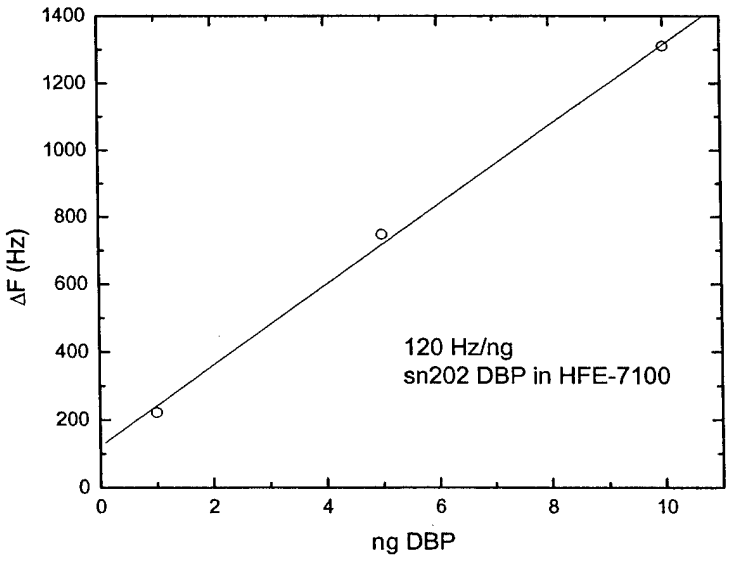


Figure 2. Mass calibration of the μCANARY using the organic DBP. Each data point is a triplicate measurement, with an average standard deviation of all the data of 4.2%.

These results indicate that for softer materials, the sensor response is less than that of harder materials, such as silicon and gold. The implications are, of course, that our minimal detection limit with the sensor is less for softer materials, such as *E. coli*. Minimal detection limits can be estimated using typical signal SD of 7 Hz; 3*7 Hz/120Hz/ng = 175 pg. This is much higher than the minimal detectable limit for the most elastically hard materials, with a modulus of 150 Hz. The results thus far for the mass calibration work are summarized in Figure 3.

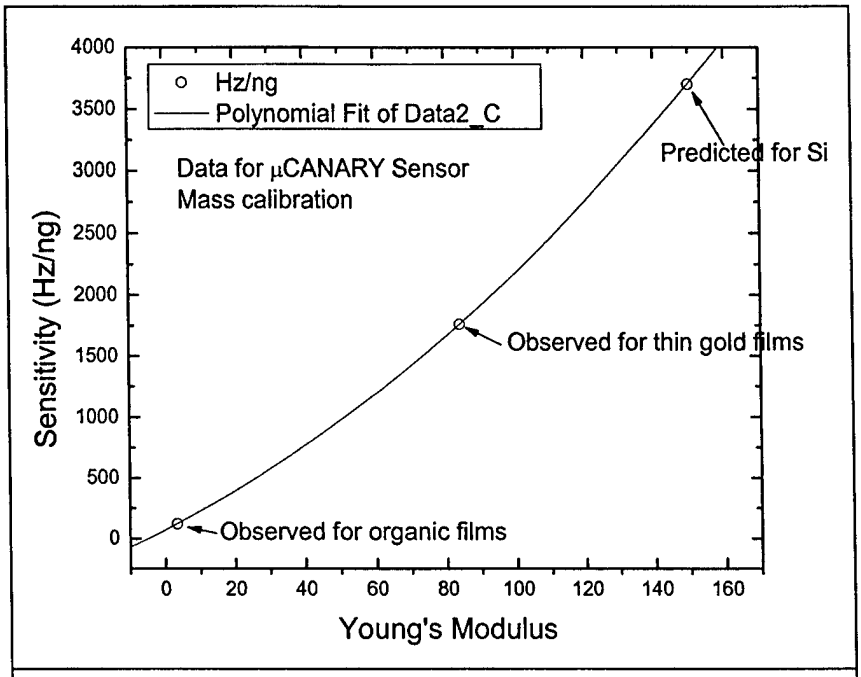


Figure 1. Mass sensitivity versus Young's Modulus of material tested.

Our final task during this period has focused on optimizing the surface chemistry for detection of *E. coli* in simple solutions. We have previously detected *E. coli* in phosphate buffer solutions; however, the surface chemistry was not optimized for sensitivity. During this report period, we have examined anti-O157 antibody concentration. For this work, we used gold-coated silicon substrates to simulate the binding chemistry used with the μCANARY sensor. Our standard surface chemistry is formation of amino thiol self-assembled monolayer (SAM) on the gold, followed by coupling of anti-O157 with glutaraldehyde. The variable in these initial experiments is the concentration of the antibody. Preliminary results examining antibody concentration are shown in Figure 4. The *E. coli* solution contained about $5x10^7$ organisms/mL, based on OD_{600}, and the antibody was incubated with the glutaraldehyde for 30 minutes. The number of *E. coli* organisms was determined using Image-Pro™ software analysis of optical micrographs.

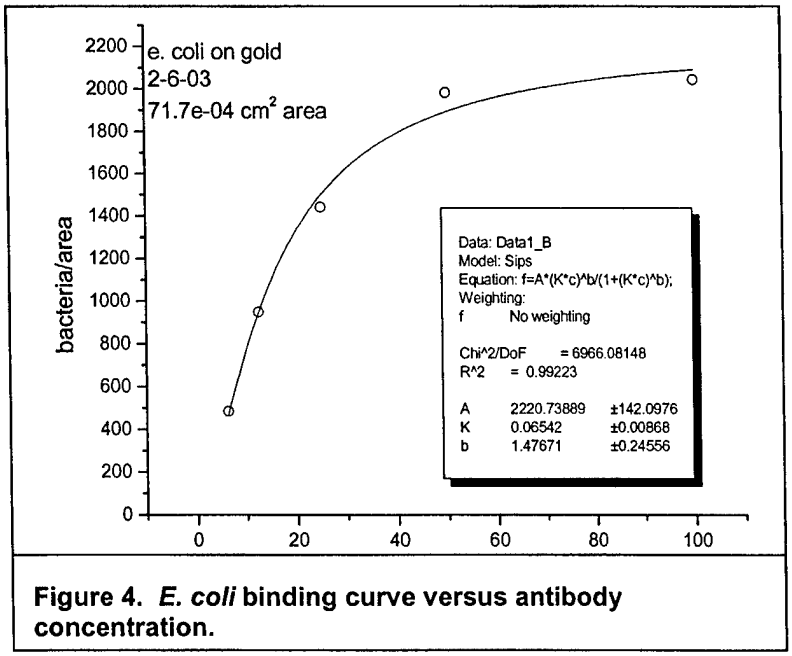


Figure 4. *E. coli* binding curve versus antibody concentration.

The specific topics include: 1) Southern blot analysis of difference products obtained by Representational Difference Analysis (RDA) of a Lineage I *E. coli* O157 against a Lineage II *E. coli* O157, 2) Cloning of these difference products, and, 3) Analysis of recombinant plasmids.

Using RDA, the genome of a Lineage I (virulent) strain of *E.coli* O157 (strain FRIK 1986; "Tester") was compared against the genome of a Lineage II (avirulent) strain of *E. coli* O157 (strain FRIK 1985; "Driver"). Sequences common to the genomes of the two strains were subtracted out, and those sequences present only in the Lineage I, Tester strain, were enriched for. These sequences referred to as the difference products, were labeled en masse with a chemiluminescent molecule, and used as probes in a Southern blot assay. Specifically, genomic DNA from both the Tester and Driver strains were digested with various restriction enzymes, electrophoresed on an agarose gel, and capillary transferred to a nylon membrane. The membrane was hybridized with the labeled probes using standard protocols. Results of this experiment indicated that the difference products contained sequences that were unique to the Tester and sequences that were homologous between the Tester and Driver strains (Figure 5).

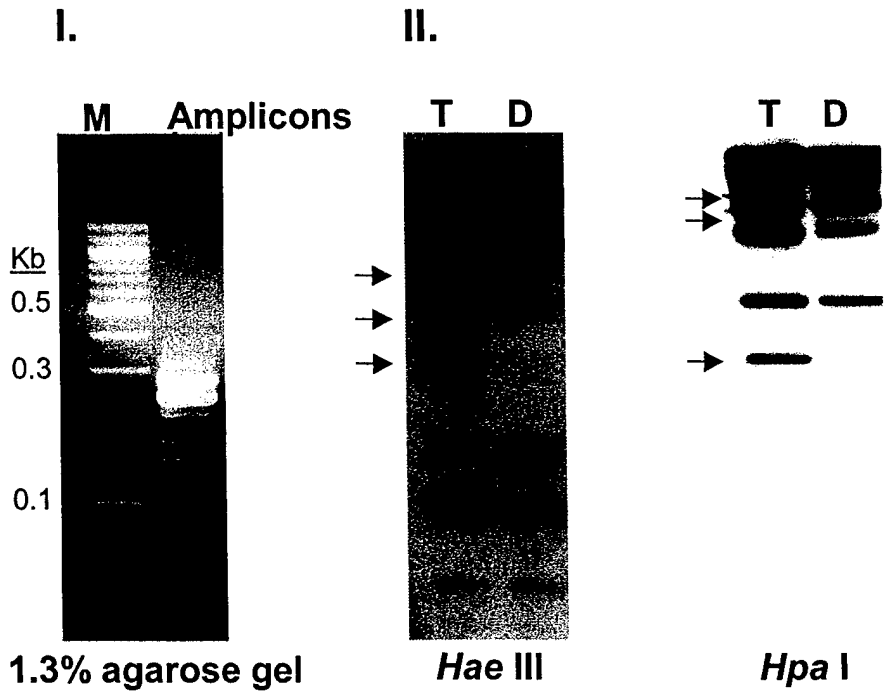


Figure 5. Analysis of difference products obtained by RDA of a Lineage I (FRIK 1986, Tester) versus a Lineage II (FRIK 1985, Diver) strains of *E. coli* O157.
Panel I, 1.3% agarose gel electrophoresis pattern. M, Molecular weight markers; A, Difference products.
Panel II, Southern blots using en masse labeled difference products as the probe. T, Genomic DNA from Tester strain digested with *Hae*III or *Hpa*I; D, Genomic DNA from Driver DNA strain digested with *Hae*III or *Hpa*I. Arrows indicate bands unique to the Tester strain.

Next, we cloned the difference products en masse by electroporation into the cloning vector, pGEM-T, with the aim of isolating each difference product, and analyzing them individually. Recombinant plasmids were transformed into *E. coli* strain DH5α, and the recombinant library generated screened using chemiluminescent, *Sau*3AI-digested Driver genomic DNA as the probe.

Non-reactive clones in the library that did not hybridize with the Driver DNA probe were identified. We identified 100 non-reactive clones.

In addition, we have evaluated each of the non-reactive clones, using colony PCR and Southern blots, for the presence of sequences unique to the Tester or homologous to both Tester and Driver strains. An example of the results obtained by this analysis is shown in Figure 6. We found that approximately 42% of the non-reactive clones analyzed have single inserts in the respective recombinant plasmids. These inserts were used as probes in Southern blot assays as described above. Approximately 25% of these inserts contain sequences that are unique to the Tester. We plan to complete the screening of the recombinant library and evaluation of non-reactive clones shortly. Next, we will sequence insert DNA of interest, evaluate sequences using bioinformatics tools, and identify sequences unique to a population of Lineage I *E. coli* O157 isolates.

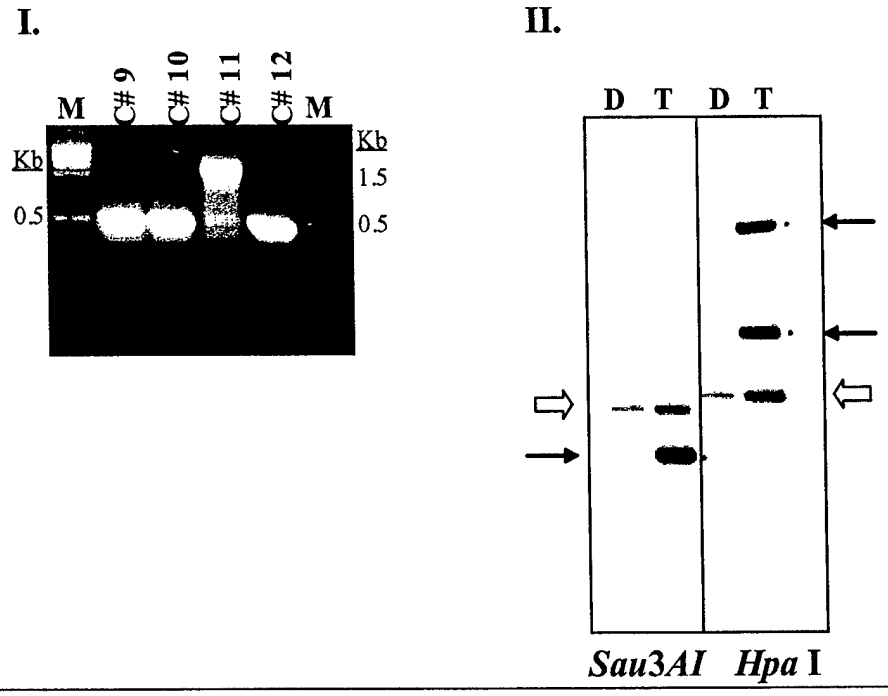


Figure 6. Analysis of non-reactive plasmid clones by PCR and use of one of these amplicons in Southern blot hybridization.
Panel I, 2% agarose gel electrophoresis of amplicons obtained by colony-PCR. M, Molecular weight markers; C# 9 – C# 12, amplicons obtained from non-reactive clones 9 -12, respectively.
Panel II, Southern blots using labeled C# 12 amplicon as a probe. D, genomic DNA from Driver strain digested with *Sau*3AI or *Hpa*I; T, genomic DNA from Tester strain digested with *Sau*3AI or *Hpa*I.
Regular arrows indicate bands unique to the Tester strain; Boxed arrows indicate bands homologous to both Tester and Driver strains.

Future Plans

To continue to develop the μCANARY sensor for detection of *Escherichia coli* O157:H7, and to characterize DNA sequences unique to *E. coli* O157 utilizing representational difference analysis, for use in developing a patho-typing system for this organism.

Metrics

Personnel working on this project:
Stephen B. Calderwood (MGH)
Chris Dube (Draper Laboratory)
Manohar John (MGH)
Indira Kudva (MGH)
Michael Callahan (Draper Laboratory/MGH)

Publications and Presentations

Griffin RW, Murray M, John M, Perna NT, Barrett TJ, Calderwood SB. Insertions, deletions, and single nucleotide polymorphisms at rare restriction enzyme sites enhance the discriminatory power of polymorphic amplified typing sequences, a novel strain typing system for *Escherichia coli* O157:H7 (manuscript in preparation).

Characterization of a Pyrolysis High Field Asymmetric Waveform Ion Mobility Spectrometer for the Detection of *Bacillus* Spores
Principal Investigator: Cristina E. Davis, Ph.D., Draper Laboratory

Executive Summary

The development of early detection technologies that are able to quickly identify biological warfare agents is important to the United States Department of Defense, the health care system, and emergency response agencies. The detector should be able to provide fast and sensitive identification of a sample on location, be able to work autonomously, be robust, field-deployable, and inexpensive. Many technologies currently available are not accurate or reliable enough or are too large for use in the field. Others currently being developed are too large, expensive, and complex to be used by the agencies that respond to suspected biological hazards.

The goal of this project is to develop and characterize a Pyrolysis High Field Asymmetric Waveform Ion Mobility Spectrometer (pyrolysis-FAIMS) to detect organic compounds released from bacterial spores through pyrolysis, with special attention on creating an inexpensive hand-held analyzer either for constant, automated air monitoring or for single point analysis. The currently available prototype FAIMS device being used for this study (Figure 1) was invented and developed at Draper Laboratory and transferred to Sionex Corporation, a startup company, for commercialization. The presence and/or change in bacterial spore count in the sampled air can be sensed and used for "first-alarm" purposes and as a trigger for a more specific biological agent detector. Specific detection of *B. anthracis* could be achieved by monitoring for fingerprint patterns of other unique biomarkers present in the spore cell walls.

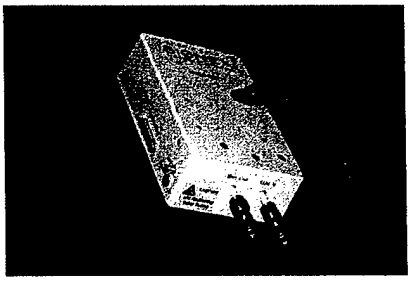


Figure 1. Sionex FAIMS unit development platform SDP-1.

Key Results

The CIMIT team has made significant progress with the optimization of the pyrolysis-FAIMS system, and the ability to detect spore biomarkers has been verified. Data was taken for *B. subtilis* spores suspended in water and was compared to data taken for water alone. This comparison shows extremely promising results, as at least three distinct peaks were visually observed in the spectra of the spore samples that were not in the water-only samples. Correlogic Systems, Inc. found at least seven major biomarker peaks using their pattern discovery and recognition algorithms. This indicates that the pyrolysis-FAIMS system is capable of detecting specific spore biomarkers.

Specific Aims

Specific Aim 1: Optimize operating conditions for pyrolytic detection of spore samples.
Specific Aim 2: Establish feasibility of FAIMS detection of various spore biomarkers.
Specific Aim 3: Evaluate system performance in regards to sensitivity, accuracy, reproducibility and effects of interferents.

Progress

Specific Aim 1: Optimization of Spore Pyrolysis.

At the beginning of this past fiscal year, we were able to show encouraging FAIMS data using pyridine. Since pyridine is volatile, pyrolysis was not necessary; we simply held the interface temperature at 130°C to prevent the material from recondensing inside of the FAIMS equipment. The resulting spectra are shown in figure 2. Pyridine does not produce negative ions, which allows one to conclude that the experimental conditions used here are mild enough to prevent full decarboxylation. This figure also demonstrates that pyridine can indeed by differentially detected with its own unique fingerprint.

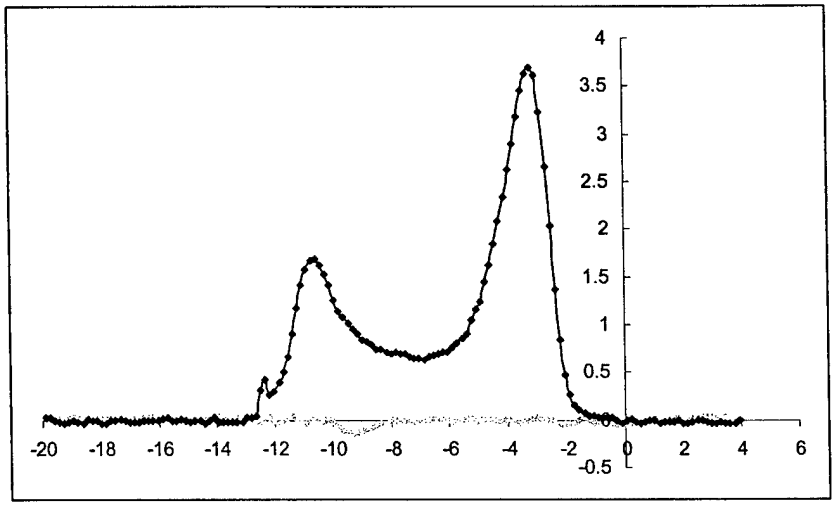


Figure 2. Positive (black) and negative (green) ion spectra for pyridine.

We then went on to examine the pyrolysis of *B. subtilis* spores suspended in water. This process was optimized and a methodology was established. The sample preparation and handling is now being performed consistently with each use of this setup (figure 3a). The *B. subtilis* spores are suspended in water; to examine 40,000 spores, we used 4 μl of a 10,000 spores/ μl sample. Likewise, if we wanted to examine 120,000 spores, we used 4 μl of a 30,000 spores/ μl sample. The 4 μl sample is placed into a quartz capillary tube that slides into the platinum coils of the pyrolysis unit probe. There is a carrier gas (He) passing through the pyrolysis unit that carries the sample after pyrolysis through a gas chromatograph (GC) column (figure 3b). This column allows for additional separation of the sample before it is fed into the FAIMS unit, through which a nitrogen (N_2) carrier gas is flowing.

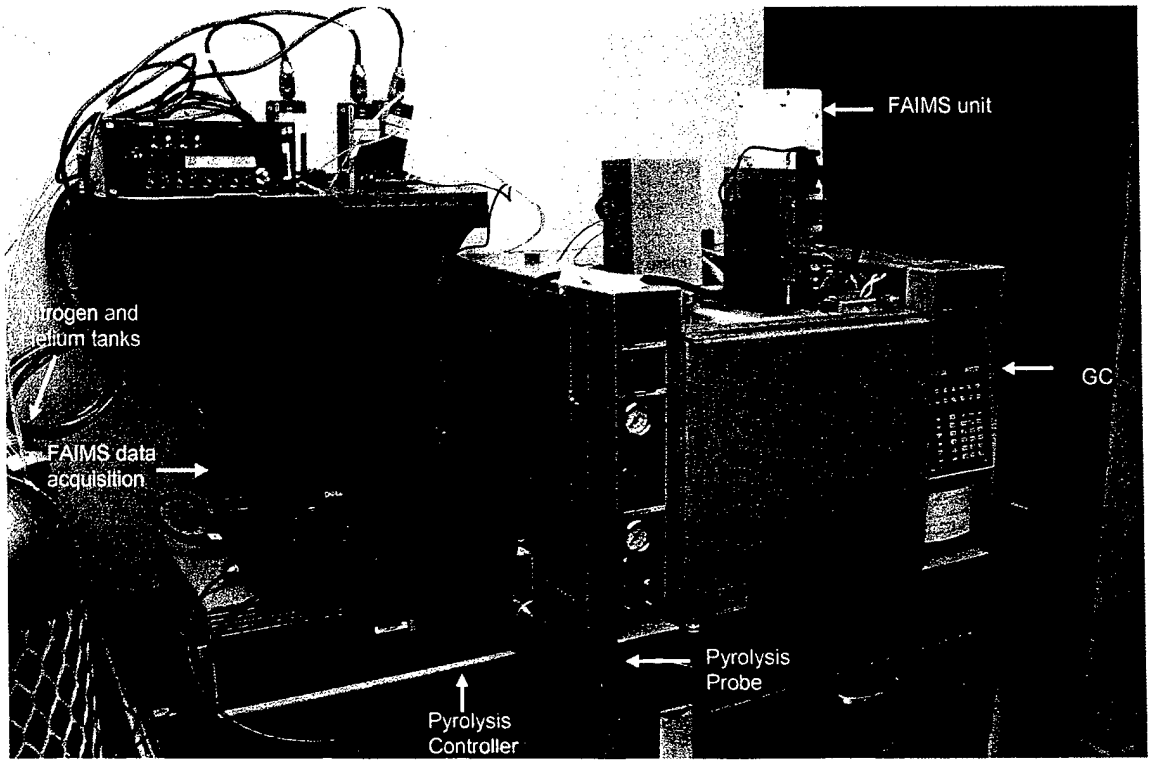


Figure 3a. Pyrolysis-FAIMS-GC equipment setup.

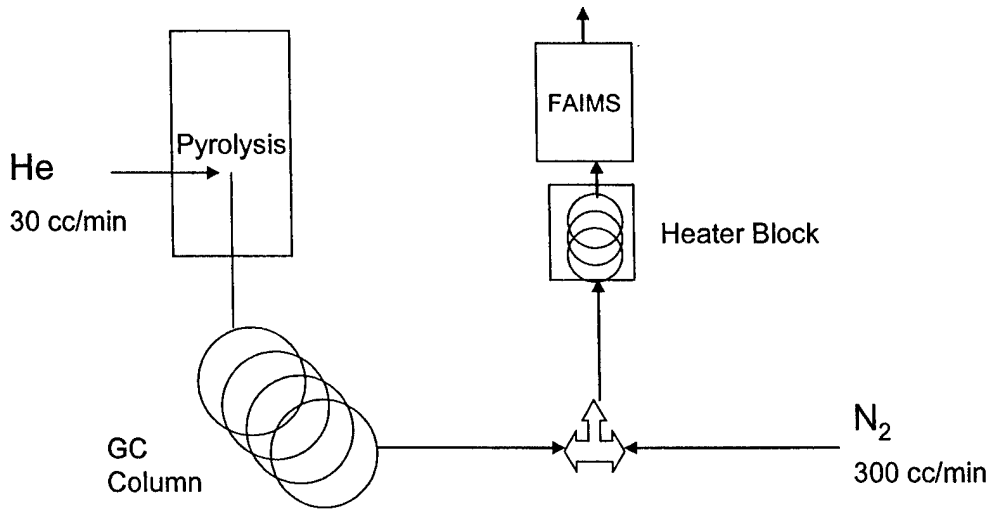


Figure 3b. Schematic drawing of gas flow in the pyrolysis-FAIMS-GC setup.

The FAIMS unit contains an ionization source. Previously, we were using a photo-ultraviolet (UV) light, but have since switched over to radioactive Nickel, ^{63}Ni, for several reasons. The UV light was oriented perpendicular to the flow of air entering the FAIMS unit, and thus much of the material passing through would condense on the bulb as it came into contact. Over time, the ionization efficiency of the UV light greatly decreased due to this residue buildup. In contrast to this setup, the ^{63}Ni is placed next to the flow of materials so that it is able to ionize the sample as it

passes through the FAIMS unit, but the material flows parallel to the ionization source as the analyte enters the unit. Due to this improved geometry, the ionization efficiency no longer decreases with time. Additionally, the ionization potential of ^{63}Ni, 67,000 eV, is significantly greater than that of the UV light, 10.6 eV. This allows for a greater ionization effect on the material passing through the unit. Due to this large ionization potential, Nitrogen, which has an ionization potential of 14.53 eV, and Helium, which has an ionization potential of 24.6 eV, will also be ionized. We now account for this in our data analysis methods.

The FAIMS data are measured on an attached laptop computer through a program created by Sionex with input and feedback from Draper Laboratory scientists. The data acquisition of both positive and negative spectra can be simultaneously viewed on the computer screen. There is a topographic chart (figure 4a) that plots the compensation voltage as a function of retention time and peak intensity in a color chart. The peak intensity is indicated by the color scale (shown to the right of the chart). The data is continuously updated so a new line of data will appear for each new spectrum every 1.6 seconds. Thus, the chart continues to scroll upwards on the screen as the data is recorded, yielding a qualitative understanding of experimental results. Additionally, the data can be viewed by a line chart (figure 4b), which plots the intensity as a function of compensation voltage. This screen updates for every new spectrum.

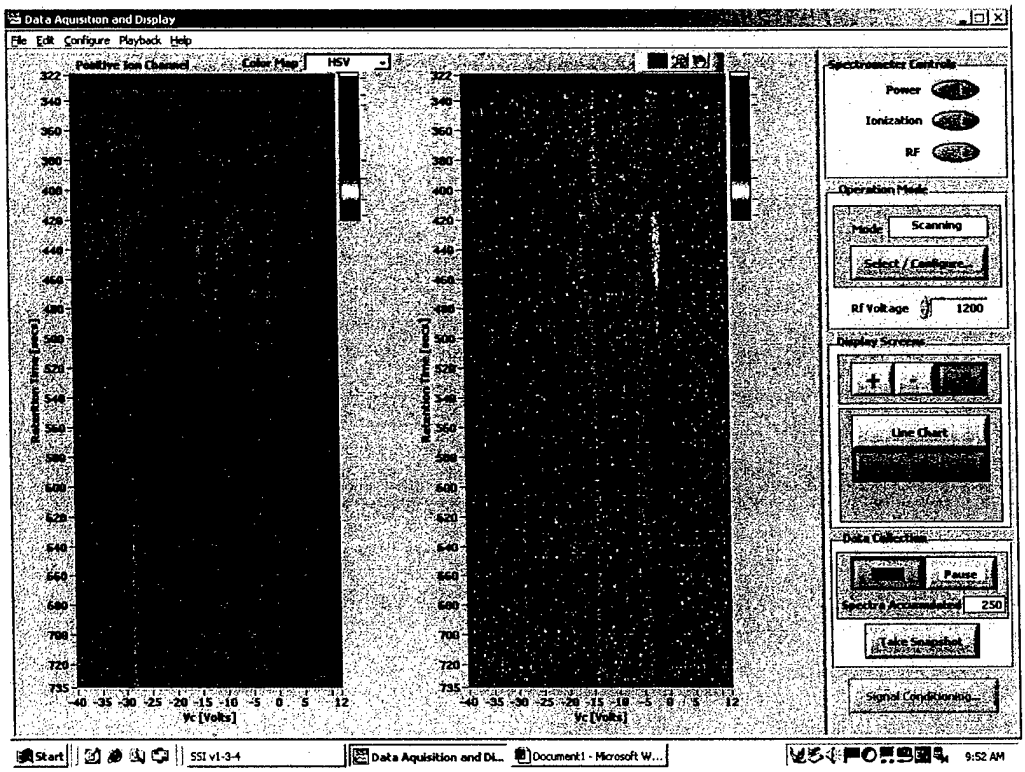


Figure 4a. Computer screen during pyrolysis-FAIMS data acquisition showing a topographic chart.

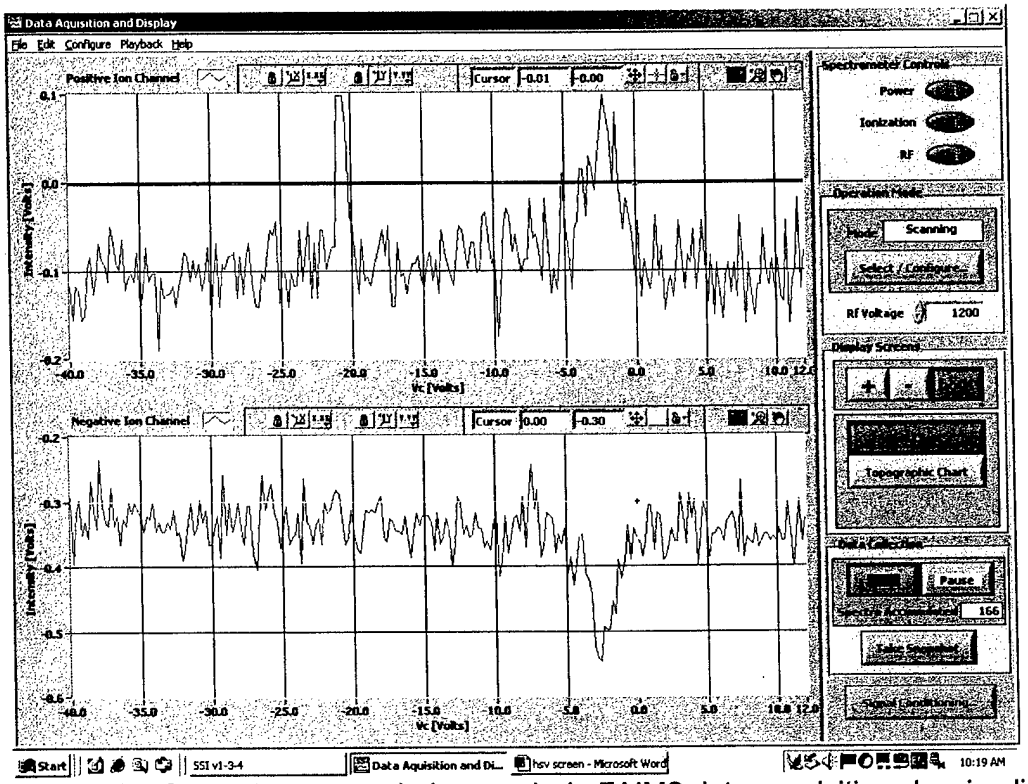


Figure 4b. Computer screen during pyrolysis-FAIMS data acquisition showing line chart.

The acquired data is saved as an Excel file which can then be analyzed with any compatible data analysis program. The Draper Laboratory FAIMS team has written several scripts in MATLAB® to analyze the data. We retrieve the data from the Excel file and have MATLAB® plot it in four different formats: a topographic chart similar to the one on the computer screen during data acquisition (figure 4c), a zoomed in view of the topographic chart to highlight the pyrolysis event (figure 4d), an array of peaks defined as high points compared to the points around them (figure 4e), and a line chart that shows the log of the signal average, normalized from zero to 1 (figure 4f). Analyzing the log of the FAIMS signal allows any minor peaks to be more easily distinguished from the surrounding noise.

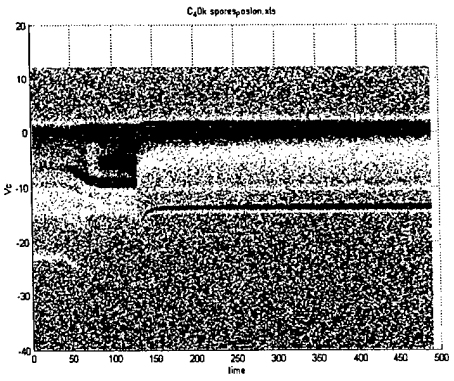


Figure 4c. Colormap of data with Vc on y-axis, time on x-axis, and peak intensity indicated by color (low = orange → yellow → green → blue → purple → pink → red = high).

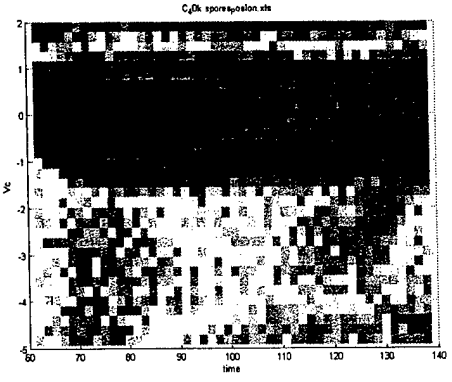


Figure 4d. Same as figure 4c, but zoomed in on user-specified time and compensation voltage range.

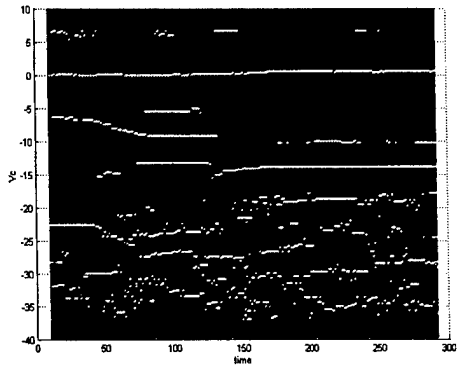


Figure 4e. Peak array. Blue background indicates low points, white pixels indicate high points. Potential peaks will be indicated by a line of white pixels across screen, as this represents consistent high points through time.

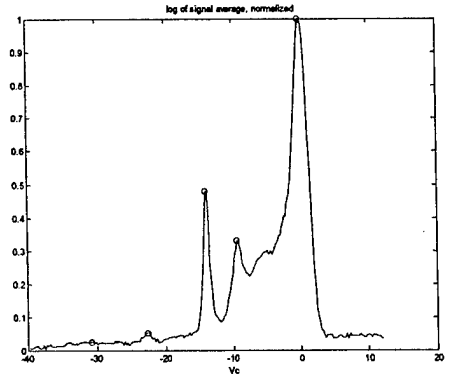


Figure 4f. Graph of the log of signal average, normalized from zero to 1, vs. the compensation voltage. Detected peaks marked with red circle.

We intend to further optimize the experimental conditions. We will perform more detailed experiments for each part of the process and optimize it accordingly.

Progress

Specific Aim 2: Feasibility of FAIMS Detection of Spore Biomarkers.

The sample preparation and apparatus setup described above were used for the pyrolysis of the spore samples compared to water controls. The FAIMS signal amplitude was plotted as a function of the compensation voltage, and the signals of water alone and spores suspended in water were compared. We found exciting results with our initial set of data, which shows at least three major distinct peaks (labeled 1, 3, and 4) that are more apparent in the spore samples than in the water control samples (figure 5). These peaks could represent specific *B. subtilis* spore biomarkers that are detectable using the pyrolysis-FAIMS technology. Since we used a small sample size, it is exciting to find such a distinction between the water background and the spores. Thus, for the larger samples that we intend to run in the future, we hope to improve this distinction even further.

This technology needs to be optimized with respect to biomarker selection to reduce false positive and false negative identification. As we have shown in figure 5, it is possible to detect *B. subtilis* spore biomarkers using pyrolysis-FAIMS. However, it is important to be able to both detect and distinguish different species of *Bacillus* spores. To this end, we have acquired three different types of *Bacillus* spores (*B. subtilis*, *B. thuringiensis*, and denatured *B. anthracis*) and will now be able to compare the fingerprints of each and thus find biomarkers that are unique to each species. We will look for diversity in the spectral data for these spores of the various *Bacillus* species.

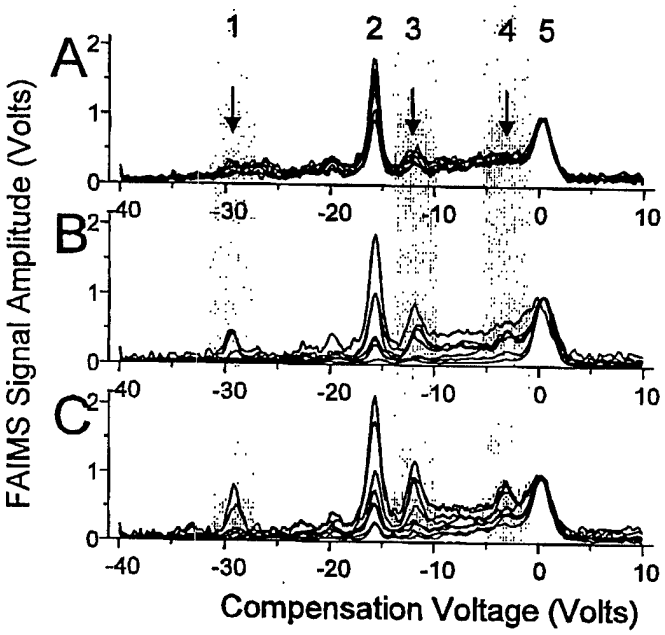


Figure 5: Major and minor FAIMS spectral biomarkers from *Bacillus* spore pyrolysis: (A) water only controls, (B) 40,000 pyrolyzed spores, (C) 120,000 pyrolyzed spores. Biomarkers 1, 3 and 4 appear to correlate with the presence of spores, and the amplitude may be concentration dependent.

We intend to take more data using the optimized pyrolysis-FAIMS conditions to look at a large number of samples. This will allow more significant statistical analysis and will also allow us to determine if there are more than three detectable biomarkers. Additionally, we will examine and compare the FAIMS detection of *B. subtilis*, *B. thuringiensis*, *B. cereus* and denatured *B. anthracis*. The FAIMS spectral data will be analyzed in conjunction with Correlogic Systems, Inc. in Bethesda, Maryland. Their software uses a pattern discovery algorithm, which analyzes complex data sets that can be manipulated through a computer-driven analog of natural selection process. It also uses self-organizing adaptive pattern recognition systems that group data together based on similarity, recognize novel events, and track rare instances of biomarkers. This software will enable us to pinpoint where specific biomarkers show up in the FAIMS spectral data.

Progress

Specific Aim 3: Pyrolysis-FAIMS Performance Evaluation.

We are encouraged with our initial results using *B. subtilis* spores regarding sensitivity. From the small data set shown in figure 5, it seems that we would be able to detect as few as 10,000 spores (one quarter of the amount of our smallest sample size) and to distinguish their signal from any noise from the system around them. The system's accuracy and reproducibility need to be determined after many samples have been analyzed using a single set of conditions. From the data above, we can see that the water sample seems to be very reproducible, as each line almost perfectly overlays the previous. We hope to improve the reproducibility of our spore data by getting data from many more samples. The more samples we use, the better our statistical analysis will be, and we can then determine the exact reproducibility and accuracy of our system. We have found that using fewer spores helps to limit the variability, and we hope to lower this variability even further as we continue to improve our protocol. We should also be able to better

separate the signals from each other by passing the sample through the GC column before the FAIMS analysis.

Future Plans

During the next fiscal year, we hope to find a set of optimal working conditions for the system and take data for many samples under these conditions. With more samples, we will be able to have a better view of how accurate our system is and how reproducible our results are. We will also continue to investigate the effects of various interferents to better understand how these can affect the system. We will find the best pyrolysis conditions, as well as the best GC conditions and FAIMS conditions to optimize the data output. Increased trial numbers will also allow us to distinguish spore peaks using Correlogic's pattern recognition software.

Metrics

Personnel working on this project:

Henry Raczkowski, B.S.	Pyrolysis-FAIM experiments
Ryan Prince, M.E.	Pyrolysis-FAIMS-GC studies, MATLAB scripts for data analysis
Isaac Costa, B.S.	Pyrolysis-FAIM experiments
Andy Dineen, B.S.	Instrumentation setup and maintenance
Angela Zapata, Ph.D.	FAIMS consulting and instumentation assistance

Publications and Presentations

Davis CE, Borenstein JT, Callahan MV, Gelfand JA, Sonenshein AL. Advances in biological weapons detection using FAIMS technology. *Invited speaker.* August 2003. Telemedicine and Advanced Technology Research Center, Fort Detrick, MD.

Davis CE, Callahan MV. Detecting weapons of mass destruction signatures and identifying personnel in austere environments using FAIMS technology. *Invited Speaker.* April 2003. Intelligence Technology Innovation Center, U.S. Central Intelligence Agency.

Davis CE, Zapata AM, Borenstein JT, Callahan MV, Gelfand JA, Sonenshein AL, Nazarov EJ, Miller RA. Biological sample analysis using differential mobility spectrometry. 12th International Symposium on Ion Mobility Spectrometry; Umeå, Sweden; July 2003.

Davis CE, Kang JM, Dube CE, Borenstein JT, Nazarov EG, Miller RA, Zapata AM. Spore biomarker detection using a MEMS Differential Mobility Spectrometer. The 12th IEEE International Conference on Solid-State Sensors, Actuators and Microsystems Conference; June, 2003.

Detection of pentane in patient breath using planar FAIMS
Principal Investigator: Cristina E. Davis, Ph.D., Draper Laboratory

Executive Summary
The goal of this study is to measure levels of pentane in the exhaled breath of selected emergency department patients with various acute clinical conditions using High Field Asymmetric Waveform Ion Mobility Spectrometry (FAIMS). First, we will test various methods of breath collection and analysis: collection in Mylar balloons, with and without devices to remove dead space air and water vapor or concentrate target chemicals, and adsorbing organic volatiles in breath on a SPME fiber assembly. Second, we will correlate measured gas levels with clinical conditions to determine their value in quantifying the systemic inflammatory response or as markers for specific organ infarctions, particularly heart attack, stroke, pulmonary embolus or ischemic bowel. We also hope to explore other gases with diagnostic potential and plan prospective trials of the resulting clinical tests.

Key Results
Funding for this program was released to Draper in April of 2003 for the beginning of the non-human studies. Brigham and Women's IRB compliance has been satisfied, and we anticipate the Department of Defense IRB compliance process should finish in the next few months. We continue to perform non-human control experiments until the IRB compliance is finalized.

This year our team has made solid scientific advances, and we have publicly presented our work several times. Members of our team have worked to continue attracting extramural funding for our FAIMS projects. Draper submitted a FAIMS proposal to NASA entitled "FAIMS for Multi-use space applications including environmental and health monitoring" for $1.4M for 3 years. The goal of this work would be develop a flight-ready, low power, low mass device for chemical and microbial environmental monitoring of the human crew compartments of the International Space Station and the Space Shuttles. This proposal leveraged results generated by CIMIT-funded work, and would be directly related to our CIMIT-funded research in that it will help to build our focus on non-invasive health diagnostic applications for the FAIMS.

Specific Aims
To implement a whole-spectral pattern recognition approach to distinguish breath biomarkers. Our theory is that low-level trace volatiles in the breath samples will be the best targets for biomarkers that will enhance disease predictive power. These volatiles may be a low-levels, and in varying patterns for many clinical disease states. It is now our plan to look at the patterns of biomarkers rather than large percentage composition signal markers, such as only pentane and ketones, for definitive disease diagnostics. We have sent preliminary data to Correlogic Systems, Inc. for analysis.

We will reconfigure our experimental setup to test the effect of pre-separating breath and bacterial headspace samples first through a GC front-end before FAIMS analysis. This may enhance biomarker separation and detection.

There are dozens of volatile organic compounds in exhaled human breath that show promise for diagnosis and management of diseases, but little technical or clinical research and development to date. Some volatile gases are produced by disease conditions and can be smelled by physicians on the patient's breath, such as ketones in starvation and ketoacidosis, feculent amines in bowel obstruction, and bacterial byproducts in anaerobic infections. Exhaled breath is used by police departments to measure blood alcohol levels at the roadside. Several diagnostic tests measure exhaled hydrogen after a specific sugar or starch load to demonstrate lactose deficiency, malabsorption, bacterial overgrowth of the small bowel, or pancreatic function in cystic fibrosis.

The office test for Helicobacter pylori requires the patient first eat ^{14}C labeled urea after which ^{14}C labeled CO_2 is detected in exhaled breath. Other radioactive labeled metabolites are used in other gastroenterology tests. Exhaled nitric oxide has been measured as a marker of inflammation in the lungs. Testing of exhaled breath has been proposed as a rapid toxicology test for carbon monoxide and methanol.

Pentane is produced by the peroxidation of linoleic and linolenic acid, polyunsaturated fatty acids found in cellular membranes, that are oxidized during tissue ischemia and reperfusion injury. Breath pentane has been found to be elevated in proportion to ischemia and inflammation in heart disease, in cigarette smoking, in ischemic bowel disease, in cirrhosis, in rheumatoid arthritis, and even in schizophrenia. Pentane shows particular promise as a marker for reperfusion injury and as such could be used at the bedside to guide the rate of infusion of thrombolytic drugs or the percent of supplemental oxygen.

Ketones are another group of volatile compounds with clinical potential to test. Diabetes mellitus and its complications, including ketoacidosis, are commonly seen in the emergency department with approximately 3-4 patients coming in a day. Ketoacidosis is sometimes diagnosed by the odor of ketone on exhaled breath, but not all clinicians can detect this particular odor. Instead, traditionally we measure acetone in urine using a colorimetric dip stick, or in serum, using color change in an Acetest tablet and serial dilutions for quantification.

Studies published to study breath constituents to date have all used gas chromatography or mass spectrometry or both. Past techniques of breath analysis have been hampered by samples saturated with water vapor, variable ambient levels of gases being measured, ambient pentane dissolved in body fat, and co-elution of isoprene. When exhaled gas is used to measure a process in the lung, exclusion of upper airway dead space gas is important, but this may not matter when we are looking at diseases in other organs. The other problems were related to old techniques of concentrating and detecting gases, using GC and MS, but may not remain problems with FAIMS.

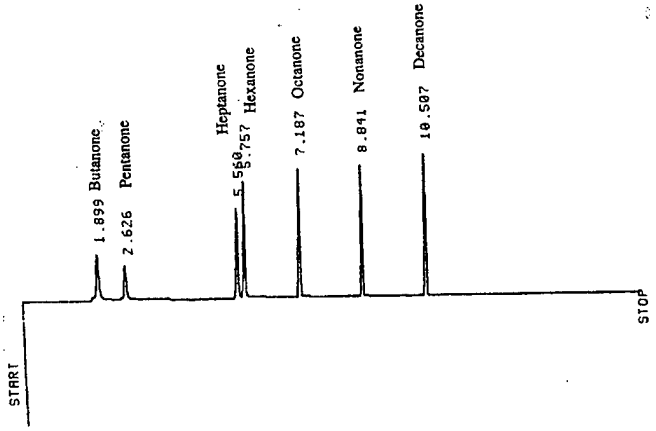


Figure 1: GC separation of a complex ketone mixture prior to FAIMS detection.

Progress

FAIMS technology can deconvolute complex ketone mixtures

Complex ketone mixtures were introduced to the FAIMS via GC separation. Gas chromatography is an analytical technique that can be used to separate volatile organic compounds based upon their partitioning behavior between a mobile gas phase and the stationary phase in the column. Starting at a low oven temperature and increasing the temperature over time to elute the high-boiling point components accomplish separating components with a range of boiling points, ie: boiling points increase with increase in molecular weight. Using this technique, we have developed a method to resolve a complex mixture of seven low molecular weight aliphatic ketones (figure 1). These ketones (C_4H_8O-$C_{10}H_{20}O$), which can be used for medical diagnosis in human breath.

Bacterial headspace measurements for future pulmonary diagnostic applications

Vegetative bacteria species are responsible for a variety of pulmonary lung infections of ambulatory emergency department patients. Previous research in the field has suggested that bacteria produce volatile compounds during proliferation, and that the patterns of compounds differ from species to species. We hypothesize that bacterial lung infections may produce small trace compounds that can be detected with the FAIMS, and that breath tests may ultimately be peformed to definitively identify which bacteria is responsible for the infection to aid clinical course of treatment.

E. coli bacteria cultures were inncolated from existing log-phase liquid cultures. *M. smegmatis* and *B. subtilis* were innocated from frozen seed cultures (-80C). A wooden dowel was used to isolate and pick colonies to innoculate bacteria culture. 5ml of LB media in a 15ml Falcon tubes. 2ml of LB media in the 14ml polypropylene tubes. All species were wildtype cultures using no antibiotics. All cultures were capped immediately at innoculation and allowed to grow for 24 hours at 37°C while agitated. Culture tubes are pierced with gas-tight side-port syringe needle. Mixing of headspace is accomplished by withdrawing plunger 5 times prior to sample collection. 0.5ml of headspace gas was sampled and immediately injected into the GC port. The needle was cleaned with acetone and air between samples, and then heated to desorb residual volatiles. The needle was cooled before using again. Figure 2 shows the GC separation of the complex mixture above the liquid bacterial culture.

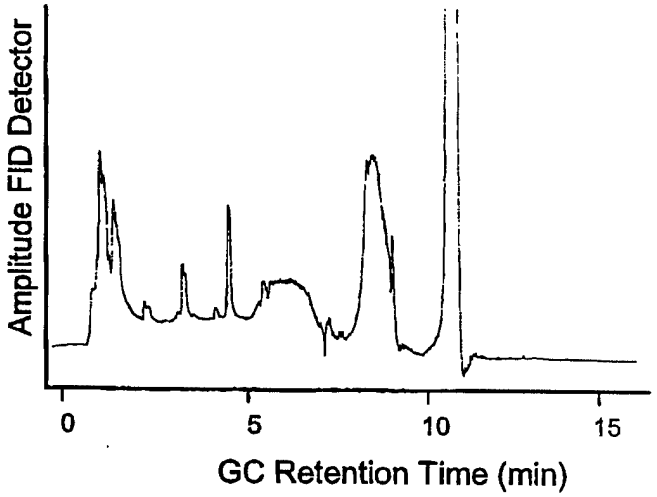


Figure 2: GC separation of biomarkers in headspace above *E. Coli* bacterial culture.

Each of the bacterial headspace biomarkers were compared across three species (Table 1). Each biomarker was assigned a unique number based on the GC retention time. The data in Table 1 suggest that the different bacteria species have different biomarkers that distinguish them. Furthermore, it appears that the mode of bacterial growth may also affect the quantity and identity of the biomarkers present in the headspace above the liquid culture. For instance, cultures that were inoculated from agar plates had different biomarker patterns than those inoculated from exponential growth phase liquid cultures. We expect that we can leverage knowledge of these biomarkers to aid in respiratory infection diagnosis in the future.

Biomarker number	B. subtilis avg	B. subtilis stdev	M. smegmatis avg	M. smegmatis stdev	E. coli (agar plate) avg	E. coli (agar plate) stdev	E. coli (liquid culture) avg	E. coli (liquid culture) stdev
1			1.00	0.14			1.04	0.03
2							1.11	0.03
3	1.26	0.03	1.21	0.03				
4	1.31	0.02	1.31	0.02			1.31	0.09
5	1.43	0.02			1.39	0.04		
6					1.90	0.05		
7					2.39	0.12		
8							2.96	0.04
9					3.70	0.13		
10					4.01	0.11		
11	4.62	0.04	4.46	0.04				
12							5.05	0.03
13							5.28	0.14
14					5.68	0.35	5.80	0.15
15					5.95	0.46	6.19	0.07
16							6.35	0.03
17			6.47	0.05			6.56	0.02
18	6.62	0.03					6.58	0.04
19							6.84	0.02
20							8.07	0.03
21							9.41	0.20
22							9.64	0.18
23							9.62	0.20
24							9.69	0.06
25					9.76	0.23	9.77	0.02
26							9.74	0.02
27							10.02	0.01
28							10.08	0.02
29							10.14	0.04
30					11.12	0.13		
31					13.12	0.20		

Table 1: Biomarkers from the headspace of three bacteria species were normalized for blank controls and then compared. The average and standard deviation of the GC biomarkers are shown in this table.

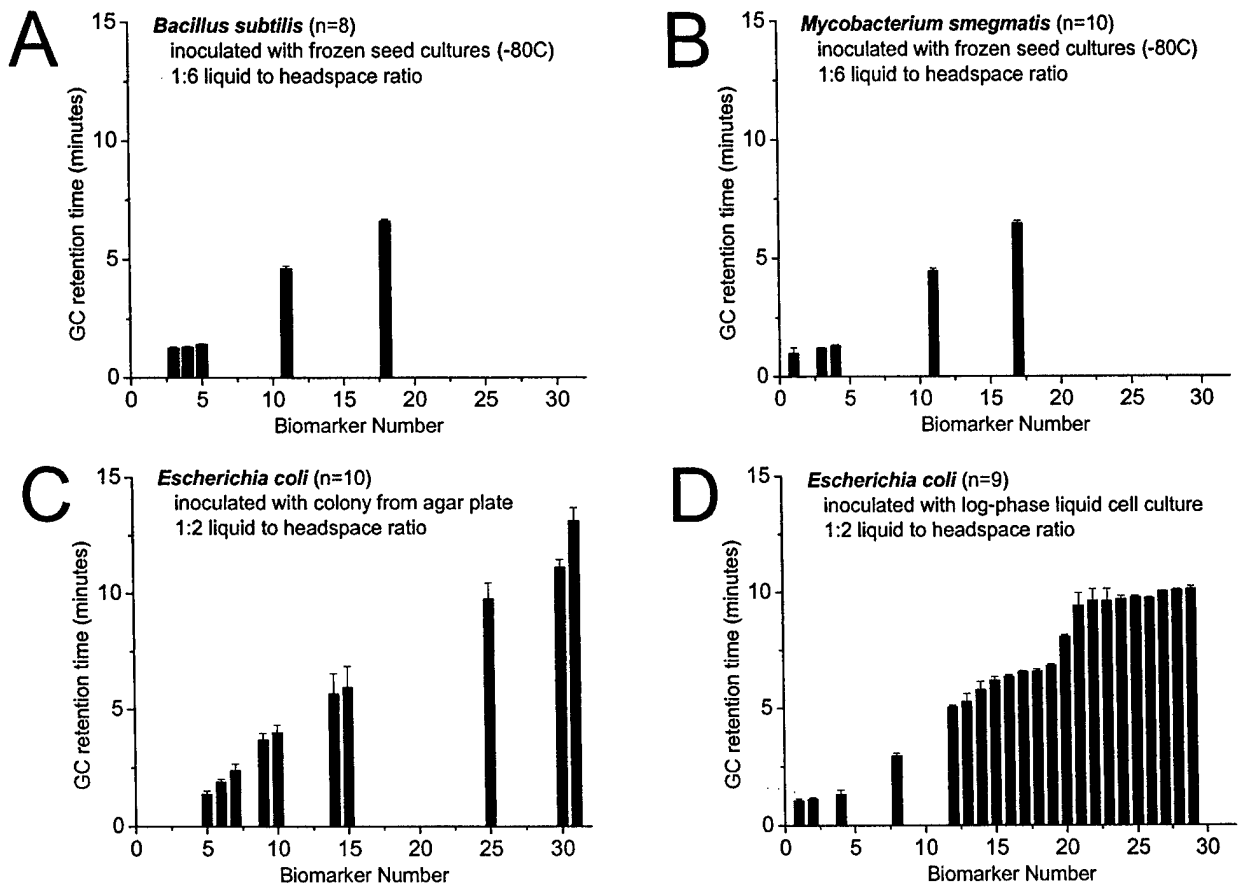


Figure 3: Biomarker comparison between different bacteria species and culture

Future Plans

In the future we may attempt to analyze our results using the ratio of various biomarkers to look for patterns in the spectra. We will also attempt to standardize our sample handling methods to reduce variation between experimental trials. We expect that once IRB and DoD compliance approvals are achieved that we will be able to collect and analyze the clinical samples for this study within the remaining study time.

Metrics

Personnel working on this project:
Michael Callahan, M.D.
Jeffrey Borenstein, Ph.D.

Publications and Presentations

Davis CE, Zapata AM, Borenstein JT, Callahan MV, Gelfand JA, Sonenshein AL, Nazarov EJ, Miller RA. Biological sample analysis using differential mobility spectrometry. 12th International Symposium on Ion Mobility Spectrometry; Umeå, Sweden; July 2003.

Nazarov EJ, Miller RA, Zhong M, Davis CE, Zapata AM, Krylov E, Eiceman GA, Kirby KW. NOx detection and identification by DMS. 12th International Symposium on Ion Mobility Spectrometry; Umeå, Sweden; July 2003.

Davis CE, Callahan MV, Gelfand JA, Borenstein JT, Miller RA, Zapata AM. Non-invasive breath diagnostics using a novel MEMS sensor. April 2003. Center for Integration of Medicine and Innovative Technology. Boston, Massachusetts.

Networked Sensor Systems Program

Patient Centric Networking and Applications
Principal Investigator: John Guttag, Ph.D., MIT

Executive Summary
We have been exploring the potential of patient-centered sensor networks. The work is motivated by the observations that today's sensor electronics and software could easily be made more capable and integrated more effectively, but, more important, that this technical improvement would yield immediate, significant benefits in patient care. The following three activities were pursued in FY03:

- PCN-Robust Patient State Sensing
- PCN-Cardiac Auscultation
- PCN-Automated Seizure Detection

Key Results
As part of this work we developed new methods and algorithms for screening for mitral valve prolapse (for which a patent application was filed) and detecting the onset of epileptic seizures. This work was tested on de-identified data provided by physicians at MGH and Children's Hospital. Preliminary results suggest that our methods are highly effective. Over the next year we will be submitting IRB's to test our tools in clinical settings.

Specific Aims
Specific Aim 1: PCN-Robust Patient State Sensing
Specific Aim 2: PCN-Cardiac Auscultation
Specific Aim 3: PCN-Automated Seizure Detection

Progress
Specific Aim 1: PCN-Robust Patient State Sensing
This project focuses on the architecture of patient-centered sensor networks. This work is motivated by the observations that today's sensor electronics and software could easily be made more capable and integrated more effectively, but, more importantly, that this technical improvement would yield immediate, significant benefits in patient care. We are pursuing two directions in this area: building prototypes and investigating deployment opportunities.

In the area of the prototype, we have worked on a redesign of our patient centric monitoring system. This design is based on a streaming database architecture, as shown in Figure 1 (page 13). This work includes a user interface that allows the user to select the signals to be monitored and set various medically relevant parameters, synthetic devices to do signal fusion, and an alerting sub-system. These cause queries to be run over the data streams and the results to be displayed to the user. The prototype was demonstrated at the MIT EECS Department's 100th Anniversary in May and at the Oxygen Partners Meeting in June.

In evaluating deployment opportunities, we have visited the Emergency Department at Brigham and Women's Hospital and several Intensive Care Units at Massachusetts General Hospital to understand how a mobile (or untethered) patient monitoring system would improve their operations.

The second prototype we are developing involves the design of a system that detects when a person has fallen. Through this prototype we will attempt to understand the issues in building a

robust mobile patient monitoring system. The design uses an HP iPaq with a built-in accelerometer.

With regards to the patient centric monitoring system, we will investigate data management techniques, data structuring approaches, and interfaces for integrating streams of data from medical devices, signal processing algorithms, and more systematic and useful approaches to alerts. The current prototype allows the user to review recent results. This feature will be extended to allow users to compare current data with earlier data, so that physicians can objectively track changes in the monitored signals over extended periods of time.

The development direction for the fall detector prototype is to add multiple accelerometers, both wired and wireless, and sensors within the environment. This will allow us to investigate how multiple sensors can be combined to produce a system that is robust to faulty sensors, sensor placement errors, and patient motion.

Progress

Specific Aim 2: PCN-Cardiac Auscultation

The main goal of this project is designing, implementing and evaluating an inexpensive to deploy and easy to use automated cardiac screening system that can be used in conjunction with an electronic stethoscope. The system aims to make a recommendation and support its decision with audiovisual diagnostic aids such as the prototypical heart beat and variable-rate playback of heart sounds. The structure of the system is shown in Figure 2. The visual prototypical beat for a normal human is shown in Figure 3. The visual prototypical beat for a patient suffering from MVP is show in Figure 4.

Our current algorithm is focused on separating patients with MVP from normal patients and patients with benign murmurs. In the last quarter we have consolidated our results and tuned the parameters of our algorithm. We have tested our detection system on de-identified data from 57 patients, with promising results.

We are targeting our current efforts at analyzing and reducing false positives. We suspect that the bulk of the false positives are due to mis-diagnosing split-S2 as MVP. We are working on automatic methods for identifying and rejecting files that have insufficient diagnostic information to make a reliable diagnosis.

In conjunction with physicians at MGH we are exploring adapting some of our auscultation techniques to the identification and classification of carotid stenosis. We have made excellent progress in this area in designing a system, called the Carotid Collar, for capturing data in this area, Figure 5. The system is based on piezo-electric sensors embedded in a cervical collar, Figure 6, to record the sounds from the carotid arteries. It also includes an EKG sensor and another piezo-electric sensor for collecting heart sounds. The software, which runs on a laptop, collects and displays data from these sources.

CIMIT funding for this aim is almost exhausted. Fortunately, we have been able to procure funding from another source. We expect that this will allow us to push this project far enough forward to deploy some test systems. We also expect to publish the results in the medical literature. We are also working with clinicians at MGH on the future possibility of collecting patient data that will allow us to investigate the utility of our carotid collar.

Progress

Specific Aim 3: PCN-Automated Seizure Detection

The goal of this project is to develop a real-time, patient-specific, epileptic seizure onset detector using scalp EEG. Our collaborators at Children's Hospital are interested in using this system to detect seizure onset more promptly so that the SPECT radio-isotope dye can be injected more promptly so that the SPECT imaging will potentially identify a smaller seizure focus.

Our strategy uses machine learning algorithms and digital signal processing. We use wavelet decomposition to generate the feature set supplied to the learning algorithm. We use a novel approach to reject artifacts, based on a library of EEG artifacts. Over the last year we explored the utility of two different architectures and two different machine learning methods for attacking this problem. The approaches were tested on de-identified data from thirty-six patients.

The best combination performs extremely well. It detects a seizure with an average delay of 8.0 +/- 3.2 seconds, and correctly declares 131 of 139 seizure events. Furthermore, the detector declared only 11 false detections in 49 hours of randomly selected non-seizure EEG.

Figure 1: Patient Centric Network: Streaming Database Architecture in Use

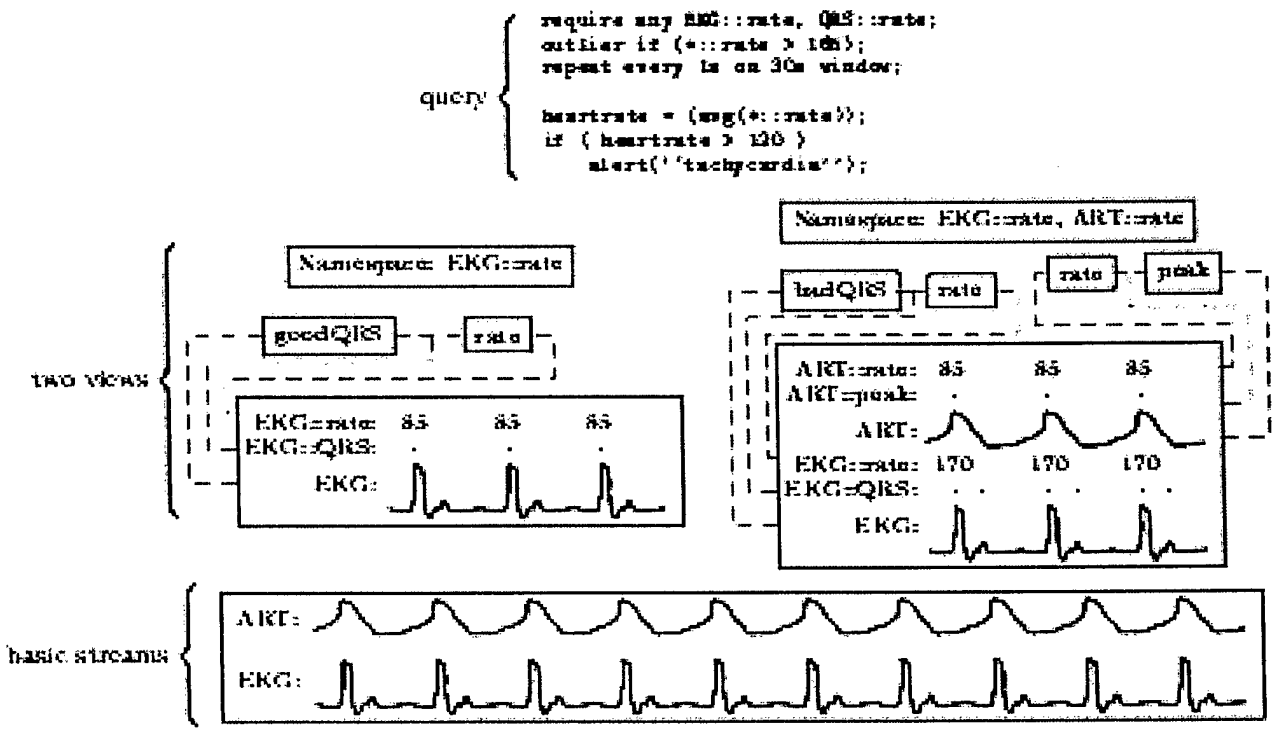


Figure 2: MIT Automated Auscultation System Block Diagram

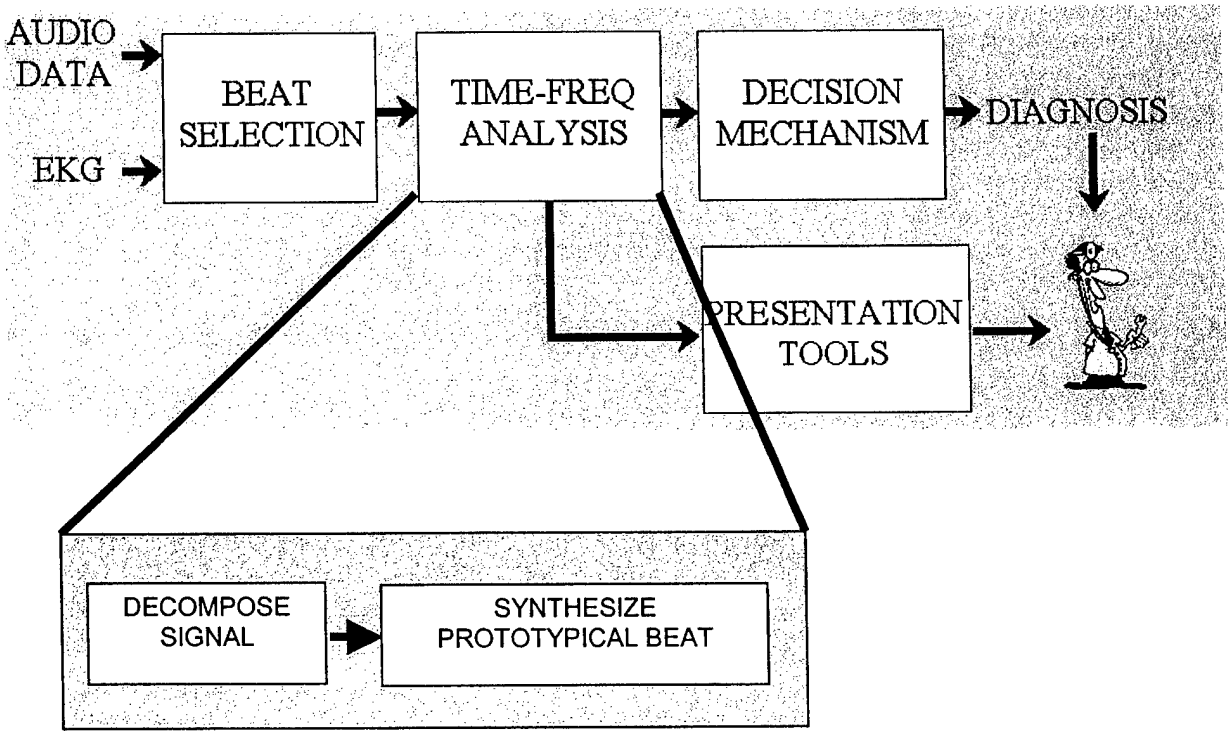


Figure 3: Prototypical Beat for Normal Human

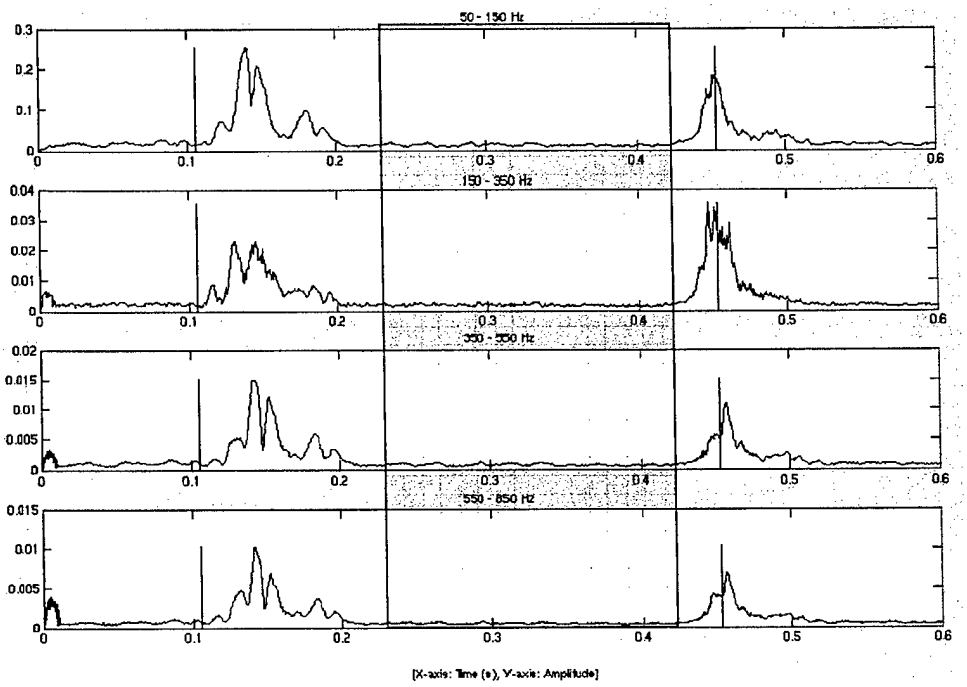
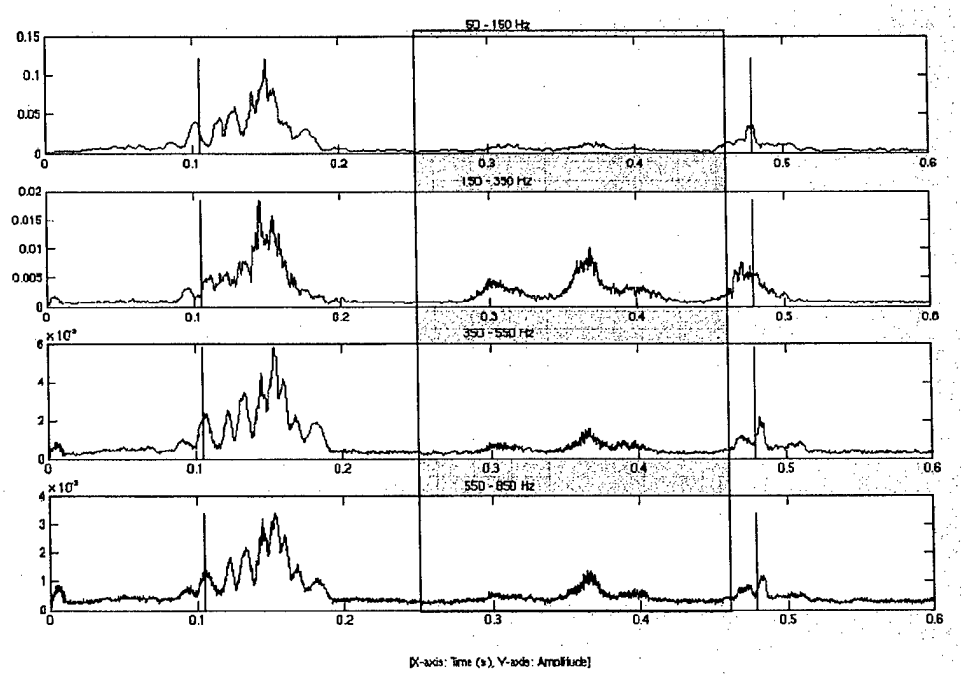


Figure 4: Prototypical Beat for MVP Patient



Future Plans

Our plans include publishing an article in an IEEE journal and possibly a medical journal, investigating patent opportunities, and working with researchers at Children's Hospital to design a tool for use in a clinical setting. Specifically, this tool will be used to investigate the effect of the timeliness of the injection of the isotope on the SPECT imaging process for locating the focus of a seizure. The hypothesis is that more prompt injection of the isotope will produce an image with a smaller seizure focus and thus less of the brain will be removed. We anticipate that we will submit an IRB to Children's this fall.

We also plan to investigate the potential applicability of our methods to enhance the effectiveness of devices that use nerve stimulation to abort seizures.

Metrics

Personnel working on this project:
John Guttag, Ph.D.
Dorothy Curtis
Deepali Garg
Jason Gift
Greg Harfst
Marcia Jung
Eugene Shih
Ali Shoeb
Zeeshan Hassan Syed
Gina Yi

Publications and Presentations

MIT Automated Auscultation System, Zeeshan Hassan Syed, Master of Engineering Thesis, MIT, May 2003.

"MIT Automated Auscultation," Patent Application, Zeeshan Hassan Syed, John Guttag, Robert A. Levine, M.D., Francesca Nesta, M.D., Dorothy Curtis, June 2003.

"MIT Automated Auscultation System." Zeeshan Hassan Syed, Masterworks Presentation, May 2003.

"Networked Sensor-based Decision Support Systems," John Guttag
CIMIT AIBS Review, May 2003.

Oxygen Partner's Meeting, June 2003.

"Enhanced SPECT Imaging Using Early Seizure Detection," Presentation to Nuclear Medicine Group at Children's Hospital, Ali Shoeb, June 2003.

"ORNet Streaming Database Demonstration," Gregory Harfst,
MIT EECS Department 100th Anniversary, May 24, 2003.

"Heartview Demonstration" Dorothy Curtis, Oxygen Partner's Meeting, June 2003.

"Automated Cardiac Auscultation," CIMIT Forum Presentation, John Guttag, June 2003.

"Carotid Collar: A Device for Ausultory Detection of Carotid Artery Stenosis," Jason Ayres Gift, Master of Engineering Thesis, MIT, September, 2003.

"Patient Specific Seizure Onset Detection," Ali Hossam Shoeb, Master of Engineering Thesis, MIT, September, 2003.

Degrees Awarded
Zeeshan Hassan Syed, Master of Engineering, May 2003
Jason Gift, Master of Engineering, September 2003
Ali Shoeb, Master of Engineering, September 2003

Diagnostics Program

EPAM Devices for Magnetic Resonance Imaging (MRI)
Principal Investigator: Steven Dubowsky, Ph.D., MIT

Executive Summary
Conventional actuators cannot be used in Magnetic Resonance Imaging (MRI) systems because of the very high magnetic fields in these systems. At MIT we are developing a new actuator technology called Electrostrictive Polymer Artificial Muscles (EPAM). Preliminary tests at Brigham and Women's Hospital (BWH) have shown that EPAM materials are MRI-compatible. The application of EPAM technology could lead to a new generation of MRI devices to improve imaging and treatment by providing actuation that can be controlled by observing real-time results in the MRI. During the current funding period, we are designing several such devices and testing their feasibility as clinical devices. During this year we first focused on manipulation mechanisms for improving the imaging capabilities of MRI. The concept is an electrically controlled receiving RF coil for MRI, which can radically change its size under remote command and thus substantially reduce the time a patient might need for a MRI session. The research is now focused on a virtually all-plastic manipulation system that could assist in surgical procedures within a closed MRI system. Specifically, the system being developed at is intended manipulate Focused Ultrasound Surgery (FUS) components within an MRI. FUS is a completely non-invasive method for destruction of deep tissue. The current mechanical manipulation system for FUS is complex, expensive, and not conducive to the sensitive and limited space within an MRI environment. Such a system could be replaced with a simpler and more suitable EPAM mechanism. As discussed below, results obtained to date have been very promising.

Key results
The development of potentially useful EPAM actuators has progressed significantly this year. Improvements in design, materials selection, and assembly processes have improved the reliability and performance characteristics of the actuators. Several alternative design concepts have been proposed and evaluated experimentally for the adjustable RF receiving coil. Such designs offer solutions that eliminate potential problems with the original design concept, including limited image quality and resizing capabilities. Design concepts for the Focused Ultrasound System have been generated and evaluated. One such device has been fabricated.

Specific Aims
Specific Aim 1: EPAM Actuators With Enhanced Performance. The objective is to enhance the performance, reliability, and repeatability of EPAM actuators for use in MRI machines.
Specific Aim 2: The Design of EPAM Imaging Coils.
The objective here is to design of a physically re-configurable RF coil actuated by EPAM actuators for changing imaging capabilities of MRI surface coils.
Specific Aim 3: To develop an all plastic manipulator.
The objective of this component of the study is to develop an all-plastic manipulation system, designed specifically for use in conjunction with Focused Ultrasound Surgery.

Progress
Specific Aim 1: EPAM Actuators With Enhanced Performance.
Since single EPAM actuators are the fundamental building blocks of the MRI devices being designed, significant effort has been focused on developing fundamentally improved EPAM actuators, and substantial progress has been made. For example, at the beginning of the funding

year, linear EPAM actuators being developed at MIT (Figure 1) had a maximum strain (in the active region) of about 57%. With recent improvements, the maximum strain amount has been increased to over 200% (Figure 2), allowing for much larger displacement. Subsequently, the amount of energy that can be stored in a single actuator has been increased substantially. Such improvement allows the overall size of the active components to be reduced without sacrificing performance.

Additionally, the specific weight of the actuators has decreased. Such improvements are key steps in taking the first step towards developing more efficient and versatile systems for effective use in a practical setting.

Figure 1. Previous linear actuators: Actuation at 6 kV yields a strain of about 57%.

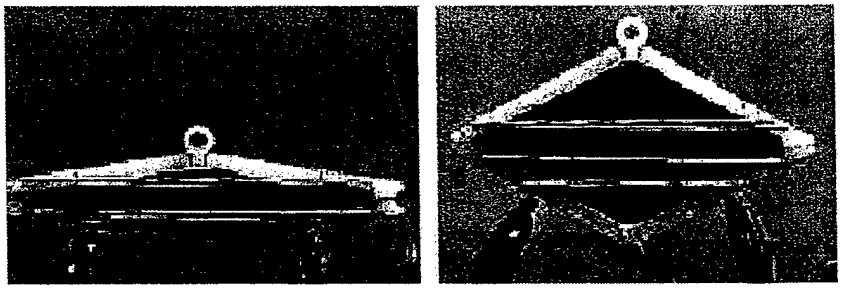


Figure 2. Example of new actuator design: Actuation at 6 kV yields a strain of about 200%.

Progress

Specific Aim 2: The Design of EPAM Imaging Coils.

The initial design concept for an adjustable RF Surface Coil or the resizable RF coil (Figure 3) has been evaluated both experimentally and conceptually. The initial design has several limitations, such as premature failure, poor shelf life properties, restricted size changing capabilities, and poor electrical properties. While some of these problems can be improved with design modifications (i.e. electrical properties), others are fundamental problems presented by material limitations (i.e. maximum size change). Consequently, other concepts, such as illustrated in Figure 4, have been proposed and are being developed. The first prototype of the Figure 4 concept is a one-dimensional version shown in Figure 5. This successfully shows an external EPAM actuator linearly changing the size of a useful RF coil.

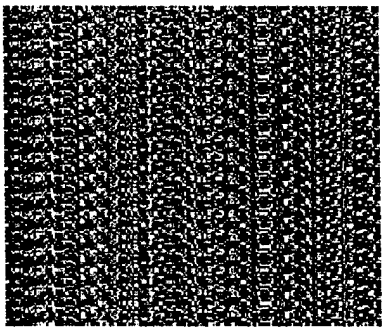


Figure 3. A conventional copper surface coil beside the initial concept for a resizable coil. This idea involved passing the RF signal through the silver material laid directly down on a shape-changing polymer.

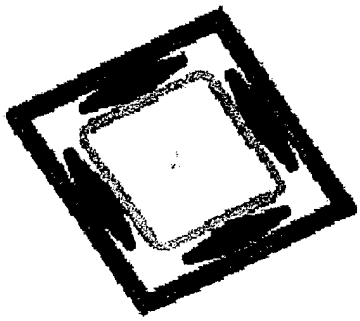


Figure 4. This concept would involve using external linear actuators to manipulate a copper frame, allowing for a greater range of size and shape changes, as well as improved conductivity for the RF signal.

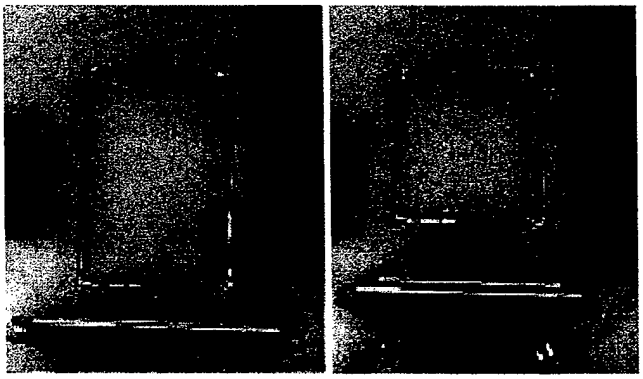


Figure 5. Re-configurable copper tube imaging coil with EPAM actuation.

Initial testing has been conducted on the above design. Figure 6 shows images taken using a variable sized coil like the one above. Images of a homogeneous doped water phantom were acquired using a gradient echo imaging sequence on a 1.5T CV/i scanner (General Electric Medical Systems, Milwaukee, WI). The resizable surface coil was manually positioned to the large or small configuration and tuning was manually achieved with a variable capacitor. A commercially available 3" diameter surface coil was used as a reference (General Electric Medical Systems, Milwaukee, WI). The imaging results (SNR throughout the imaging volume) and the changes in each possible configuration were as expected. The results were comparable to those from a commercially available imaging coil, and different performance can be attributed to the rectangular shape of the prototype as compared to the circular shape of the conventional coil. In this test setting, the shape of the copper coil was changed manually. However, the results clearly indicate a significant change in imaging capability. Mean and standard deviations were taken in three regions of interest (ROI): outside the volume of the phantom (noise), 2.5cm from the surface of the phantom (signal 1) and 7.5 cm from the surface of the phantom (signal 2). Statistical analysis of the results demonstrated several expected results: The ratio of signal 1 to signal 2 was smaller (4.1) for the coil in its large configuration, implying greater homogeneity; the smaller coil produced a relatively larger superficial signal to noise ratio (SNR), showing higher peak SNR (occurring close to the coil, at position 1); the SNR for the large

configuration coil was relatively larger at position 2 than for the small configuration coil, indicating greater penetration for the larger configuration. These results are consistent with our expectations.

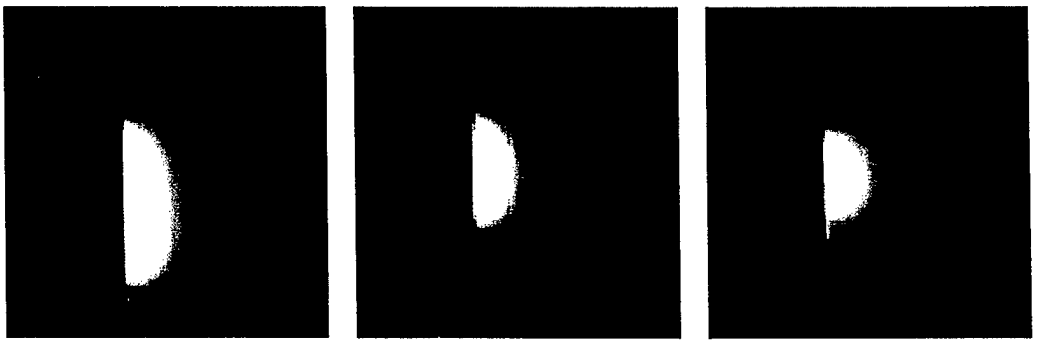


Image from rectangular coil in large configuration: Greater coverage, depth, and homogeneity.

Image from rectangular coil in small configuration: Greater SNR.

Image from commercial imaging coil (GE) of similar dimensions.

Figure 6. MRI images from a re-configurable coil using a homogeneous doped water phantom.

As a consequence of reconfiguring the coil size, the resonant frequency shifts. The tuning capacitor used to compensate for this shift can be replaced by a varactor diode in clinical applications. The capacitance of the diode is a function of bias voltage, and thus the coil can be tuned remotely or with a feedback system.

Progress

Specific Aim 3: To develop an all plastic manipulator.

As proposed, several design options have been developed and evaluated for an MRI compatible positioning system. Each design was evaluated based on both the required specifications for a clinical system and the capabilities of EPAM actuators. Based on these criteria, an experimental illustration of one such device was fabricated (Figure 7). The device pictured below can attain a linear position over a 12 cm range in steps of 5 mm. This matches one requirement of the clinical system. The system uses a stepping mechanism to position an object. The correct position is obtained by activating the actuators in a pre-defined sequence of on/off commands (based on current and desired position). The system draws no power in a static position, requires no feedback, and contains only MRI compatible materials. It is also very lightweight, inexpensive, and easy to manufacture. The two dimensional version of the above device is currently being built based on the model shown in Figure 8.

Figure 7. FUS Manipulation System Mechanism

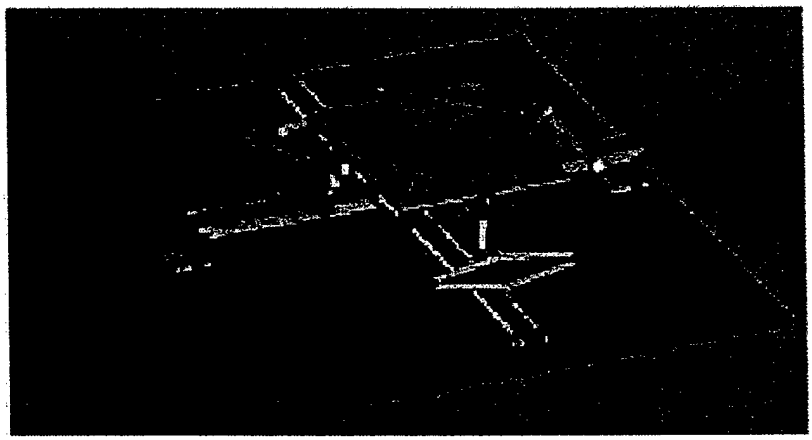


Figure 8. FUS Manipulation System Concept

Based on recent advances in EPAM capability (increased strain mentioned above), other design options have also become feasible. Since recent actuators have demonstrated large strains at nearly constant force, the potential to combine these with feedback to develop traditional position control has become an option. Another option being explored is the concept of combining a large number of these actuators, constructed at varying sizes, to create a digitally controlled positioning system. This alternative is now feasible based on the ability to achieve a larger variety of displacements. The increased capabilities and versatility of EPAM also make possible the development of other MRI applications.

Future Plans

Improvement of EPAM actuators is an ongoing research goal at MIT. Understanding and optimizing the performance and characteristics of these actuators will continue to be an important objective in the upcoming period.

Metrics

Personnel working on project:
Prof. Steven Dubowsky, MIT, Principal Investigator
Vivek Sujan, MIT, Post-Doctoral Researcher
John Vogan, MIT, Graduate Student
Daniel Kacher, MRI & Image Guided Therapy Program at BWH, Senior Engineer

Publications and Presentations

In preparation.

A method and device for performing bladder mapping
Principal Investigator: W. Scott McDougal, M.D., MGH

Executive Summary
The purpose of this project is to develop a methodology by which the entire bladder surface epithelium can be recorded reliably and reproducibly in one composite picture so that specific areas where lesions are or were at one interval can be reliably relocated at another time interval. This requires the development of specific landmarks and the ability to put composite photographs together of the bladder since there is no one lens system which would allow the entire bladder to be viewed at a specific point in time. The hypothesis is that employing a two-lens system simultaneously records various portions of the bladder which may be overlaid using a computer program thus creating a composite picture, i.e. a bladder map.

Key Results
We have obtained all the instrumentation for this project.

Specific Aim
To capture a video image with the use of lasers for location and map the bladder.

Progress
In addition to acquisition of instrumentation, we have developed a phantom bladder, have successfully photographed segments of the phantom and have determined that six individual photographs can be compositely overlaid to create a bladder map. However, we have determined that a more reproducible methodology involves the use of video, which we have also developed. A video recording system with the ability to capture various static images has been developed. We have also determined that a laser marker would be helpful for locations and this currently is in the process of being developed.

Future Plans
To utilize a laser marking system to perform the composite and to begin the trial on patients once all approvals have been obtained.

Metrics
Personnel working on this project:
W. Scott McDougal, MD
Shahin Tabatabaei, MD

Publications and Presentations
In preparation.

Radio Frequency Impedance Mapping for Medical Imaging
Principal Investigators: Aaron K. Grant, Ph.D., and Daniel K. Sodickson, Ph.D. Beth Israel Deaconess Medical Center

Executive Summary
Radio frequency impedance mapping (RFIM) is a proposed new medical imaging modality that aims to produce images of internal anatomy that exhibit the local electrical properties (namely, electrical conductivity and permittivity) of tissues inside the body. In RFIM, an array of radio frequency (RF) coils is placed on the patient's body, and the electrical properties of the array are measured by applying a small amount of RF power to the array and measuring its response. The electrical properties of the array are modified by the coupling of the array's electromagnetic field to the patient's body, and these modifications (known collectively as 'loading' effects) can be used to extract information about the electrical conductivity and permittivity inside the patient's body. Information about conductivity and permittivity is expected to be useful for a variety of clinical applications, including cancer screening, characterization of ischemic tissue, and monitoring of cerebral edema.

Prior to the funding period, the basic principles of RFIM had been investigated using relatively crude computer simulations. The results of these simulations were promising, and it was at this time that application was made for CIMIT funding. During the funding period, progress has been made on several fronts, and many of the basic principles of RFIM have been validated experimentally.

Key Results

Specific benchmarks during the funding period include:

- Acquisition of a cluster of 10 linux computers for use in electromagnetic modeling and image reconstruction for RFIM
- Development of parallel computer programs for electromagnetic modeling
- Implementation of algorithms for image reconstruction
- Construction of a set of coil arrays for use in RFIM
- Acquisition of RF test equipment for performing measurements of coil array properties
- Demonstrations that the aforementioned hardware and software can be used to measure the conductivity and permittivity of homogeneous imaging phantom with sufficient accuracy to be of clinical interest
- Demonstrations that linear arrays of RF coils can encode spatial information about the distribution of conductivity in inhomogeneous imaging phantoms
- Construction and testing of an array for experiments in fully three-dimensional imaging

Specific Aims

Outlined below are a series of benchmarks aimed at prototype construction. Although more remains to be done, we have substantially completed these benchmark goals.

Progress

Coil design and dielectric measurement

The aim of this portion of the work was to determine good design parameters for RF coils and to use them in measuring the dielectric properties of homogeneous imaging phantoms. The latter goal was deferred to the second specific aim, as described below.

Design choices for RF coils were guided by a combination of experimental and theoretical work. It was determined that high-Q coils constructed by etching relatively narrow (1/4" or less) conducting strips on printed circuit boards sufficed for this work. Such high-Q coils showed good sensitivity to loading effects when they were tuned, using appropriate capacitors, to a frequency on the order of 100 MHz. At lower frequencies the loading effects were, as expected, somewhat smaller, while at higher frequencies it proved more difficult to accurately model the electrical properties of the coil in our reconstruction software.

The electrical properties of our coils were determined by measuring their so-called 'S-parameters' with a Hewlett-Packard network analyzer. As a result, it was necessary to match the impedance of the coils to approximately 50 Ohms (the input impedance of the network analyzer) in order to gain good sensitivity to loading. We used a combination of experimental and theoretical work to optimize the impedance matching, and concluded that the input impedance of the coil, when loaded, should be somewhat larger than 50 Ohms on resonance.

A typical coil used in this work is displayed in Fig. 1, together with a circuit schematic.

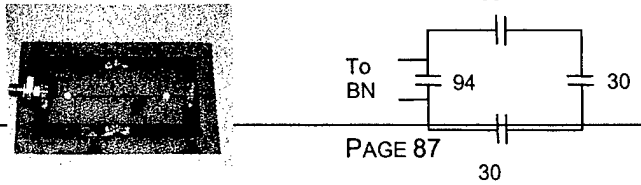


Figure 1. A typical coil, together with a circuit diagram. The term "BNC" refers to the BNC cable used to connect the coil to the network analyzer.

Arrays of such coils were used subsequently to obtain quantitative measurements of the dielectric properties of homogeneous imaging phantoms, the second goal of this specific aim.

Coil arrays and measurement of the impedance matrix
The aim of this work was to assemble to the coils described above into arrays and to determine a robust technique for measuring the impedance matrix of such arrays. A second aspect of this work involved the development, in software, of high-fidelity mathematical models of the array for use in image reconstruction.

After exploring various possibilities, it turned out that the most robust technique for extracting information about the array's impedance matrix was to simply record the S-parameters of the array as measured by the network analyzer, and to use these in place of the impedance matrix in image reconstruction. Since the S-parameters and the impedance matrix encode essentially the same information, this simple strategy is sufficient. To enable measurements on arrays of modest size, we obtained a twelve-port test set for use with our network analyzer. This test set allowed us to analyze arrays consisting of up to twelve coils. The network analyzer was further augmented by connecting it to a personal computer equipped with software to automate measurements of the complete set of S-parameters for any given array.

Using data acquired with the network analyzer, we proceeded to measure the dielectric properties of homogeneous imaging phantoms. This served to test both the experimental apparatus and our image reconstruction software. Image reconstruction was performed by creating a computer model of the coil array and the phantom, and computing the S-parameters using electromagnetic simulations. The dielectric properties of the model of the phantom were iteratively adjusted until the simulated S-parameters matched the experimentally measured S-parameters. In order to ensure that the numerical model faithfully represented the experimental array, measurements of the S-parameters of the array *in the absence of an imaging phantom* were used to characterize the array and to fix certain parameters in the numerical model.

A simple two-coil array experiment is displayed in Fig. 2, together with the numerical model of the array. In this instance, the array was used to measure the dielectric properties of a series of imaging phantoms filled with agar gel containing varying amounts of salt as shown in Fig 3. Such gels are expected to have relative permittivities of order 80, and conductivities that scale linearly with salt concentration. The reconstructed values of conductivity and permittivity are displayed in Table 1. These values are comparable to those expected for saline solution of similar concentration, as we would expect because the gel is composed of 98% saline (by mass). Furthermore, we see that the permittivity values are approximately constant with saline concentration, while the conductivity shows the expected linear scaling. To futher quantify the accuracy of our reconstructions, we performed a similar experiment on pure saline solution, and the measured dielectric properties (relative permittivity 72, conditivity 0.54 S/m) agree at the 20 percent level with the expected properties (relative permittivity 78, conductivity 0.51 S/m).

Salt concentration	0 g/liter	5 g/liter	10 g/liter
Conductivity (S/m)	0.03	0.82	1.56
Relative Permittivity	88	91	90

Table 1. Reconstructed conductivity and permittivity values for agar gels containing varying quantities of salt.

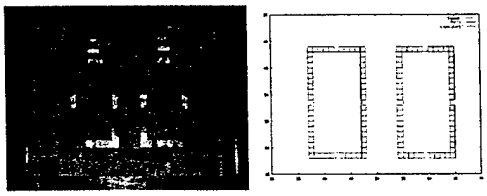


Figure 2. A two-element coil array (left) together with a display of the finite-difference model of the array.

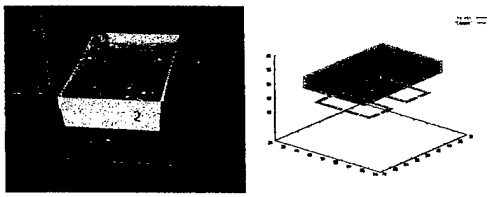


Figure 3. On the left, a dielectric measurement on agar gel (left) and the corresponding finite-difference model.

In vitro testing and software development
The aim of this phase of the work was to test the ability of RFIM to encode spatial information about the local conductivity and permittivity of imaging phantoms, and to develop software for array modeling and image reconstruction.

The software developed during the course of this work is comprised of some 8,000 lines of C++ code. The most computationally intensive portions of the algorithm were written to run in parallel on ten machines simultaneously in order to obtain faster reconstructions times. The resulting software library includes algorithms for:

- Solution of Maxwell's equations using finite-difference time-domain methods
- Numerical modeling of RF coil arrays and computation of their S-parameters
- 'Calibrating' these numerical models to produce high-fidelity representations of the experimental arrays used in this work
- Solving for the dielectric properties of the body to be imaged in terms of the measured S-parameters

During this phase of the work, a variety of simple arrays were constructed and used to image simple phantoms filled with saline solution and/or agar gel containing varying concentrations of salt. In one such experiment, the four coil linear array of Fig 4 was used to image a region consisting of three 'voxels' situated over the array as displayed in the finite-difference model on the right of the figure. A phantom was constructed by placing saline-filled containers over the array as shown on the left in Fig 5, and the data were reconstructed to yield the conductivity map shown on the right. The conductivity map shows that RFIM successfully distinguishes between regions of space filled with air and saline solution.

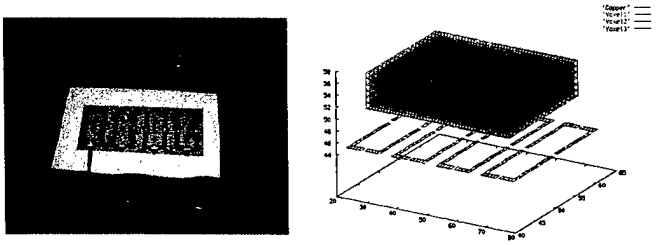


Figure 4. A four-element array and the corresponding finite-difference model, including the imaging voxels.

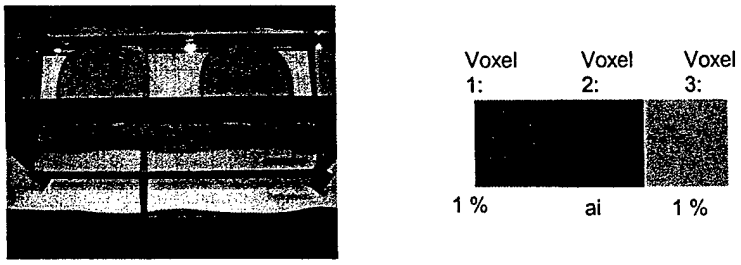


Figure 5. A conductivity mapping experiment (left) and the reconstructed conductivity map (right), where image intensity is proportional to conductivity.

A six-element array intended for three-dimensional imaging experiments is shown in Fig. 6. The six elements are situated on the faces of a cube surrounding an imaging volume measuring approximately 8 cm on a side. The imaging volume was then filled with cubes of agar gel with varying conductivity to fill in a 2x2x2 cubic array as shown on the right of the figure. The resulting data are currently in the process of being reconstructed.

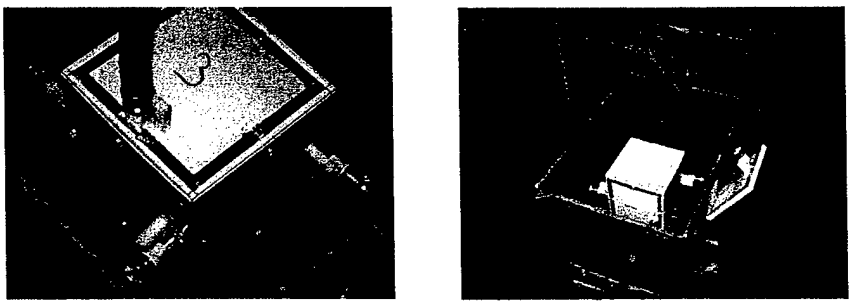


Figure 6. A six element array for three-dimensional imaging. On the right, the imaging volume inside the array is filled with agar cubes of varying conductivity.

Future Plans

Much of the work during the funding period was aimed at the development of basic tools for experimenting with RFIM. Our results have established the basic feasibility of RFIM, and we are now in a position to scale up the size and complexity of our arrays to begin work on more realistic imaging problems that might arise in clinical work. We have demonstrated the ability of RFIM to measure conductivity and permittivity with sufficient accuracy to discriminate between different tissues inside the body, and we have also demonstrated the ability to map local variations in electrical properties of imaging phantoms.

In future work we intend to extend and enhance our current apparatus, and to explore various other applications of RFIM. One such application is the possibility of using RFIM to detect glass shards (such as might occur in injuries resulting from a car accident or explosion) by using the large contrast in conductivity between glass and biological tissue. A second possibility is to combine RFIM with MRI by constructing RFIM coil arrays that are also capable of MRI data acquisition. This would combine the benefits of MRI's high spatial resolution and RFIM's sensitivity to tissue electrical properties.

Metrics

Personnel working on this project:
Aaron Grant, Ph.D.
Daniel Sodickson, Ph.D.

Publications and Presentations
In preparation.

Robust Elastography for High-Resolution Strain Imaging in the Vulnerable Atherosclerotic Plaque
Principal Investigator: Raymond Chan, Ph.D., MGH

Executive Summary
The goal of this project has shifted slightly to focus primarily on the development of a high-resolution OCT-based robust multidimensional strain estimator for characterization of atherosclerotic plaque biomechanics and comparison of OCT-derived strain estimates with those from IVUS imaging.

Key Results
Over the past year our experiments with vessel phantoms and diseased coronary arteries demonstrated that with conventional OCT imaging and motion region-of-interest constrained optical flow estimation, strain estimates from within the vessel wall appeared to be more blurred than expected. In the current quarter, we have sought to address this problem by first identifying the root cause, and then by making improvements to the image acquisition system and to the processing algorithms used for strain estimation.

Specific Aims
Our specific aims are:

- Development of fast and robust estimators of arterial wall velocity and strain for high-resolution mapping of vascular tissue biomechanics
- Investigation of strain and elastic modulus distributions in atherosclerotic plaques *ex vivo* to correlate local lesion biomechanics with plaque composition determined by histopathology

Progress
In experiments conducted this year, we determined that the low resolution of OCT-derived strain fields was a result of the high degree of regularization required to compensate for the random image intensity fluctuations and rapid speckle structure decorrelation. The higher imaging noise and decorrelation observed in OCT relative to IVUS results in strain estimates with poorer signal-to-noise characteristics for a given level of regularization. Therefore, more regularization is required to obtain a noise-robust strain field from OCT. Furthermore, the brightness conservation constraint imposed by optical-flow estimation is too strict since variations in overall image intensity can occur during the imaging process.

To address the signal-to-noise problem, we modified the OCT system to allow for fringe-resolved data acquisition. A new LabView-based acquisition system was developed to digitize each OCT polarization channel at a sampling rate of 5MHz. The resulting data captures the OCT fringe signal, providing not only signal amplitudes, but also additional phase information with significantly higher pixel density in the axial direction (Figure 1). These improvements consequently allow for tissue velocities to be estimated from a larger number of pixels with both amplitude and phase information, increasing the noise sensitivity of motion tracking.

To address the problems with brightness conservation, we have also completed coding of a motion-tracking algorithm based on maximization of linear correlation coupled with a tissue incompressibility constraint. This algorithm does not make any assumptions about constant image intensity over time and we are in the process of validating these results in phase-sensitive OCT images from polyvinyl-alcohol phantoms and from *ex vivo* human aortic specimens.

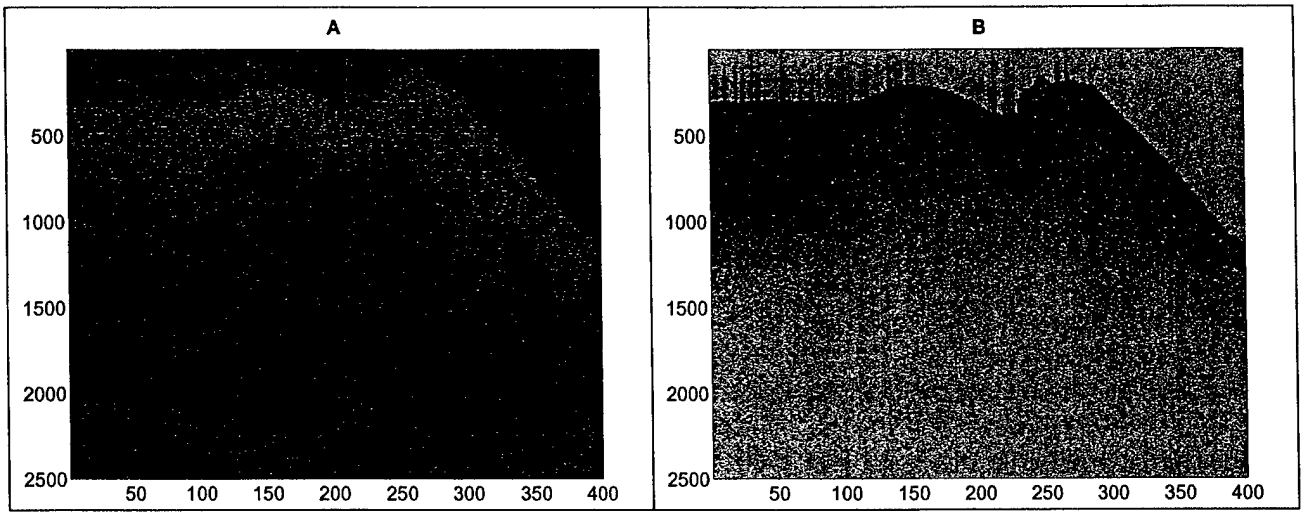


Figure 1. A. Example fringe-resolved OCT data from an *ex vivo* aortic specimen. B. Corresponding OCT image with amplitude and phase information. Note that 2500 samples are available in each image column for velocity and strain estimation, as compared with only 250 samples from the prior acquisition system.

Future Plans

We anticipate that further modifications and testing of new algorithms will be completed in the next few months.

Metrics

Personnel working on this project:
Raymond Chan, Ph.D.
Nicusor Iftimia

Publications and Presentations

Chan R.C., Karl W.C., and Lees R.S., *Robust estimation of arterial strain from non-invasive carotid ultrasound images.* in *Second Joint Meeting of the IEEE Engineering in Medicine and Biology Society and the Biomedical Engineering Society*. 2002. Houston, TX.

Chau A., Chan R.C., Iftimia N., Kaazempur-Mofrad M., Kamm R.D., Tearney G.J., Bouma B.E., *Elastography of coronary vessels using optical coherence tomography*, in *SPIE Photonics West 2003*, San Jose, CA.

Chan R.C., Chau A., Iftimia N., Shishkov M., Kaazempur-Mofrad M.R., Tearney G., Bouma B.E., *Intravascular optical coherence elastography*, submitted to 2004 IEEE International Symposium on Biomedical Imaging: From Nano to Macro, Arlington, VA.

Chan R.C., Chau A., Iftimia N., Shishkov M., Kaazempur-Mofrad M.R., Tearney G., Bouma B.E., *Vascular optical coherence elastography*, to be submitted to Optics Express.

In Vivo Detection of Inflamed Plaques in Rabbits Using FDG and a Novel Beta-Detecting Catheter

Principal Investigator: Ahmed Tawakol, M.D., MGH

Executive Summary

Cardiovascular disease remains the leading cause of morbidity and mortality in the United States, largely due to events caused by rupture of a vulnerable atherosclerotic plaque (VP). Currently the most reliable clinical tools used to diagnose coronary disease, (myocardial perfusion imaging and coronary angiography), are able to detect obstructive lesions, but can not detect VP. As such, a method to detect VP is needed.

The overall goal of this work is to develop a catheter-based method to detect vulnerable coronary artery plaques on the basis of their uptake of a radionuclide tracer. The proposed project is an extension of work supported by the CIMIT New Concepts Award: "Detection of Vulnerable Atherosclerotic Plaques with Radionuclide Technology". In the prior autopsy study, we successfully demonstrated that ^{18}F-fluorodeoxyglucose (FDG) concentrates in macrophage-rich plaques in a rabbit model of atherosclerosis. In the proposed study, we will test the ability of a novel catheter-based, intra-vascular nuclear detector to identify macrophage-rich plaques *in vivo*, in the same rabbit model that was used for the autopsy study.

The proposed study is supported by preliminary data on FDG uptake in abdomino-thoracic aortas excised from rabbits with experimental atherosclerosis. Activity detected in these ex vivo specimens with the novel detector correlated with well counting measurements, ($r=0.89$, $P<0.001$) and atherosclerotic regions were readily distinguished from control, (11.9 ± 2.1 vs. 4.8 ± 1.9 cps in atherosclerotic vs. control regions, $P<0.001$). Moreover, the catheter-determinations of FDG uptake correlated with macrophage area by histology ($r=0.7$, $P<0.01$)

On the basis of the prior autopsy study, and the promising preliminary data with this new scintillation detector, we will determine the ability of this method to differentiate macrophage-rich plaques from non-atherosclerotic areas *in vivo* in rabbits with experimental atherosclerosis. We will also attempt to increase the sensitivity of the catheter by bringing the detector closer to the wall, and by improving catheter optics.

If this *in vivo* rabbit study is successful, it will open a new possibility for detection of inflammatory plaque in living patients with FDG imaging, and will also provide a method for detection of other features of plaque that could be identified by other radionuclide tracers.

Key Results

Approval to begin the experiment was granted by DoD in Spring of 2003.

Specific Aims

- To test the hypothesis that macrophage-rich atherosclerotic lesions can be detected in living rabbits using an intravascular beta detector to identify FDG accumulation.
- An FDG-uptake "map" of the abdomino-thoracic aorta will be obtained in vivo with the beta-ray detector
- Animals will be sacrificed and aortas excised
- The FDG uptake 'map' will be correlated to macrophage density as determined by histology.
- To test the hypothesis that performance of the catheters can be enhanced by two approaches:

- By increasing scintillation events by improving apposition between the scintillator and vessel wall. This will be accomplished by placing the scintillating polymers on the tip of an inflatable balloon.
- By improving detection of scintillation events by focusing photons emitted by the scintillator onto optical fibers via an etched diffractive microlens.

Progress

Since approval was received in the Spring of 2003, the initial investment of effort in this project was to produce the atherosclerotic animals that are needed for this investigation. To accomplish this, we surgically induced balloon de-endothelialization injury of the infradiaphragmatic aorta in New Zealand rabbits. This is followed by high cholesterol diet feeding. At 10 weeks, fluorodeoxyglucose will be administered to the experimental rabbits and controls, after which intravascular detection with the beta ray detector will be attempted.

A parallel effort is underway at IntraMedical (our industrial collaborators) to improve the detector's sensitivity. A new prototype of the detector has been constructed, and will be available for intravascular studies once the experimental rabbits have matured. We expect delivery of a prototype in 4-6 weeks.

Because of the several-month delay in starting the protocol, a 1-yr no-cost extension was requested (and has been granted) to continue the experiments.

Future Plans

Our team plans to do the following:

- To test the hypothesis that macrophage-rich atherosclerotic lesions can be detected in living rabbits using an intravascular beta detector to identify FDG accumulation, and
- To test the hypothesis that performance of the catheters can be enhanced by two approaches.

Metrics

Personnel working on this project:
Ahmed Tawakol, M.D.
Greg Bashian, M.D.
Kussai Aziz, M.D.

Publications and Presentations

In preparation.

Project: Diagnosis of Pancreatic Cysts
Principal Investigator: Brett Bouma, Ph.D., MGH

Executive Summary

Pancreatic cystadenomas represent a spectrum of malignancy. Serous cystadenomas are benign adenomas and rarely demonstrate malignant behavior. Mucinous cystadenomas may be benign, atypical, or malignant and surgical resection is often curative. Pseudocysts consist of localized collections of fluid that mimic cystadenomas and may be removed with drainage. Endoscopic ultrasound (EUS) has emerged as a powerful tool for the diagnosis of cystadenomas because of its ability to provide high quality images and to direct fine needle aspiration (FNA). Although the use of EUS represents a major advance over CT scanning, the diagnostic accuracy of EUS for cystadenomas remains rather low. The National Cooperative Pancreatic Cyst study, centered at Mass. General Hospital (MGH) has demonstrated an accuracy of 56% for the diagnosis of benign mucinous cystadenomas and 73% for malignant cystadenomas in 112 patients who have undergone surgical excision. One of the primary weaknesses of EUS imaging demonstrated in the study was the lack of sufficient resolution to differentiate between mucinous and serous epithelia as well as the inflammatory tissue lining pseudocysts. This investigation will examine the possibility of employing optical coherence tomography (OCT), an emerging high resolution endoscopic imaging technique, with EUS. The ability to reliably differentiate the major types of pancreatic cystadenomas using mucosal imaging will represent a major advance in the management of patients with this potentially curable pancreatic malignancy.

Key Results

An OCT microscope was developed and focal parameters were optimized for imaging morphologic and microscopic features of pancreatic cysts. Sufficient resolution was obtained to allow the identification cyst epithelia. Morphologic features, also diagnostic of cyst type, were observed and correlated with histology.

Specific Aim

To examine the possibility of employing optical coherence tomography (OCT), an emerging high resolution endoscopic imaging technique, with EUS.

Progress

Ten pancreatic specimens, obtained during Whipple resection and autopsy, have been imaged with OCT. Histology was obtained in each case. A variety of pancreatic malignancies were included in this specimen set, including two mucinous cystic lesions. Our goal was to determine whether OCT could provide morphologic and microscopic information relevant to cyst diagnosis. Although several morphologic parameters hold potential, the most promising diagnostic approach was to directly resolve and identify the epithelial cells of cysts. Our findings indicate that through modification of the light delivery system, adequate resolution could be achieved to meet this goal.

Figure 1 Images of duodenum acquired with low (left) and high (right) resolution. In the high-

resolution image, villi can clearly be resolved.

In order to gauge the ability of OCT to discriminate fine pancreatic tissue structure, a number of specimens of pancreatic tissue, as well as stomach and gall bladder, have been imaged and submitted for histology. Accurate registration of imaging locale with histology is difficult, but nevertheless we have determined OCT is capable of determining tissue microstructural detail. Importantly, OCT is capable of distinguishing thickened epithelial tissue from adjacent tissue layers.

Figure 2 Image of a multiloculated cyst with enlarged epithelium.

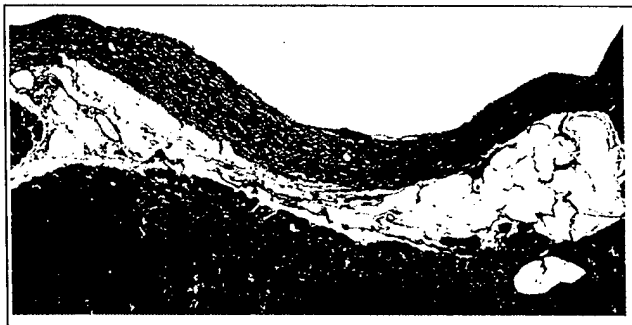


Figure 3 Pancreatic ductal epithelium. The flat cuboidal epithelium is not resolved by OCT.

Figure 4 Mucinous cyst. The thin band in at the surface of the OCT image (right) is consistent with enlarged epithelium of the mucinous cyst.

Metrics

Personnel working on project:
B.E. Bouma, PhD
G.J. Tearney, MD, PhD
G. Lauwers, MD
W. Brugge, MD
C. Fernandez-del Castillo, MD
C. Kauffman

Publications and Presentations
In preparation.

Spectrally Encoded Confocal Microscopy

Principal Investigator: Brett Bouma, Ph.D., MGH

Executive Summary

Medical imaging technology has advanced over the last twenty years to provide physicians with indispensable information on the macroscopic anatomy of patients. Imaging techniques such as radiography, magnetic resonance imaging, computed tomography, and ultrasound, allow non-invasive investigation of large-scale structures in the human body with resolutions ranging from 100 μm to 1 mm. However, for many applications, such as the detection of early stages of cancer, higher resolution is necessary for proper diagnosis. In addition, clinical procedures such as screening for carcinoma and the surgical detection of tumor margins require higher resolution diagnostic imaging methods. To address these and other clinical problems in situ, a non-invasive imaging technology with a resolution that approaches that of standard histopathology (0.5 - 1.0 μm) must be used. The proposed work will develop a new method for optically imaging tissue with high resolution and will evaluate the ability of this approach for providing diagnostic information relevant for the intraoperative identification of tumor margins. Our technology is based on the concepts of reflectance confocal microscopy and is referred to as Spectrally Encoded Confocal Microscopy, SECM.

Key Results

We have developed a system for acquiring SECM images at a rate of 30 frames per second, more than three-orders of magnitude faster than our prototype system and sufficient for real-time, cellular resolution imaging in living subjects.

Specific Aim

To develop a new method for optically imaging tissue with high resolution and will evaluate the ability of this approach for providing diagnostic information relevant for the intraoperative identification of tumor margins.

Progress

Spectrally encoded confocal microscopy (SECM) is a single optical fiber based confocal microscopy technique that has the potential to enable endoscopic reflectance confocal microscopy[1]. SECM eliminates the need for a rapidly scanning mechanical mechanism at the distal end of the imaging probe by encoding one spatial dimension of the confocal image by wavelength. Spectral encoding can be accomplished by launching broad bandwidth light into a small diameter, flexible single mode fiber. At the distal end of the probe, the output from the single mode fiber illuminates a diffractive optical element (e.g. transmission diffraction grating). An objective lens focuses each diffracted wavelength to a distinct spatial location within the specimen (Figure 1). After being reflected from the tissue, the encoded optical signal is recombined by the diffraction element and collected by the single mode fiber. The core of the single-mode fiber accepts only in-focus light in a manner similar to the pinhole aperture of conventional confocal microscopes. Outside the probe, within the system console, the spectrum of the returned light is rapidly measured and converted into confocal remittance as a function of sample location. The other dimension of the image can be scanned using mechanical means at much slower speeds (4-30 Hz). SECM can produce confocal images with a large field-of-view and a high number of resolvable points.

SECM GRISM-based probe

The design of an endoscopic confocal microscope probe is restricted by the limitations in overall device diameter. The length of a multiple element, high-NA microscope objective required to perform adequate optical sectioning typically exceeds the allowed diameter. Consequently, the optical axis of the objective must coincide with the longitudinal axis of the probe. This becomes

problematic in SECM as strong diffraction by a grating necessitates off-axis illumination and transmission.

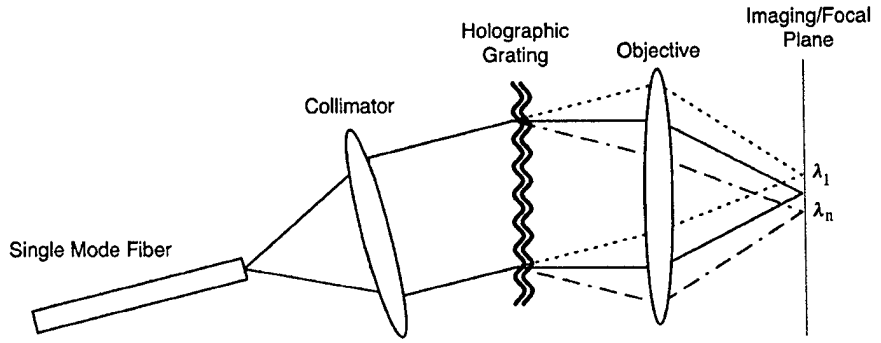


Figure 2 SECM concept. Broad bandwidth light is delivered through a single-mode fiber and collimated onto a diffraction grating. The angularly dispersed light is then focused to different spectrally encoded locations in the focal plane of the objective lens.

We have developed an small-diameter SECM probe that enables on-axis spectral dispersion, based on a dual prism grating combination (DP-GRISM)[2]. A schematic of the probe including the DP-GRISM is shown in Figure 2. The DP-GRISM allows the broadband light to be strongly dispersed while keeping the center wavelength on axis. The DP-GRISM consists of two silicon prisms of high index of refraction assembled with a high periodicity (1100 lpmm) holographic Dickson grating. The prisms' apex angles operate the grating at Littrow's angle and surfaces are AR coated to minimize losses.

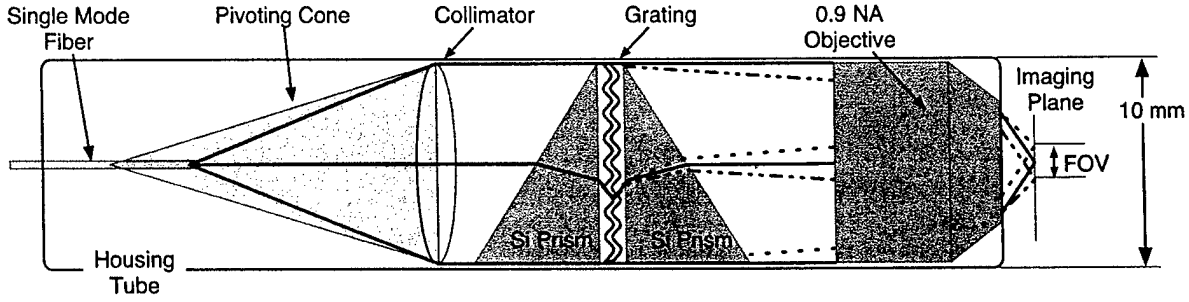


Figure 3 Schematic of the SECM probe. Ray tracing, in black and dotted lines, shows the propagation of light through the collimator, DP-GRISM and modified LOMO objective. The pivoting cone scans the slow axis of the image by tilting in and out of the plane of the page.

In order to create a two-dimensional image, the dimension orthogonal to the spectrally-encoded axis is scanned using a miniature stepper motor. The motor tilts the single-mode fiber and collimator, both housed in a metal pivoting cone. The above components, along with a 0.9 NA water immersion objective (LOMO 30x which was machined to 10 mm diameter) are housed in a stainless steel tube.

The SECM probe was tested using a semiconductor optical amplifier broad bandwidth light source (λ_0=1.32 μm, FWHM=70 nm) and an optical spectrum analyzer. The SECM system yielded images with a field of view of 658 μm, a lateral resolution of 1.1 μm and an axial resolution of 4.6 μm. A confocal image of onion skin, shown in Figure 3, obtained using our probe, demonstrates cellular membranes and intracellular details. These features were seen up to a depth of 500 microns.

Figure 4 Image of onion skin obtained with the SECM handheld probe. Each image is 300x600 pixels, corresponding to 300x650 microns, and taken at a depth of 100 microns. The wavelength encoded axis is along the x-axis (horizontal-axis) of this image.

While the previous work demonstrated the potential of SECM for endoscopy, images took several minutes to acquire due to the poor sensitivity of the spectrometer utilized in these experiments. An alternative to broad bandwidth illumination and spectral detection is utilization of a rapid wavelength-tuning source. In this case, when light with a rapidly changing wavelength is transmitted through the SECM probe, the spot is scanned across the sample. This point-by-point illumination removes the need for spectral detection of the remitted signal, since the signal as a function of time represents the signal as a function of transverse location within the sample.

Polygon based tuning source

In order to obtain high-speed SECM images having a large field-of-view and a high number of resolvable points, the tuning source must meet several requirements. To be used with the DP-GRISM probe, the tuning range of the source must be approximately 70 nm to preserve the large field-of-view. The instantaneous linewidth of the tuning source must match the spectral resolution of the DP-GRISM probe (0.1-0.2 nm) in order to maximize the number of resolvable points. Finally, the tuning source is required to have a high power and peak-to-background spectral density ratio to achieve a high signal-to-noise ratio and dynamic range.

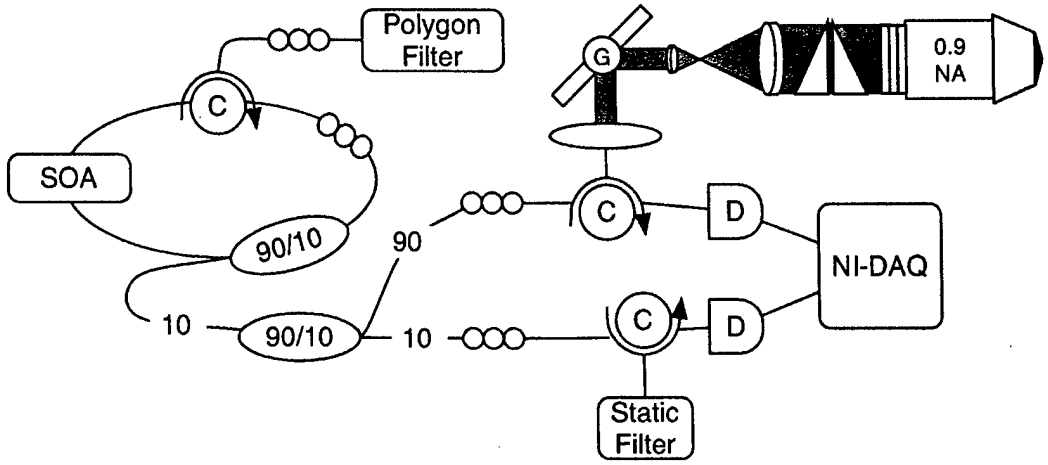


Figure 5 Schematic of the high speed SECM setup. The semiconductor optical amplifier (SOA) is inserted inside a fiber optic ring laser. A narrow wavelength band is filtered and amplified by passing the filtered light back through the SOA. Output light directed to the probe via a

circulator. C: circulator. G: galvanometer mounted mirror. D: photodetector.

We have developed a novel rapidly tuning source based on a fiber optic ring, a semiconductor optical amplifier (SOA) and a new scanning polygon based filter[3]. The filter consists of a diffraction grating, a telescope and a spinning polygon. The diffraction grating provides angular dispersion for the incident light, separating the different wavelengths. The diverging angular dispersion from the grating, which is placed at the front focal plane of the first lens, is converted into converging angular dispersion after the second lens of the telescope. The polygon reflects back only the spectral component within a narrow resolution band as a function of the angle of the front facet mirror of the polygon. The narrowband spectrum is fed back to the SOA for regenerative amplification, leading to rapidly-tuned narrowband laser emission (Figure 4).

The tuning source yields 6 mW average output power over a 70 nm tuning range at a repetition rate up to 15.7 kHz, which corresponds to 15,700 line-scans per second. The wavelength tuning range of the source is centered at 1.32 μm, corresponding to the operating wavelength of the DP GRISM. The instantaneous linewidth of the laser output is 0.1 nm. The peak-to-background spectral density ratio is -80 dB, providing a high signal-to-noise ratio and dynamic range.

High Speed SECM

We have built an SECM bench top system to assess the potential of SECM imaging using our rapidly wavelength swept source[4]. The bench top system, shown in Figure 4, comprises the modified LOMO objective previously used in the SECM probe, the DP-GRISM, a 4:1 AR coated achromatic telescope, and a galvanometer-mounted mirror for scanning the slow axis of the image. The field of view of our swept-source SECM system is 440 microns (wavelength encoded axis, y-axis) x 400 microns (slow axis, x-axis). Due to bandwidth limitations of our current detector, our images are acquired at 4 frames/second. Improvements in detector electronics will enable acquisition at a rate of 30 frames/second.

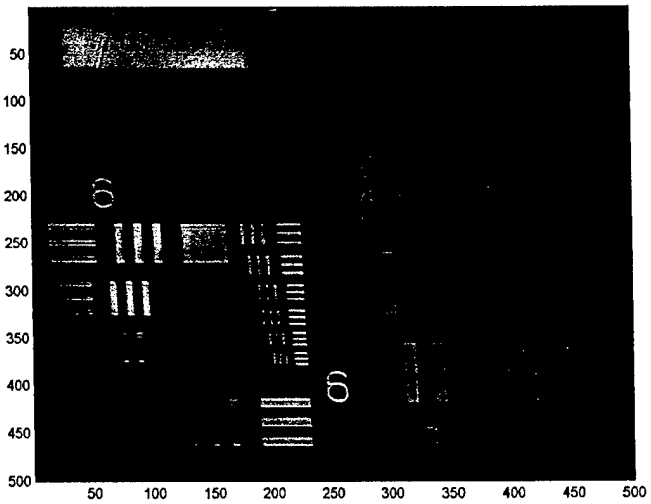


Figure 6 Swept-source SECM image of a US Air Force resolution target. The bar spacing for the smallest element is 2.2 microns. The wavelength-encoded axis is along the x-axis. This image is 500x500 pixels and 400 (y-axis) x 440 microns (x-axis).

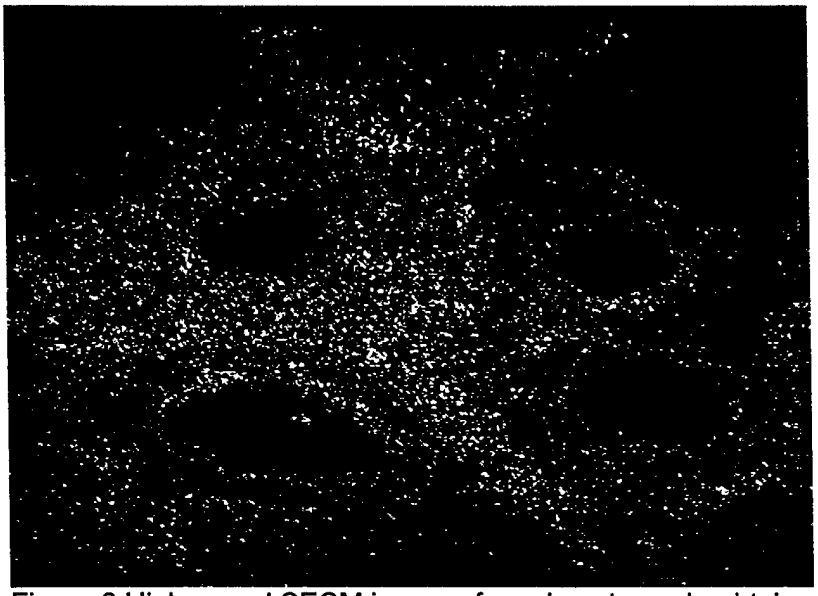


Figure 6 High-speed SECM image of porcine stomach, obtained in vitro. Evidence of gastric pit architecture is clearly visualized as well as structures lining the pits, consistent with the epithelium.

Figure 5 shows an image of a US Air Force resolution chart obtained using our swept-source SECM system. The smallest bars with a spacing of 2.2 microns are clearly resolved. Images of porcine stomach obtained in vitro using the swept-source SECM system demonstrate crypt and pit architecture as well as subcellular features (Figure 6).

SECM enables endoscopic confocal microscopy by eliminating the need for high speed mechanical scanning within the probe. We have demonstrated SECM imaging through a 10 mm probe based on a small and flexible single-mode fiber, the DP-GRISM and a modified high NA microscope objective. The addition of a rapidly scanned tuning source allows high-resolution, large field-of-view SECM images to be acquired at high frame rates.

Future Plans

Future work will utilize the DP-GRISM probe and the swept-source SECM system to investigate potential applications of endoscopic confocal microscopy in patients.

Metrics

Personnel working on this project:
Brett Bouma, Ph.D.

Publications and Presentations

Tearney GJ, Webb RH, Bouma BE. Spectrally encoded confocal microscopy. Optics Letters 1998;23:1152-1154.

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Early Diagnosis of Osteoarthritis by Polarization Sensitive Optical Coherence Tomography (PS-OCT)

Principal Investigator: Johannes F. deBoer, PhD., MGH

Executive Summary

Osteoarthritis or degenerative joint disease is the leading cause of chronic disability in developed countries. The hallmark of osteoarthritis is the degeneration of cartilage, however, earlier changes are associated with collagen disorganization, increased water content and alterations in glycosaminoglycans. Among the later recognized changes are cartilage thinning, fibrillation and surface erosion.

Our hypothesis is that the disorganization and degradation of collagen is accompanied by a loss of birefringence, which precedes joint cartilage thinning and wear. Quantifying the loss of collagen birefringence with PSOCT could provide an early indication of the onset of osteoarthritis
To test this hypothesis, *in vitro* PS-OCT scans will be performed of waste human joint cartilage from the orthopedic department at Massachusetts General Hospital. Tissue samples will be scanned with our existing PSOCT instrument. Ink marks placed on each tissue sample will enable direct correlation to be made between PSOCT images and histologic sections. Birefringence will be quantified at several locations in each specimen. After scanning, samples will be processed for histological analysis using picrosirius red staining and analyzed with polarization microscopy to determine collagen type I (red) and type III (green) content. Histological findings will be correlated with quantitative measurements of specimen birefringence.

Key Results

Joint specimens have been collected following total knee replacement surgeries and measurements have been made on osteoarthritic cartilage using PS-OCT. Preliminary results demonstrate that PS-OCT can visualize clear and distinct differences between healthy cartilage and osteoarthritic cartilage *in-situ*.

Specific Aim

To investigate *in vitro* the relation between cartilage degeneration and loss of collagen birefringence in order to evaluate PSOCT as a diagnostic tool for the early detection of osteoarthritis.

Progress

Specimens were collected following 5 total knee replacement surgeries at Massachusetts General Hospital. Samples of articular cartilage at several locations on each specimen were imaged using polarization sensitive optical coherence tomography; both intensity and phase retardation images were acquired. The images were qualitatively compared to histology.

The histology of the healthy region in a specimen (figure 1a) shows fairly normal cartilage with no fibrillation and normal cellular density. Histology of the osteoarthritic region (figure 2a) demonstrates thickened articular cartilage, with increased cellularity and fibrillation in the superficial zone. The PS-OCT intensity images in both cases (figures 1b and 2b) appear to be similar; the cartilage appears amorphous, differing only on the surface where the osteoarthritic cartilage appears more granular.

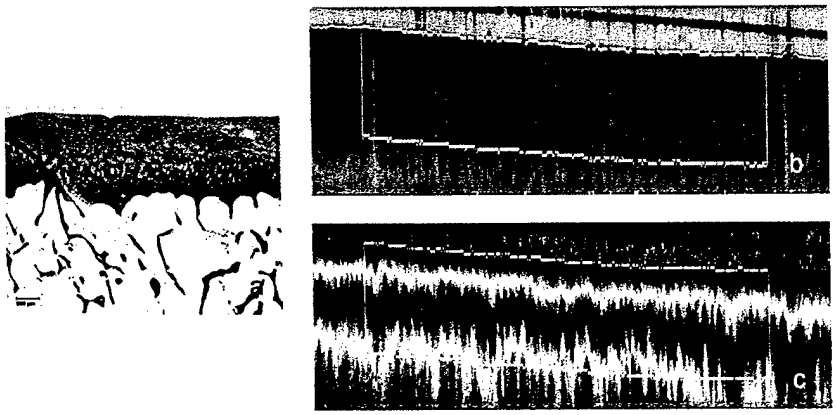


Figure 1. (a) Histology of healthy articular cartilage specimen shows normal thickness and cellular density. PS-OCT images were acquired *in-situ* prior to histology. (b) The intensity image shows a fairly smooth surface and an amorphous sample. On the other hand, the phase image (c) shows banding (alteration from dark to light to dark) which is aligned collagen that is strongly birefringent and thus relatively healthy. The PS-OCT images are 5mm x 1.5 mm. The box outlines the region of interest from which the rate of change of the phase was determined.

The polarization sensitive phase retardation images show distinct differences between the normal and osteoarthritic samples. In normal cartilage ordered collagen fibers result in strong birefringence of the tissue which appears as an ordered banded pattern in the phase image (figure 1c). As osteoarthritis progresses, the collagen begins to breakdown become more disorganized resulting in a decrease in the birefringence and thus a loss of the banding that appears in the polarization sensitive images (figure 2c). The rate of change in the phase can thus be used to

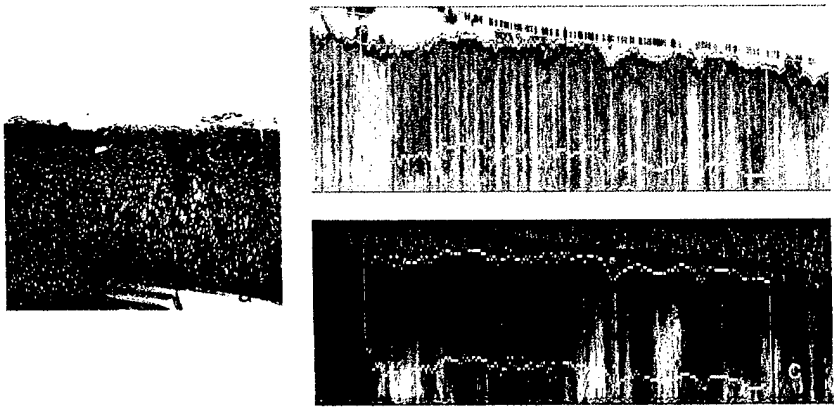


Figure 2. (a) Histology of a severely osteoarthritic cartilage shows thickened articular cartilage, increased cellularity and fibrillation in the superficial zone. The intensity image (b) is not drastically different from that of healthy cartilage with the exception of the granular surface. The phase image (c) shows the difference from the healthy sample. The loss of birefringence (loss of banding) compared to figure 1c suggests advanced pathology. The PS-OCT images have the same parameters as figure 1.

quantify the degree of pathology of the tissue. Extracting the slope at multiple locations on a sample shows local variations in the degree of pathology. A sample can have fairly normal cartilage on the periphery but the cartilage gradually deteriorates. This deterioration results in a gradual decrease in the rate of change in phase.

Future Plans
To grade the histology, a protocol had to be established for the picosirius red staining in order to determine collagen type I (red) and type III (green) content. This protocol has been established and we plan to grade the histology in the next quarter and quantitatively correlate the histology grading with the PS-OCT findings.

Metrics
Personnel working on project:
J.F. de Boer
M.C. Pierce
N.A. Nassif

Publications and Presentations
An abstract entitled "Quantitative Evaluation of Osteoarthritis progression Using Polarization Sensitive Optical Coherence Tomography" by N. Nassif, M.C. Pierce, B. H. Park, B. Cense, and J.F. de Boer has been submitted to SPIE Photonics West, and will be presented in January of 2004.

Photochemical tissue bonding: enabling studies and application to microsurgical reconstruction of peripheral nerves
Principal Investigator: Robert Redmond, Ph.D., MGH

Executive Summary
Photochemical tissue bonding (PTB) is a novel tissue repair technique that combines photosensitizing dyes with visible laser light to produce intermolecular covalent cross-linking of collagen. Unlike previous tissue welding techniques, PTB is non-thermal and avoids the tissue damage inherent with a photo-thermal approach. PTB has been explored in a variety of tissues and is ideally suited to tissues requiring a watertight seal and precise coaptation without the introduction of foreign material. Initial results using PTB as a new technique of peripheral nerve repair have proved encouraging. We proposed a two-pronged approach: a basic study to define the optimal chemical properties of photosensitizing dyes to enable PTB, and a thorough comparison of the clinical and economic efficacy of PTB neurorrhaphy versus state-of-the-art nerve repair in a rat sciatic nerve model.

We have performed a thorough evaluation of multiple photosensitizing dyes, finding toluidine blue and rose bengal to be the most effective. We have also completed the first part of our operative study and are currently tabulating the results. At the present there is insufficient data to predict the role PTB may play in peripheral nerve repair in the future, however preliminary results are encouraging.

Key Results
The CIMIT team has screened more than 20 dyes for photochemical activity and crosslinking ability in an *ex vivo* tendon bonding model. These were all compared to the currently used dye, rose bengal. Of these, toluidine blue showed an almost equal efficiency in bonding tendon as rose bengal. It has the advantage of absorbing red light that penetrated deeper into tissue. In regards to Specific Aim 2, only a portion of the data analysis is complete (see Figure 4). This data indicates a slight benefit from standard suture repair of transected peripheral nerves over that of an epineurial cuff with PTB repair. However, the epineurial cuff repair with PTB appears to be better than an epineurial cuff repair without PTB, showing some benefit to the use of PTB itself. As yet, the technology is in the early stages of its development and we are unable to determine at this time whether PTB will be a useful adjunct to surgical repair of peripheral nerves.

Specific Aims
Specific Aim 1: To determine physicochemical and photochemical parameters of dyes for optimal PTB.
Specific Aim 2: To determine the technical merit of PTB as a microsurgical nerve repair tool in an *in vivo* rat sciatic nerve repair model.
Specific Aim 3: To establish the efficacy of PTB neurorrhaphy as a microsurgical nerve repair tool as compared to standard epineurial repair via an outcome study.

Progress
Specific Aim 1: To determine physicochemical and photochemical parameters of dyes for optimal PTB.
This section has been completed. Initially a total of 25 commercially-available dyes were screened for suitable absorption properties in regions of the visible spectrum where suitable laser sources are available. Of these 25 dyes, a total of 10 were selected as possessing suitable absorption characteristics and were then tested further for PTB activity using bonding of bovine tendon ex vivo as the model system. Of these dyes toluidine blue was shown to be the only one that was more effective than the rose bengal currently used for PTB. Toluidine blue also has the advantage of absorbing further in the red part of the spectrum than rose bengal and will therefore be effective at

greater depths due to the scattering properties of tissue. This may be important in highly scattering tissues for efficient PTB.

This part of the project is completed and a potentially new photosensitizer has been identified for PTB applications that require bonding at greater depths beneath the tissue surface.

Progress

Specific Aim 2: To determine the technical merit of PTB as a microsurgical nerve repair tool in an *in vivo* rat sciatic nerve repair model.

Our initial aim for this part of the experiment was to develop and optimize three distinct techniques utilizing PTB as a nerve repair tool. Our ex-vivo studies demonstrated that two of these techniques, *end to end* (Figure 1) and *collagen gel cap* (Figure 2) did not achieve a reliable repair and were hence abandoned. We focused our efforts on the third technique, *epineurial cuff* (Figure 3), which could be reliably reproduced both ex-vivo and *in vivo*. Preliminary data showed that PTB produced an intact nerve repair with minimal inflammation.

Figure 1

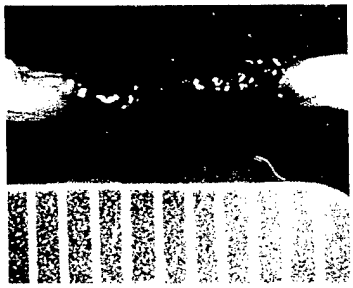


Figure 2

Figure 3

The epineurial cuff method has now been established and used in a study in which animals underwent sciatic nerve transection followed by four types of treatment (no repair, sutured repair, epineurial cuff alone or epineurial cuff with PTB). The gold standard for nerve repair at present is microscopic suture repair; hence this group has been used as our positive control while the no repair group was used as our negative control. The length of this portion of our study was 90 days and has now been completed. Throughout the duration of the experiment, we compiled data for the functional recovery of the limb (gait analysis for recovery of function) which is currently being analyzed.

All experimental animals have been euthanized and the various tissues are undergoing analysis. Gastrocnemius muscle mass from both the operative (experimental) leg and the non-operative (control) leg were obtained at harvest and used to produce a ratio that indicates the preservation of muscle mass by successful regeneration of the sciatic nerve after the various repairs studied. These results are listed below in Figure 4. The repaired sciatic nerve was also removed from each animal at harvest, and fixed in glutaraldehyde for histologic processing which is ongoing at present. Histomorphometric analysis of the repaired nerves will then be performed to quantify the number of regenerating axons and myelin thickness for each repair type.

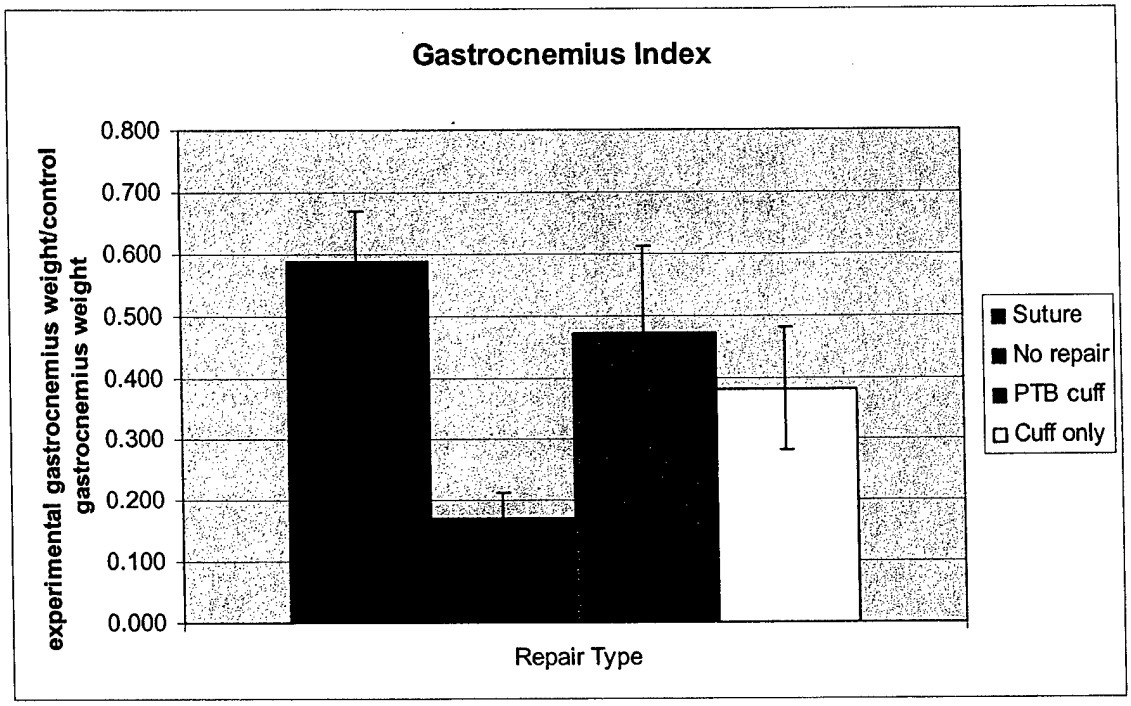


Figure 4

Progress

Specific Aim 3: To establish the efficacy of PTB neurorrhaphy as a microsurgical nerve repair tool as compared to standard epineurial repair via an outcome study.

This portion of the experiment is dependent on information obtained from aim 2, and therefore will not be started until all data from that experiment is complete.

Future Plans

As mentioned above, two specific aims of this project are completed and we are now tabulating the data. Gait analysis has been performed for all experimental animals every 10 days throughout the experiment and is now being tabulated. Final results for gait analysis are not available at present. Gastrocnemius muscle weights have been measured and averaged for each experimental group and are presented graphically in Figure 4. Statistical analysis has not been performed but the numbers indicate a benefit from primary suture repair, closely followed by epineurial cuff with PTB repair. One problem with our study was that the tension on the nerve following PTB/cuff and suture repair was different. More tension exists in the PTB repair. We have now added another experimental group where the tensions are the same in each case, an important consideration given that increased tension following repair has been shown to reduce recovery of function. Nerve tissue is currently being processed for histology. When this is complete, histomorphometric analysis of the neural tissue can be performed to quantify the numbers of regenerating axons per repair type and the degree of myelination of the axons, thus providing further data in support of one nerve repair technique over the others.

Metrics

Personnel working on this project:

Presentations:

Robert Redmond, Ph.D., MGH

Irene Kochevar, Ph.D., MGH

Publications and Presentations

"Photochemical Tissue Bonding for Skin and Nerve Repair", presented by Chris Amann, B.S. Wellman Laboratory of Photomedicine, Research Series. Massachusetts General Hospital, April 2003.

"Photochemical Tissue Bonding: A Novel Nerve Repair Technique", presented by Timothy Shane Johnson, M.D. at the14th Annual Richard J. Smith MD Resident/Fellows Hand Conference, Massachusetts General Hospital, May, 2003.

An abstract detailing the results of Aim 2 will be submitted for presentation at the 49th annual meeting of the Plastic Surgery Research Council when data collection is complete.

A manuscript detailing the results of Aim 2 will be submitted for publication when data collection and interpretation is complete.

Speckle Imaging for Plaque Characterization
Principal Investigator: Guillermo Tearney, M.D., Ph.D., MGH

Executive summary
In our research we investigate the analysis of time-varying speckle patterns as a measure of the biomechanical properties of atherosclerotic plaques. Due to the low-viscosity of lipid, scatterers within a compliant lipid pool exhibit rapid Brownian motion as compared to stiffer fibrous regions of the plaque. Laser speckle patterns are highly sensitive to scatterer motion; hence, the analysis of temporal variations in speckle patterns allows the determination of the biomechanical properties of plaques and identification of plaque type.

Key results
We have developed a method to identify and characterize atherosclerotic plaque types by the analysis of time-varying speckle fluctuations and have shown that the decorrelation time constant of speckle fluctuations provides a measure of the intrinsic biomechanical properties of atherosclerotic plaque under *in vitro* static conditions. In our study of over 30 aortic plaques, we demonstrated that compliant lipid plaques had a significantly lower decorrelation time constant than fibrous and calcific plaque types. We have extended this method to investigate the identification of plaque types during tissue translation and deformation and have demonstrated that speckle decorrelation decreases with increasing deformation rates. Hence, additional information on the biomechanical properties of atherosclerotic plaque may be obtained by measuring speckle decorrelation at different stages of the ECG cycle. We have also investigated the use of optical fiber bundles and have been successful in obtaining speckle images of phantom materials using a single mode fiber bundle.

Specific Aims
Specific Aim 1: To identify and characterize atherosclerotic plaque types in aortic specimens *ex vivo* by the temporal analysis of laser speckle patterns.
Specific Aim 2: To investigate the efficacy of the temporal analysis of speckle patterns to identify vulnerable plaque in the presence of tissue motion.
Specific Aim 3: To miniaturize the speckle imaging system for *in vivo* intracoronary applications.

Progress
Specific Aim 1: To identify and characterize atherosclerotic plaque types in aortic specimens *ex vivo* by the temporal analysis of laser speckle patterns.
In the first phase of this research we tested a method for characterizing the biomechanical properties of atherosclerotic plaques based on the temporal analysis of laser speckle patterns. This feasibility study was performed on five excised human aortic specimens. Laser light (632.8 nm) was focused to a single 100mm spot on the sample and speckle images were obtained at 30 frames per second using a CCD camera. Cross-correlation of the time-varying speckle patterns was performed and the speckle decorrelation time constant was calculated to obtain a measure of tissue stiffness. The results of this study suggested that the speckle decorrelation time constant was significantly lower for lipid plaques versus stable fibrous plaque and normal aortic tissue.

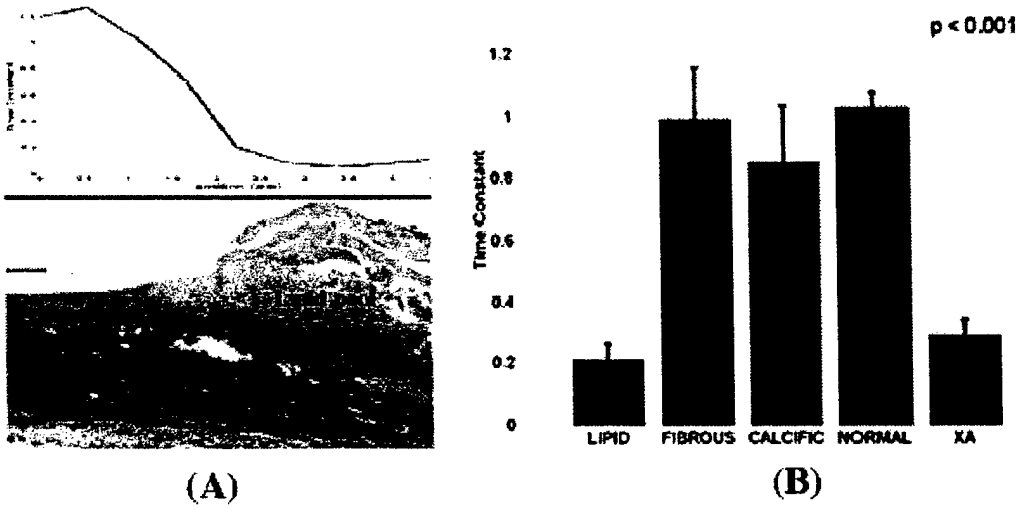


Figure 1: (A) The decorrelation time constant calculated for a lipid plaque compared with the corresponding histology. **(B)** Histogram showing decorrelation time constants obtained from time varying speckle images of different atherosclerotic plaque types. The results obtained from 36 aortic specimens confirmed that compliant lipid plaques (necrotic cores) had a significantly lower decorrelation time constant than fibrous and calcific plaque types. Non-necrotic lipid-rich xanthomas (XA) had a slightly higher time constant than necrotic core plaques.

Development of a robust experimental setup to analyze speckle pattern fluctuations in excised aortic tissue

An experimental setup was designed and developed for line and area scanning to obtain speckle images over a region of interest. A faster CCD camera was incorporated in the system to acquire speckle images with higher temporal resolution at 240 frames per second. Over thirty aortic plaques were analyzed using time-varying speckle scans and compared with the corresponding histology. The decorrelation time constants obtained from the speckle images were correlated with atherosclerotic plaque types identified using histology (Fig. 1). The results of Part I and Part II of this study indicate that atherosclerotic plaque types can be identified *ex vivo* by temporal and spatial laser speckle fluctuations.

Progress

Specific Aim 2: To investigate the efficacy of the temporal analysis of speckle patterns to identify vulnerable plaque in the presence of tissue motion.

Speckle pattern fluctuations are highly sensitive to motion. As a result, intracoronary applications of this technique may be affected by motion of the imaging catheter as well as vessel deformation over the cardiac cycle. In Specific Aim 2 of this project we investigated the behavior of speckle patterns in the presence of tissue motion. Motion was incorporated in our system by linear translation or deformation of the plaque by stretching the aortic specimen between two motorized stages. Speckle images were obtained during translation and deformation of the specimen. Each speckle image was divided into patches and the decorrelation time constant calculated over each patch was plotted as a color map as shown in Fig. 2. These experiments were performed using both tissue mimicking phantoms and human aortic specimens.

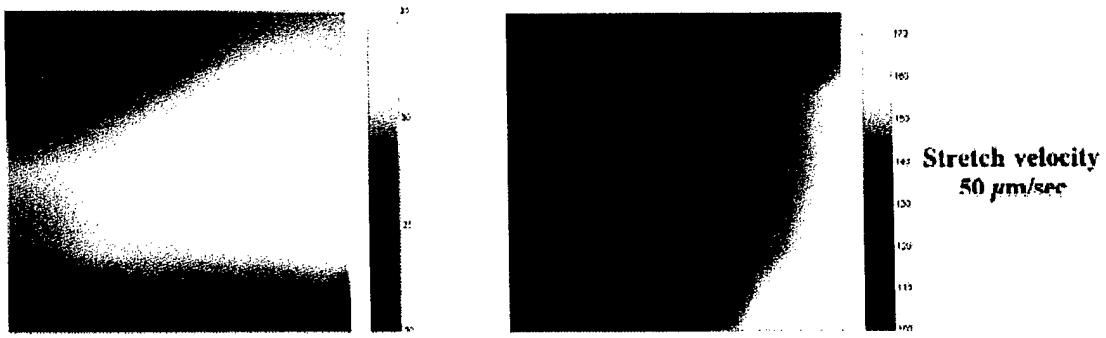


Figure 2: Phantom experiments: Color maps showing the decorrelation time constant calculated from the speckle fluctuations of a heterogeneous PVA phantom. The stiffer region of the phantom can be identified in the static and deforming cases as bright yellow regions in each color map having a higher decorrelation time constant compared with the surrounding PVA matrix.

(i) Experiments with tissue mimicking phantoms

Polyvinyl alcohol (PVA) cryogel was used as a tissue mimic for the phantom studies. Rectangular strips (thickness = 0.3 mm) of PVA cyrogel with varying stiffness were constructed by freezing and subsequently thawing the PVA solution. By increasing the number of freeze-thaw (FT) cycles, the stiffness of the resulting PVA material could be increased. Figure 2 shows the results of the spatial and temporal analysis of speckle images obtained from a heterogeneous PVA phantom in which a stiffer PVA material (3 FT cycles) is embedded within a surrounding PVA matrix of lower stiffness (1FT cycle).

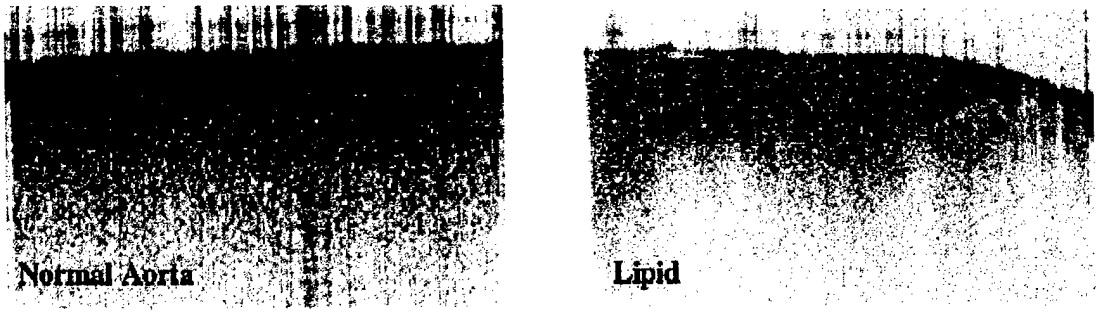


Figure 3: Aortic tissue specimens: OCT images of a normal aorta and thick-cap lipid rich plaque.

(ii) Experiments with aortic tissue

We constructed a system to deform tissue under controlled *in vitro* conditions, in which aortic tissue deformation was performed by stretching the specimen using two opposing linear motorized stages. The spatial distribution of decorrelation time constants computed from speckle images of aortic specimens

(Fig. 3) were plotted as color maps (Fig. 4). The color maps computed from two aortic specimens at stretch velocities of 10mm/s, 50mm/s, 100mm/s and 200mm/s are shown in Figure 4 along with the average decorrelation time constant, τ, calculated over each color map.

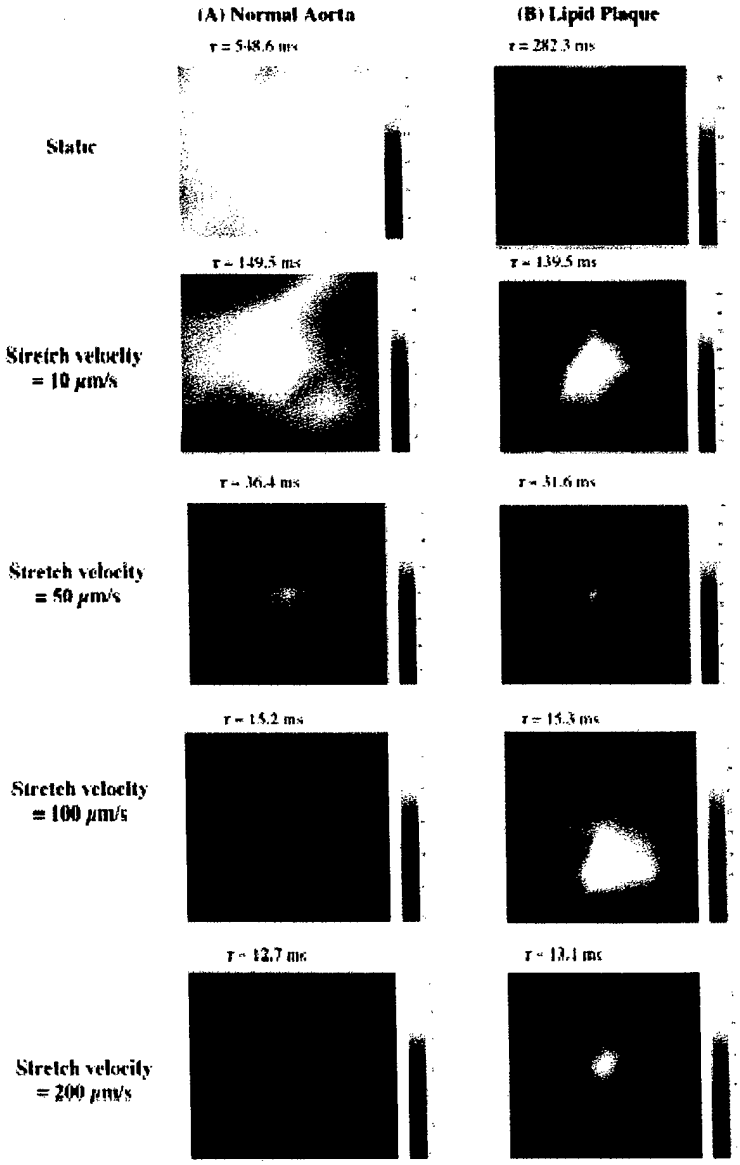


Figure 4: (A) and **(B)** below show color maps representing the spatial distribution of decorrelation time constants calculated from speckle fluctuations of **(A)** a normal aorta, and **(B)** a thick-cap lipid rich plaque. The mean decorrelation time constant calculated over each colormap is given in the figure. The bright regions within the color maps exhibit higher decorrelation time constants and the darker regions depict lower decorrelation time constants indicating rapid Brownian motion of scatterers with the plaque.

Our results demonstrate that in the static case, the differences between decorrelation time constants for aortic tissue types are large as shown by the example in Figure 4, where, τ= 548.6ms for the normal aorta and t=282.3 for the thick-cap lipid rich plaque. This large deviation in τ allowed for highprecision in the identification of different plaque types in the static *in vitro* cases. During aortic deformation we observed that the separation in the average value of τ for different plaque

types decreased with an increase in the rate of deformation. Since deformation rates vary with the ECG cycle, we expect that speckle patterns acquired at different stages of the cardiac cycle will provide additional information about plaque elasticity than that obtained from the static case alone.

This study has provided us with greater insight into the complexity the problem of identifying vulnerable plaque from speckle fluctuations. We find that the analysis of scatterer motion within a plaque from speckle patterns provides abundant information on the biomechanical properties of atherosclerotic plaque. In the next phase of our research we will conduct further studies to characterize the effect of tissue deformation and translation on the Brownian motion of scatterers within a plaque and develop algorithms to relate the speckle pattern fluctuations during plaque deformation to the intrinsic biomechanical properties of plaques. Additionally, we will begin to utilize the spatial variation of the decorrelation time constants to measure the dimensions and elastic properties of individual plaque components, such as thin fibrous caps.

Progress

Specific Aim 3: To miniaturize the speckle imaging system for *in vivo* intracoronary applications. We are currently investigating the use of optical fiber bundles to obtain speckle images for intracoronary applications. As a result of this research, speckle fluctuations from coronary plaques *in vivo* may be analyzed with a small diameter, flexible catheter. In our preliminary investigation into the miniaturization of the speckle imaging system, we have tested the use of multimode and single mode optical fiber bundles to obtain speckle images in phantoms *in vitro.* We have found that speckle patterns obtained using multimode fiber bundles are extremely sensitive to motion of the optical fiber due to mode mixing. As a result, multimode fiber bundles typically used in commercial angioscopes may not be a viable option for use in living patients. However, we have had initial success using standard single mode fiber bundles to obtain speckle patterns from PVA phantom material and are constructing a flexible single mode fiber bundle angioscope to obtain these data *in vivo.*

Future Plans

To further develop speckle imaging system for *in vivo* intracoronary applications.

Metrics

At the present time, we have two post-doctoral associates working on this project, Dr. Seemantini Nadkarni, and Dr. Milan Minsky-Singh. Dr. Guillermo Tearney and Dr. Brett Bouma are supervising the project.

Publications and Presentations

We anticipate that a manuscript describing the research results of this project will be submitted by 10/1/03.

An abstract describing the static decorrelation results was presented at SPIE Photonics West 2003. We will be submitting an abstract for presentation at Optical Society of America, Biomedical Topical Meetings, 2004 that will describe decorrelation patterns in the presence of phantom and tissue motion.

Real-time intraoperative functional imaging for the assessment of myocardial injury and graft patency during simulated off-pump coronary artery bypass surgery.
Principal Investigator: Tomislav Mihajlevic, M.D. Brigham and Women's Hospital

Executive Summary

The near infrared imaging system previously used to validate the feasibility in small animals systems has been modified for large animal surgery and has undergone specific customizations to optimize imaging quality. These modifications were mainly in the light supplies and software for image acquisition. The goals of this project were to investigate the feasibility and accuracy of real-time intraoperative NIF imaging in an open-chest porcine model of OP-CAB surgery.

Key Results

In addition to testing the accuracy of real-time NIF vascular imaging techniques with the fluorophore mentioned (IR-786), we have been using the FDA-approved agent indocyanines green (ICG) as well as testing other similar heptamine indocyanines which have varying hydophobicities.

Specific Aims

Specific Aim 1: Access the accuracy of real-time NIF vascular imaging techniques.
Specific Aim 2: Access the accuracy of real-time NIF vascular combined with myocardial viability imaging techniques in detecting myocardial ischemia and necrosis.

Progress

Specific Aim 1: Access the accuracy of real-time NIF vascular imaging techniques.
We have successfully tested the NIF imaging system in open-chest porcine models using various fluorophores and different concentrations. We have further confirmed our results with fluorescent microspheres. Tests have also been completed in a cardiopulmonary bypass model to assess both vascular anatomy and cardioplegia delivery.

Progress

Specific Aim 2: Access the accuracy of real-time NIF vascular combined with myocardial viability imaging techniques in detecting myocardial ischemia and necrosis.
We have begun this portion of the project by examining ischemia in the setting of poor delivery of cardioplegia. We are in the process of obtaining myocardial pH measurements for correlation.

Future Plans

To continue to investigate the feasibility and accuracy of real-time intraoperative NIF imaging in an open-chest porcine model of OP-CAB surgery.

Metrics

Personnel working on this project:
Tomislav Mihaljevic, M.D.

Publications And Presentations

Real-time intraoperative near-infrared fluorescence imaging during large animal cardiac surgery Edward G. Soltesz MD, Rita G. Laurence BS, Alec M. DeGrand BS, Delphine M. Dor BS, Roger J. Hajjar MD, Lawrence H. Cohn MD, Tomislav Mihaljevic MD, John V. Frangioni MD PhD. BWH Research Fellows Poster Exhibition/Presentation, May 9, 2003. Abstract submitted to Society of Molecular Imaging.

Edward G. Soltesz MD, Rita G. Laurence BS, Alec M. DeGrand BS, Delphine M. Dor BS, Lawrence H. Cohn MD, John V. Frangioni MD PhD, Tomislav Mihaljevic MD. Assessment of

cardioplegia delivery in cardiac surgery using real-time intra-operative near-infrared fluorescence imaging. Abstract submitted to American Heart Association Scientific Sessions 2003 and Society of Molecular Imaging.

Untethered Physiologic Monitoring Focus Area

Untethered Monitoring
Principal Investigator: Nathaniel Sims, M.D.

Executive Summary
This proposal is to design and develop a prototype for a new monitoring system as a module of the Warfighters' Physiologic Monitoring System (WPSM) for the OFW program. This monitoring system will provide a minimally intrusive, reliable, low-cost, wireless, on-body sensor platform for life signs detection and health status assessment in chaotic environments, such as combat, emergency triage, and bio-terrorism events.

Today's traditional hospital system monitor specific physiologic metrics and provide alarm notifications to highly skilled caregivers. The same technology has been incorporated into fitness monitoring devices. Neither of these monitoring systems offers adequate responsiveness or artifact resistance for use in chaotic environment scenarios.

The proposed monitoring system design will consist of four components: a sensor platform, a health state assessment algorithm, a wireless communication network and a body-worn packaging for the sensor array.

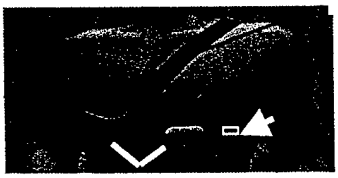
Key Results
All tasks and deliverables through August 31, 2003, have been completed on schedule, on budget. The complete system prototype with final documentation will be delivered to the Life Signs Detection Program Manager at Natick Labs on September 30th, 2003.

The prototype includes a basic sensor array (for measuring heart rate, temperature, and motion), an "alive/dead" health state algorithm, and a wireless communication network. The sensor array is packaged in a thoracic textile belt. A stretch sensor for monitoring respiration is incorporated into the design of the belt. Inclusion of this respiration sensor in the prototype, goes beyond the required demonstration as a separate proof-of-concept milestone, and reflects the team's dedication to exceeding the requirements of the original agreement.

Specific Aims
Specific Aim 1: Develop a prototype for a minimally intrusive, reliable, low-cost wireless thoracic sensor platform for remote physiologic monitoring.
Specific Aim 2: Develop a packaging prototype that allows the monitoring system to be worn on the soldier's body with minimal intrusion in combat environments.
Specific Aim 3: Develop a health state assessment algorithm that evaluates the LSDS sensor data to determine the likelihood that the monitored soldier is alive and well, alive and likely wounded, or dead.
Specific Aim 4: Prototype a wireless communications network for sending individual life signs data to a receiver at a remote location.

Progress
Technology scavenging for best-of-breed components and down-selection. (6 to 9/01/02)
Proof-of-concept demonstration of *basic* sensor array with two vital signs sensors (an R-Wave detector that provides heart rate, and a temperature sensor) and one life signs "context" sensor (an accelerometer that detects motion and body orientation). (10/02)
Prototype demonstration of *basic* sensor array packaged in on-body form factor. (4/03)





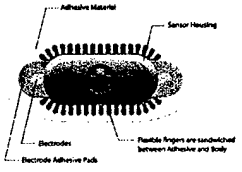
Proof-of-concept demonstration of *extended* sensor array with respiration. (4/03)
Integration of respiration sensor from extended platform with basic sensor array. (5/03-8/03)
Laboratory testing and validation. (7/03-9/03)

Documentation
Needs and requirements document completed. (8/02/02)
Functional specifications document completed. (8/15/02)
User Manual for LSDS Adhesive Patch. (3/03)
User Manual for LSDS Textile Chest strap. (3/03)
Technology down-selection documentation completed. (6/02/03)
Analysis and documentation of battery options with substitution of rechargeable battery. (6/02/03)
Analysis and documentation of optional ECG front-end. (6/15/03)

Future Plans
Laboratory testing and validation. (7/03-9/03)
Prototype demonstration and hand-off of *integrated, extended* sensor array. (9/30/03)
Documentation:
Final User Manual. (9/30/03)
Hardware and Firmware Design Specification (9/30/03)
Hardware schematics. (9/30/03)
Manufacturing overview. (9/03/03)
FDA requirements overview. (9/30/03)
Validation Test Report. (9/30/03)

Progress
Specific Aim 2: Develop a packaging prototype that allows the monitoring system to be worn on the soldier's body with minimal intrusion in combat environments.
Human factors analysis and determination of soldier "keep-out zones" for body worn sensors in combat environment. (7/02)


Prototype form factor options, including textile chest strap and adhesive patch.

In related studies not supported by CIMIT funding: User acceptability testing of design concepts from CIMIT (2 above) and Walter Reed (2) tested at Fort Polk, Louisiana by independent testing group. Sixty test subjects wore each design for 24 hours, completing surveys and ranking the designs. The CIMIT chest strap ranked number 1 and the CIMIT adhesive patch ranked number 2.

Downselection to textile chest belt. (3/02)
Design refinements and integration with sensor platform. (4/03-8/03)

Future Plans
Construction of final units (9/02/03 – 9/26/03)
Delivery of integrated textile chest belt. (9/03)

Progress
Specific Aim 3: Develop a health state assessment algorithm that evaluates the LSDS sensor data to determine the likelihood that the monitored soldier is alive and well, alive and likely wounded, or dead.
Physicians Forums were held to gather a basic set of rules for health state assessment given the LSDS sensor set. (7/02-7/03)
Basic algorithm structure was developed to allow three-tier health state assessment: (1) basic rules set to reside in sensor platform, (2) user-adjustable rules on receiving platform, and (3) use of "personal baseline" rules set on remote, receiving platform. (5/03 – 9/03)
Validation and refinement of algorithm with basic rules set in sensor platform and on the "remote hub" demonstration software (laptop platform). (6/03-9/03)

Future Plans
Final validation of algorithm in integrated LSDS (9/02/03 – 9/26/03)
Final Health State Assessment Algorithm Specification documentation. (9/30/03)

Progress
Specific Aim 4: Prototype a wireless communications network for sending individual life signs data to a receiver at a remote location.
Develop wireless communications protocol specification (10/02)
Select and validate wireless communications hardware (9/02 – 10/02)
Refine communications protocol for final wireless hardware selection (12/02)
Extend wireless protocol for integration of LSDS platform into wired WPMS prototype (5/03 – 7/03)

Future Plans
Final Wireless Communications Protocol Specification document (9/30/03)

Metrics
Personnel working on this project:
Nathaniel Sims, M.D.
Ed George, M.D.
Penny Ford-Carleton

Publications and Presentations
Advanced Technology Applications for Combat Casualty Care Convention (September, 2002) – Dr. Sims

U.S. Army Soldier Systems Center Presentation for Governor Romney (March 2003) – Dr. Sims

Institute for Soldier Nanotechnology Opening (May 2003) – Dr. Sims, Ms. Ford Carleton, Mr. Hickcox (booth)

Capital Hill Health Technology Demonstration (July 2003) – Ms. Ford Carleton (booth)
Advanced Technology Applications for Combat Casualty Care Convention (August, 2003) –Dr. George

Patents
Three patent filings pending: system concept, algorithm design, and respiratory sensor.

Core Programs

Industry Liaison Program
Program Director: Janice E. Crosby, R.N., M.B.A., MGH

Executive Summary

CIMIT 's Industry Liaison Program continues to be a vital link between industry and CIMIT's programs and investigator community. Currently, CIMIT is working with over 45 companies at various stages of membership. Developing sustained relationships with each company is definitely a "contact sport". For each company, a customized plan is developed to ensure that their membership goals are met and the benefit of their membership to our investigator community is maximized. This involves researching available, appropriate, and interested clinicians as collaborators, encouraging "B2B" interactions, and proving meeting coordination services to facilitate these introductions. From the initial work done through the Industry Liaison Program, CIMIT has now developed a number of new models for collaboration with industry, from small, start-up businesses to major healthcare and technology conglomerates.

A major accomplishment this past year was formalizing a program to work with small businesses. In collaboration with CIMIT's Office of Technology Implementation, a new CIMIT Core Program was established. The CIMIT Translational Support Program provides a unique opportunity to support our investigator community while establishing working partnerships with an extensive network of small businesses that can accelerate innovation in patient care.

Facilitating multi–company collaborations to support CIMIT's Scientific Programs is a core competency of the Group. In the OR of the Future Program, the Group played an instrumental role in bringing together 12 companies with a multi-disciplinary surgical team from the MGH to reengineer the perioperative process. The Group continues to coordinate additional research efforts in the ORF Program as well as facilitating the implementation of the industry collaborative model to other clinical sites.

Key Results

- Continued expansion of CIMIT's network of Industry partners. The Industry Liaison Program (ILP) continues to be a vital link between industry and CIMIT's programs and investigator community. Currently, CIMIT is working with over 45 companies at various stages of membership. Three new companies joined the ILP with 12-15 additional companies in the introductory stage.

- Formalizing CIMIT's program to work with small businesses. In collaboration with CIMIT's Office of Technology Implementation, a new CIMIT Core Program was established. The CIMIT Translational Support Program provides a unique opportunity to support our investigator community while establishing working partnerships with an extensive network of small businesses that can accelerate innovation in patient care. The new program builds on a CIMIT core competency to facilitate and manage multi-disciplinary, multi-departmental and multi-institutional collaborative research.

- Facilitating multi–company collaborations to support CIMIT's Scientific Programs. In the OR of the Future Program, CIMIT played an instrumental role in bringing together 12 companies with a multi-disciplinary surgical team from the MGH to reengineer the perioperative process. Support continues to be provided for the additional collaborative research efforts in the ORF, including 4 clinical trials supported entirely by industry partners. As well, the Group is now helping to implement this collaborative model beyond the OR,

including a "Doctor's Office of Future", "Home of Future", "Research Facility of Future", and other advanced procedure rooms "of the Future".

Specific Aims

Specific Aim 1: Continue to expand CIMIT's network of industry members in the Industry Liaison Program.

Progress

- Currently, CIMIT is working with over 45 companies at various stages of membership. These companies bring to CIMIT diverse expertise, interests, and technology solutions that range from specific devices to diagnose and treat diseases to process infrastructure and IT capabilities. They also bring experience, perspective, and the ability to commercialize innovation, all essential to the translation process. For each of these companies, a customized plan is developed to ensure that their membership goals are met and the benefit of their membership to our investigator community is maximized. This involves researching available, appropriate, and interested clinicians as collaborators, encouraging "B2B" interactions, and proving meeting coordination services to facilitate these introductions. We currently have 34 active company members, with 3 companies joining this year and many more in introductory stages. Members include:

10 Blade, Inc	Johnson & Johnson - Cordis
Ascension Technology, Inc.	Johnson & Johnson - COSAT
Baxter Healthcare Corp.	Johnson & Johnson - Ethicon Endosurgery
B-K Medical Systems, Inc.	Karl Storz Endoscopy-America, Inc.
Boston Scientific Corp.	Medtronic, Inc.
Draeger Medical, Inc.	Mobile Aspects, Inc.
Foster-Miller, Inc.	Olympus America, Inc.
Foxfire Interactive Corp.	Omnicell, Inc.
GE Medical Systems, Inc.	OmniGuide Communications, Inc.
Getinge-Castle, Inc.	Pentax Precision Instrument Corp.
Granite Peak Technology, Inc.	Percardia, Inc.
Guidant Corp.	Pfizer, Inc.
Harvard Clinical Tech. Inc.	Physical Sciences, Inc.
Hewlett-Packard Co.	Radianse, Inc.
HydroCision, Inc.	TissueLink Medical, Inc.
IDEO	Tyco Healthcare Group, LP
Instrumentarium Corp.	Welch Allyn, Inc.

Additionally, the Group is actively working with the following companies, on their way to CIMIT membership:

Access Wellness Tech., Inc.	Manifest Tech., Inc.
Advanced Precision Engin., Inc.	Precision Dynamics, Inc.
Ambient Tech., Inc.	Proven Process, Inc.
Andromed, Inc.	Steris, Inc.
Bioscale, Inc.	TNCO, Inc.
Biosense Tech., Inc.	Traversent, Inc.
Dentagenics, Inc.	
Innovision, Inc.	
Live Data, Inc.	

- As membership in the ILP grows in size and complexity, the need for a better system to manage our process has grown. To that end, plans are underway to convert our current database to an easier, more robust, and more flexible knowledge system. The new system, called MindModel (MM), is a relational database that allows users to store and recall information on any topic. It can create databases about people, companies, products, or ideas *without programming*. Web-based MM will be expanded beyond the scope of our current database to include CIMIT Program and Award information, as well as investigator biographies.

- The ILP continues to act as the primary connective link between the CIMIT investigator community and industry. Examples of this include researching appropriate and interested clinicians on behalf of industry members for corporate sponsored research arrangements; accelerating the pace of research by our investigator community by introducing the expertise and proprietary technology solutions of our company members; providing "B2B" connections among our company membership, allowing for product improvements to the benefit of our investigators; and matchmaking our investigators to small business members interesting in a collaborative SBIR process to advance their work.

Future Plans

- Our expectation is that, due to CIMIT's new SBIR Facilitation Program, many new smaller companies will be drawn to CIMIT and our investigators community. In addition, the Group is actively pursuing R&D and prototyping businesses that will provide guidance and consultation as our innovations advance to the prototyping stage in exchange for membership benefits. These smaller organizations will augment the growing list of midsize and large companies attracted to the CIMIT consortium.

Specific Aim 2: Support CIMIT Scientific Programs that require industry collaboration.

Progress

- In the OR of the Future Program, the Group has expanded industry involvement beyond the initial commitment by 12 companies to provide the equipment, funding, and engineering support required to open the room. We are now facilitating clinical trials with 4 companies (Instrumentarium, Hewlett-Packard, Tensys, and GE Medical Systems), totaling $300,000 in support, and planning others. These trials allow for the introduction of first-to-market technologies into the ORF, providing our clinicians with the opportunity to evaluate and provide critical feedback on these cutting-edge devices and to influence design changes. In addition, these trials provide funding and publishing opportunities for ORF clinicians.

Future Plans

- The Group is now working with other clinical sites interested in adopting the ORF model for reengineering their process and implementing productivity and safety enhancement systems. These sites include:
    - The "Doctor's Office of Future" – Dr. Gregg Meyer, Medical Director, Mass. General Physicians Organization
    - The "BWH OR of the Future" – Dr. Raphael Bueno, Brigham & Women's Hospital
    - The "Research Laboratory of the Future" – MGH Research Facility, on the inventory management of hazardous biomaterials
    - The "Home of the Future" – A CIMIT Working Group aligned with the MIT Changing Places Group, Partners Telemedicine and Partners Home Care

Specific Aim 3:
Support small business members and the CIMIT investigator community through the facilitation of SBIR/STTR grants.

The Group, as part of the SBIR Facilitation Program, helps companies identify clinical problems that can be solved with their technology; provides matchmaking coordination to find appropriate and interested clinician collaborators; and provides project management and administrative support for SBIR grants – from concept development to implementation and application in the health care setting. The Group is also actively canvassing additional companies and investigators for participation in this new program.

Progress

Three CIMIT SBIR Grants have been awarded:

- NCRR Phase 1 – *Improving Healthcare Efficiency using Real Time Location* (with Radianse, Inc. and James Stahl MD)
- NSF Phase 1 – *Supply tracking for Smart Anesthesia Workstation using RFID* (with Mobile Aspects, Inc. and Warren Sandberg, MD, PhD)
- NINR Phase 1 – *Transparent Patient Safety System using RFID* (with Mobile Aspects, Inc. and Keith Isaacson, MD)

Six CIMIT SBIR Grant proposals were submitted to NIH and DoD in August 2003:

- NIH Phase 1 – *Task Identification for Contextual Clinical Decision Support* (with Granite Peak Tech., Inc. and Julian Goldman, MD)
- NIH Phase 1 – *Healthy Heart eLearning System* (with Foxfire Interactive Corp. and Diane Carroll, RN, PhD)
- NIH Phase 1 – *Miniaturized Buried Distracter* (with Advanced Precision Engineering, Inc., Len Kaban, MD, and Alex Slocum, PhD)
- NIH Phase 1- *Hazardous Agent Tracking Information System for Research Facility* (with Traversent, Inc., Penny Ford-Carleton and Ron Newbower, PhD)
- NIH Phase 1- *Woven Material for Orthopedic Scaffold* (with Foster-Miller, Inc. and Sonya Shortkroff, PhD)
- DoD Phase 1 – *Patient Safety Perioperative Readiness Support System* (with Live Data, Inc. and Warren Sandberg, MD, PhD

Future Plans
Support the submission of 10 SBIR grants per quarter.

Specific Aim 4: Catalyze Strategic Alliances with major medical device, electronics and IT companies.

Progress
The most serious, ongoing level of mutual commitment, suitable for companies with major technological resources and presence in this market, is that of "strategic alliance partner". Although none have been established to date, CIMIT has been instrumental in facilitating the recent collaboration between the Harvard Genetics and Genomics Center and Hewlett Packard (a CIMIT ILP member).

Future Plans

CIMIT is working to establish partnerships with selected companies that having been collaborating with CIMIT and share CIMIT's vision for the development and integration of technology into health care. We envision between four and six major companies becoming members of the CIMIT Strategic Alliance. Potential targets include: J&J, Medtronic, GE, HP, a telecom company and a software company. Initial kick-off planning meeting will be held at CIMIT's Annual Briefing with additional meeting convened in FY04.

Industrial Liaison Program: CIMIT Communications Group

Executive Summary

The CIMIT Communications Group was formed as an integral part of the Industrial Liaison Program. This CIMIT team is comprised of Rita E. Watson, MPH, Director, and Ferol Vernon, Communications Specialist, who assists with graphics, photography, and web management. The goal of this office is to create a CIMIT identity through words and images so that the CIMIT message and mission is effectively conveyed and portrayed.

Key Results

The CIMIT team has just compiled a Communications Book that outlined our goals as described in a presentation to the CIMIT Steering Committee on March 3, 2003. As of September 10, 2003 our team is pleased to report that over the past six months we have accomplished all of our goals – on time and under budget. By designing a broad range of multi-media materials and leveraging in-house talent, we have been able to redirect funds and cost-effectively respond to all internal and external requests to the Communications office.

Progress

- Press Policy created
- CIMIT website completely re-designed so that all relevant information is on the home page and searchable with a "one click away" method
- Seven CIMIT Newsletters to date – created in a one page format with news and photos – these are available electronically and in hard copy
- One-Page descriptions with photos for all nine CIMIT Programs
- Two Relational Databases (one is up and running; another is in progress – at a major cost savings)
- Two Trade Show Presentations
- Created Electronic Master Calendar with instructions for use
- Published ten news articles and fifteen press releases from the wire services
- Produced one television segment on the VIRGIL Chest Trauma Training System

Future Plans

- Production: all written materials – and posters, both text and design, for the 5th CIMIT Annual Briefing
- Press: work with reporters to initiate more news stories featuring CIMIT
- Internal library: create a centralized resource of accurate information

Education Program

Program Directors: Thomas J. Brady, M.D., and Lynn R. Osborn, M.B.A., MGH

CIMIT Forum Presentations: October 1, 2002 through September 30, 2003

Date	Topic	Speakers
10/01/02	**Opportunities for Machine Learning in the OR of the Future**	Leslie Kaelbling, PhD, Associate Director, Artificial Intelligence Lab, Massachusetts Institute of Technology *David Rattner, MD, CIMIT Program Leader: Minimally Invasive Surgery; Chief of the Division of General and Gastrointestinal Surgery, Massachusetts General Hospital*
10/01/02	*Assessing the Performance of Surgical Teams*	*J. Forrest Calland, MD, Research Fellow, University of Virginia*
10/8/02	*Fully Automated Methods for Brain Morphometric Analysis: Applications to Imaging Biomarkers and Computer Aided Diagnostics*	*Anders Dale, PhD, Associate Director of the MGH/MIT/HMS Athinoula A. Martinos Center for Functional and Structural Biomedical Imaging*
10/8/02	**Toward Real-Time Imaging of Myocardial Strain**	*Jerry L. Prince, William B. Kouwenhoven Professor, Electrical and Computer Engineering, Johns Hopkins University*
10/15/02	**Technology Innovations For Civilian Disasters: Training, Surveillance, and Response**	*Jonathan L. Burstein, MD, Assistant Director, Harvard Center for Public Health Preparedness for Science and technology,*
10/15/02	**Nanotechnologies for the Soldier of the Future**	*Edwin L. Thomas, Ph.D., Director, Institute for Soldier Nanotechnologies,* *Massachusetts Institute of Technology*
10/22/02	*Magnetic Resonance Imaging and Spectroscopy of Atherosclerotic Plaque with Intravascular RF Coils*	*Jerome L. Ackerman, PhD, Director, Biomaterials Laboratory, MGH/MIT/HMS Athinoula A. Martinos Center*
10/22/02	**MRI for Delivery and Surveillance of Mesenchymal Stem Cells**	*Robert J. Lederman, MD, National Heart, Lung, and Blood Institute, National Institutes of Health*
11/5/02	**Angiogenesis and Lymphangiogenesis in Tumors: New Insights from Intravital Microscopy**	*Rakesh K. Jain, PhD, Department of Radiation Oncology, Massachusetts General Hospital; Andrew Werk Cook Professor of Tumor Biology, Harvard Medical School*
11/5/02	**Are Protons in Your Future?**	*Jay Loeffler, MD, Chief, Radiation Oncology, Massachusetts General Hospital; Andres Soriano Professor of Radiation Oncology, Harvard Medical School*
11/12/02	**Ablation of Ventricular Arrhythmias**	*Vivek Reddy, MD, Director, Experimental Electrophysiology Laboratory, Cardiac Arrhythmia Service, Massachusetts General Hospital*
11/19/02	**Needle Electrode Radiofrequency Ablation of Ventricular Myocardium**	**William G. Stevenson, Director of the Clinical Cardiac Electrophysiology Program, Brigham and Women's**

Date	Topic	Speakers
		Hospital; Associate Professor of Medicine, Harvard Medical School
11/26/02	**Minimally Thoracoscopic Video Lobectomy: Experience With the Robot (n=1) for Lobectomy**	*Raphael Bueno, MD, Brigham and Women's Hospital*
11/26/02	**What is Wrong with Robots: How to Make Computer-Aided Surgery Effective**	*Gray S. Rogers, MD, Professor of Surgery and Dermatology, Tufts University/ New England Medical Center*
12/3/02	**Making Stem Cells Behave: Strategies for Rational Stem Cell-Based Therapies**	*David Scadden, MD, Director of Experimental Hematology and Director of Hematologic Malignancies, Massachusetts General Hospital; Co-Director of the Partners AIDS Research Center; Associate Professor of Medicine, Harvard Medical School*
12/3/02	**Novel Therapies for Fighting Disease Causing T-Cells: Diabetes**	*Denise L. Faustman, MD, PhD, Associate Professor of Medicine, Harvard Medical School; Director of Immunobiology, Massachusetts General Hospital*
12/10/02	**Role of Mullerian Inhibiting Substance (MIS) in the Treatment of Ovarian Cancer**	*David MacLauglin, PhD, Massachusetts General Hospital*
12/10/02	**High-Resolution Imaging of Coronary Atherosclerosis by Optical Coherence Tomography**	*Gary Tearney, MD, PhD, Department of Pathology, Massachusetts General Hospital*
12/17/02	**Noninvasive Surgery and Therapy by Using Focused Ultrasound Guided by MRI**	*Kullervo Hynynen, PhD, Associate Professor, Brigham and Women's Hospital and Harvard Medical School*
12/17/02	**Current Novel Clinical Tools in the Treatment and Prevention of Embolic Stroke**	*Alexander Norbash, MD, Director, Neuroradiology, Brigham and Women's Hospital*
1/07/03	**The Development of Diffuse Optical Tomography and Its Applications**	*David Boas, PhD, Massachusetts General Hospital's NMR Martinos Center*
1/07/03	**Phonosurgery**	*Steven Zeitels, MD, FACS, Director, Division of Laryngology, Massachusetts Eye and Ear Infirmary*
1/14/03	**Mechanical Control of Cell and Tissue Morphogenesis**	*Donald E. Ingber, MD, PhD, Professor of Pathology, Harvard Medical School and Children's Hospital*
1/14/03	**Micromechanical Forces as a New Paradigm of Wound Healing Devices**	*Dennis Paul Orgill, MD, PhD, Interim Director, Burn Unit, Brigham and Women's Hospital; Associate Professor of Surgery, Harvard Medical School*

Date	Topic	Speakers
1/21/03	***The Role Of Biomedical Engineering In Drug Development***	*Robert Rubin, MD, Associate Director, Division of Infectious Disease, Brigham and Women's Hospital*
1/21/03	**Protein Drug Delivery: Advances in Biochemical, Physical and Formulation Technologies**	Larry Brown, ScD, Chief Technology Officer, Epic Therapeutics
1/28/03	**Three Grand Challenges in Bioinformatics**	**Isaac Kohane, MD, PhD, Director, Children's Hospital Informatics Program; Associate Professor of Pediatrics, Harvard Medical School**
1/28/03	**PatientSite: Transforming Patient Services, Communication, and Involvement**	*Daniel Sands, MD, MPH, Beth Israel Deaconess Medical Center, the Center for Clinical Computing; Clinical Director of Electronic Patient Records and Communication, CareGroup Healthcare System; Assistant Professor of Medicine, Harvard Medical School*
2/4/03	**Biomedical Applications of Spectral Imaging**	*Gregory Bearman, PhD, NASA's Jet Propulsion Laboratory*
2/4/03	**Eye Tracking in Retinal Imaging**	*Daniel Ferguson, MS, Physical Sciences Inc.*
2/11/03	**Novel devices – chest tubes**	*Jennifer White, MD*
2/11/03	**A Synthetic Dural Sealant and Adhesion Barrier**	*Rees Cosgrove, MD, MGH*
2/18/03	**Non-Invasive Markers For Assessing Developmental Potential Of Human Eggs And Embryos: Introduction** **Protein Profiling Of Human Embryo Culture Media** **Testing for soluble HLA-G**	*Catherine Racowsky - BWH* *Matt Retzloff, MD, BWH* *Danny J. Schust, MD, BWH*
2/25/03	**Key Design Elements For Drug-Delivery Endovascular Stents**	*Campbell Rogers *CIMIT*
2/25/03	**Nanotechnology Applications To Stent Design And Manufacturing**	*Julio Palmaz, Univ. Tex, San Antonio*
3/4/03	**Intraoperative Near-Infrared Fluorescence Imaging**	*John V. Frangioni, M.D., Ph.D, BIDMC*
3/4/03	**Molecular Imaging With MR: Prospects And Problems**	*Lee Josephson, MGH*
3/11/03	**Human Factors Design Issues With Medical Equipment**	*Kim Vicente, MIT*
3/11/03	**Data Mining Techniques And The Development Of Assessment Variables**	*Carla Pugh, MD, Stanford*

Date	Topic	Speakers
	From Clinical Simulation Data	
3/18/03	G-Protein Coupled Receptors As Biosensors	*Ethan A. Lerner, M.D., Ph.D. Associate Professor Dermatology, Harvard Medical School, Assistant Dermatologist, Mass General*
3/18/03	Representation Of Odor Information: From Biology To An Artificial Nose.	*John Kauer, Tufts*
3/25/03	From Scans To Sutures: Computer-Assisted Orthopedic Surgery	*Randy Ellis, PhD, MIT* *Queens Univ, Kingston, Ontario via Russ Taylor JHU*
3/25/03	The Future In Spine	*Steve Hochschuler,* *'shochschuler@texasback.com'; 'shochschulertbi@aol.com'* *hockdeal@aol.com*
4/1/03	Polymer Electronics for Ultra-Sensitive Chemical and Biological Sensors	*Tim Swager, PhD, MIT*
4/1/03	Non-Invasive Breath Diagnostics Using A Novel MEMS Sensor	*Cristina Davis, Draper Labs*
4/8/03	Using The Respiratory System For Heat Exchange	*Max Ferrigno, MD, BWH*
4/8/03	Trends and Innovations in Clinical Monitoring: A review and research agenda	*Julian Goldman, MD, MGH*
4/15/03	Peripheral Vascular Interventions: Opportunities and Challenges	*Ken Rosenfield, MD, MGH*
4/15/03	Characterization and Fabrication of the NanoGate for Nanoscale Fluidic Research	*Alex Slocum, PhD, MIT*
4/22/03	Creating Proactive Environments for Healthy Living	*Stephen Intille, MIT* *Kent Larson, PhD, MIT*
4/22/03	Living Longer More Complex Lives: Taking Technology From Hospital To Home	*Kenneth L. Minaker*
4/29/03	Darkness at Noon: the Comatose Brain.	*Bill Butler, Kahn*
4/29/03	Harvey Mudd Team Portable Water Purification System For WFI Production	*Judy Hsu, Senior Engineering Major, Project Manager* Adam Mills, Senior Engineering Major
5/6/03	Microvolt T-Wave Alternans Testing to Reduce Risk of Sudden Cardiac Death	*Richard Cohen, MIT*

Date	Topic	Speakers
5/6/03	**New Bioengineering Approaches to Ischemic Mitral Valve Repair: From 3D Imaging to Artificial Muscle.**	*Robert Levine, MD, MGH*
5/13/03	**The Genetics of Congenital Diaphragmatic Hernia** **five presentations – full two hours**	*Pat Donahoe* *Jay Schnitzer* *Drucilla Roberts* *Liz Perkins* *Daniel Ryan*
5/20/03	**The NIBIB and Frontiers in Biomedical Imaging**	*Rod Pettigrew, PhD, NIBIB, NIH*
5/20/03	**Old Pyramids to New Paradigms: Simulation's Challenge to 4,000 years of Medicine**	*Steve Dawson, MGH*
5/27/03	*Imaging Of Choroidal Vasculature And Neovascular Membranes* *Diabetic retinopathy: Basic biology of vessel formation* **Macular Degeneration: PDT for treating occular angiogenesis**	*Paola Salvetti, Schepens Eye Research Institute* *Pat D'Amore, Schepens Eye Institute* *Joan Miller, Mass Eye & Ear*
6/3/03	**Enhanced Viewing of Tissues Using Polarized Light**	*Dominic Pelletier, Syris Scientific, LLC*
6/3/03	**high resolution mammography Breast Tomosynthesis**	*Elizabeth Rafferty, MD - MGH Radiology*
6/10/03	**Electrospun PCL Scaffolds for Tissue Engineering of Cartilage**	*Sonya Shortkroff, MD, BWH*
6/10/03	**Optical Imaging of Cancer In Situ**	*Rox Anderson*
6/17/03	**MIT/Sloan/CIMIT Medical Innovations** **Beyond CABG: Novel Devices and Approaches**	Michael Osofsky, MIT/Sloan *David Steinmiller* *MIT/Sloan*
6/17/03	**Automated Cardiac Auscultation**	*John Guttag, MIT*
6/18/03	**Vagus Nerve Stimulation**	**Steve Schachter, MD, Assistant Professor, Neurology, Beth Israel Deaconess Medical Center, and Harvard Medical School**
6/24/03	**Medical Tools For The Military First**	Geoffrey S. F. Ling, MD, PhD, Lieutenant

Date	Topic	Speakers
	Provider	Colonel, Medical Corps, U.S. Army
6/24/03	**Results In Mitral Valve Surgery and Results With IMA Takedown and Midcab**	*Lawrence Cohn, MD, Chief, Cardiac Surgery, Brigham and Women's Hospital* *Tomislav Mihaljevic, MD, Associate Surgeon, Director, Cardiac Surgery Laboratory, Brigham and Women's Hospital*
7/08/03	**Nanotechnology For Therapeutics**	*Jr. M.D., Ruth Dow Doan Professor of Professor of Medicine; Chief, Division of Allergy & Clinical Immunology; Director, Center for Biologic Nanotechnology, University of Michigan*
7/08/03	**Nanotechnology Meets Biology: From Ultrasensistive Detection of Proteins To Screening Small Molecule Protein Interactions**	Charles Lieber, PhD, Mark Hyman, Jr. Professor of Chemistry, Department of Chemistry and Chemical Biology, Division of Engineering and Applied Sciences, Harvard University
7/15/03	**Disease As A Materials Process**	Lionel C. Kimerling, PhD, Thomas Lord Professor of Materials Science and Engineering; Director, Materials Processing Center, Massachusetts Institute of Technology
7/15/03	**The Coming Merger of Living Cells and Microdevices**	*Mehmet Toner, PhD, Professor of Biomedical Engineering, Harvard Medical School and Massachusetts General Hospital; Senior Member of the Scientific Staff, The Shriners Burns Hospital; Director, The Microsystems Bioengineering Core Facility, MGH*
7/22/03	**Nanoscience and Nanotechnology Research Programs at NIH**	*Jeffrey Schloss, PhD, NIH BECON Chairman*
7/22/03	**Nanomechanics of living cells: Using nanoscale contact to define and alter cell state**	*Krystyn Van Vliet, PhD, Materials Science and Engineering Department, MIT*
7/29/03	**Microenvironment Governing of Stem Cells**	*David Scadden, MD, Director of Experimental Hematology and Director of Hematologic Malignancies, Massachusetts General Hospital; Co-Director of the Partners AIDS Research Center; Associate Professor of Medicine, Harvard Medical School*
7/29/03	**Multifunctional Microdevices for Intelligent Drug Delivery: Pores, Particles, and More**	*Tejal A. Desai, PhD, Associate Professor of Biomedical Engineering, College of Engineering, Boston University*

Date	Topic	Speakers
		Engineering, Boston University
9/9/03	**RFID : Applications and Opportunities in Healthcare**	David Brock, PhD, Research Scientist, Laboratory for Manufacturing Productivity, Principal Research Scientist & Director, Auto ID Center, Massachusetts Institute of Technology
9/9/03	A Less Painful Way to Diagnose Prostate Cancer	*Michael Jaklitsch, MD, Assistant Professor of Surgery, Harvard Medical School; Associate Surgeon, Brigham and Women's Hospital*
9/16/03	**ACL Injuries: Past and Present Treatments**	*John C. Richmond, MD, Chief, Adults Orthopedics; Co-Director, Sports Medicine, Tufts-New England Medical Center* *Gregory Altman, PhD, Assistant Professor, Department of Orthopedics, Tufts University, School of Medicine; President and Founder, Tissue Regeneration, Inc*
9/16/03	**Enhanced Primary Repair of the Anterior Cruciate Ligament** CIMIT funded Investigator	*Martha Meany Murray, MD, Instructor in Orthopedic Surgery, Harvard Medical School; Orthopedic Surgeon, Children's Hospital of Boston and Brigham and Women's Hospital*
9/23/03	**The Challenge of Tissue Engineering Heart Muscle**	Buddy D. Ratner, PhD, Washington Research Foundation Professor of Bioengineering and Chemical Engineering at the University of Washington
9/23/03	**Critical Issues In The Engineering Of A Blood Vessel**	Robert Nerem, MD, Georgia Tech/Emory Center for the Engineering of Living Tissues
9/30/03	Whose Carotid Needs to be Treated? Current Results of Surgical Endarectomy **Results Of Stenting With Embolic Protection**	**L. Nelson Hopkins, MD, Professor and Chairman, Neurosurgery and Professor of Radiology, Department of Neurosurgery and Toshiba Stroke Research Center, University at Buffalo, State University of New York** *Adel Malek, MD, PhD, Assistant Professor in Surgery, Harvard Medical School and Beth Israel Deaconess Medical Center* *Kenneth Rosenfield, MD, Director, Cardiac and Vascular Invasive Services, Cardiac Division, Massachusetts General Hospital* *Speakers* *Arthur Day, MD, Neurosurgery, BWH*

Date	Topic	*Speakers*
		Steve Feske, MD, Department of Neurology, BWH Alexander Norbash, MD, Radiology, BWH *Michael Belkin, MD, Vascular Surgery, BWH*
	Panel Discussions **Moderated by Don Baim, MD, BWH and Andy Whittemore, MD, BWH**	

Office of Technology Implementation Program
Program Director: Jonathan Rosen, Ph.D., MGH

Executive Summary
The CIMIT Office of Technology Implementation (OTI) (formerly Technology Development) continues to provide individualized guidance to prospective and active CIMIT Investigators in the areas of Intellectual Property creation and portfolio management, project design and planning, partnering assessment and transaction support, and during this past year, has added the new service of Translational Support.

The OTI annual program cycle focuses on four phases of support to CIMIT and the Consortium Community: Recruitment and assessment of collaborative research proposals (January to July), Technology Implementation for funded investigators (August to January), Transaction support to member licensing and sponsored research offices (year round as required), and SBIR Translational Support for Investigators and small businesses working with CIMIT (year round on quarterly submission cycle).

Key Results
This Annual Report summarizes OTI activities from October 1, 2002 through September 30, 2003. In FY02, CIMIT introduced the individualized Patient Impact Profile (iPIP) to the CIMIT Award selection process for projects evaluated and approved for funding in FY03. This complimentary analysis of Patient Impact, Patent Potential, and Barriers to Implementation was conducted on each of the 120 proposals received that year in addition to our standard Peer Review Scientific Merit, and Programmatic Fit analysis.

Specific Aims
Specific Aim 1: Improve the realizable potential to improve patient care of CIMIT funded programs and projects.

Progress
For the first time in FY02, CIMIT introduced the individualized Patient Impact Profile (iPIP) to the CIMIT Award selection process for projects evaluated and approved for funding in FY03. This complimentary analysis of Patient Impact, Patent Potential, and Barriers to Implementation was conducted on each of the 120 proposals received that year in addition to our standard Peer Review Scientific Merit, and Programmatic Fit analysis. Almost two-thirds of the 42 funded projects were predicted to have significant barriers to implementing their results, and more than half were determined to have limited or low potential to generate foundation patents in their field. This may be a contributing factor to the relatively low number of new patents filed during this past year.

In contrast, in this second year of application (FY03), the iPIP was used more aggressively in the selection process and without changing the requirements for scientific merit or programmatic fit, CIMIT raised the percentage of high patent and implementation potential from 38% of projects to 64% for projects funded for the FY04 year just started on October 1, 2003.

Specific Aim 2: Design Individual Implementation Plans for each funded project

Progress
Between August and November, 2002, the OTI interviewed each of the 43 recipients of CIMIT Awards for FY03. Based on these interviews, the OTI prepared detailed reports for each of the institutional technology transfer offices describing which investigators at that center were funded by CIMIT, were likely to produce new invention disclosures, would need Material Transfer Agreements, and would be potential technology transfer opportunities during the coming year. As

a result of this activity, several institutions assigned case managers in advance to high potential investigators to facilitate their patent and licensing activities.

Specific Aim 3: Support Successful Transfer of CIMIT Technologies

Progress
During this past year, several successful licenses were completed for CIMIT-supported technologies including MEMS-based detector designs, fMRI for pain management, and two nano-particle drug delivery systems. Other projects were significantly advanced in finding suitable partners and at the close of the fiscal year, fourteen projects were in engaged in active discussions with potential licensees.

Specific Aim 4: Establish a New Core Service in Translational Support for CIMIT

Progress
During the past year, the OTI has determined that the SBIR and the STTR programs available from all government agencies can be an effective tool to support CIMIT investigators whose projects are ready for advanced prototyping, manufacturing process development, and advanced medical application developments. Working with the CIMIT Industrial Liaison Program (ILP), the OTI identified nine opportunities for CIMIT investigators to partner with small businesses to apply for SBIR funding. Of these first applications, four have been funded and five are awaiting review.

With CIMIT support this new program of Translational Support has been expanded in the current year and between 30 and 40 applications are expected during the year.

Future Plans
Plans to develop full and formal implementation plans for each investigator were not fully realized this past year. Due to higher than expected resource requirements to complete this goal, only 28% of the recipients received completed plans during the year. A more complete effort is expected for the coming year.

Regulatory Affairs Program

Program Director: John J. Smith, M.D., J.D., MGH

Executive Summary

Maximum clinical impact of safe and effective new medical technologies is heavily dependent on timely Food and Drug Administration (FDA) marketing approval and third-party payer coverage and payment decisions. The Regulatory Affairs Program at CIMIT provides a unique, nationally-recognized resource to address regulatory and coverage/payment challenges throughout the product development lifecycle.

During FY 2003, the Regulatory Affairs Program continued to work with stakeholders to make the existing regulatory and coverage/payment system more efficient, transparent and predictable. A major focus on conflict of interest in medical research culminated in a CIMIT/Harvard Medical School/Stanford University Forum on Conflict of Interest, held in Boston in October 2002. Three forum-related white papers have been release to warm receptions from the stakeholder community, with multiple scholarly articles based on this research either published, accepted for publication or submitted for publication.

The CIMIT Health Policy Internship Program continues to expand. During FY 2003, two interns were placed at the Centers for Medicare and Medicaid Services (CMS), including the program's first intern from industry. An initial intern from the Harvard School of Public Health was placed in the Commissioner's Office at FDA. The Regulatory Affairs Program also worked closely with FDA in FY 2003, with the Director of Regulatory Affairs participating in a mini-sabbatical program at the FDA's Center for Devices and Radiological Health (CDRH).

Closer to home, the Program partnered with the MGH Center for Technology Assessment to provide a regulatory analysis of drug-eluting coronary arterial stents for MGH leadership and beyond, and worked with numerous companies participating in the OR of the Future project. Finally, monthly publication of the popular Regulatory Affairs Newsletter continues.

Aims

1. Identify key systemic regulatory and coverage/payment issues facing the device development process across product lines.

2. Develop and apply a process for developing workable solutions to identified regulatory and coverage/payment issues.

3. Maintain an infrastructure for addressing systemic regulatory and coverage/payment issues in device development; maintain adequate capacity to address product-specific questions, as well as educate the CIMIT community on regulatory issues.

Results

1. Conducting an October 2002 CIMIT/Harvard School of Medicine/Stanford University Forum on Conflict of Interest in Medical Research, together with extensive underlying research.

2. Continuing and expanding the CIMIT Health Policy Internship. From its early focus on CMS and students at the Harvard School of Public Health, this program has been expanded to include the Office of the Commissioner at FDA and industry employees. Project areas during FY 2003 included post-coverage claims analysis, funding clinical trials designed to support CMS coverage decisions, and rulemaking at FDA.

3. Participation in FDA/CDRH initiative to leverage academic medical resources for use in regulatory decisions. The Director of Regulatory Affairs participated in a pilot mini-sabbatical program designed to evaluate anticipated agency programs.

4. Scholarly research resulting in published articles on conflict of interest in medical research, medical technology coverage and payment, and the use of imaging biomarkers in new medical product approval.

5. Continuing project-specific regulatory and coverage/payment analysis, focusing largely on the OR of the Future project.

6. Monthly production of Regulatory Affairs Newsletter.

Plan for Fiscal Year 2004

1. Conclude conflict of interest project, finalizing scholarly publications.

2. Continue CIMIT Health Policy Internship, with one project already underway with FDA.

3. Work with FDA and CMS to leverage CIMIT resources for regulatory decision-making.

4. Identify and address key systemic regulatory and coverage and payment issues crucial to the CIMIT stakeholder community.

5. Provide project-specific regulatory and coverage and payment analysis.

6. Continue monthly production of Regulatory Affairs Newsletter.

7. Pursue extramural funding as appropriate, in conjunction with MGH Institute for Technology Assessment.

Publications and Presentations

Scholarly Publications:

1. Smith JJ, Henderson JA, Baim DS. The FDA and Reprocessing of Single-Use Devices: A Revised Policy and New Questions. *Journal of Vascular and Interventional Radiology* 13(12):1179-82 (2002).

2. Henderson JA, Smith JJ. Financial Conflict of Interest in Medical Research: Overview and Analysis of Federal and State Controls. *Food and Drug Law Journal* 57(3):445-456 (2002).

3. Smith JJ, Sorensen AG, Thrall JH. Biomarkers In Imaging: Realizing Radiology's Future. *Radiology* 227:633-638 (2003).

4. Smith JJ, Henderson JA. Bringing New Medical Technology to Market: Understanding CMS Coverage and Payment Determinations. *Regulatory Affairs Focus* (June 2003).

5. Smith JJ, Berlin L. Malpractice Issues in Radiology: Medicare Fraud and Abuse. *American Journal of Roentgenology* 180:591-595 (2003).

6. Henderson JA, Smith JJ. Financial Conflict of Interest in Medical Research: Overview and Analysis of Institutional Controls. *Food and Drug Law Journal* 58:251-267 (2003).

7. Wang SS, Smith JJ. Potential Legal Barriers to Increasing CMS/FDA Collaboration: The Law of Trade Secrets and Related Considerations. *Food and Drug Law Journal* (in press).

8. Henderson JA, Smith JJ. Financial Conflicts of Interest in Medical Research: The Potential Value of Regional Variation at the Institutional Level (submitted to *Research Policy*).

CIMIT White Papers:

1. Henderson JA, Smith JJ. Financial Conflict of Interest in Medical Research: Overview and Analysis of Federal and State Controls (2002).

2. Henderson JA, Smith JJ. Financial Conflict of Interest in Medical Research: Overview and Analysis of Institutional Controls (2002).

3. Henderson JA, Smith JJ. Academic, Industry and the Bayh-Dole Act: An Implied Duty to Commercialize (2002).

4. Henderson JA, Smith JJ. Clinical Introduction of Drug-Eluting Stents in the United States: Regulatory and Legal Considerations (2003).

Newsletters:

1. CIMIT Regulatory Affairs Newsletter.

Presentations by the Director of Regulatory Affairs:

1. Refresher Course at the Radiological Society of North America Scientific Assembly and Annual Meeting. Understanding How You Get Paid: Medicare and the Third Party Payer Coverage and Reimbursement Process (Chicago, IL, November 2002).

2. Society of Computed Body Tomography and Magnetic Resonance. Medically Principled CT-Screening: Theory, Techniques and Controversies. Medicolegal and Regulatory Issues (Boston, MA, November 2002).

3. National Institute for Health Care Management Conference: Accelerating Quality Improvement in Health Care: Strategies to Speed the Diffusion of Evidence-Based Innovations. CIMIT and the Development of Medical Technology (Washington, DC, January 2003).

4. American Roentgen Ray Society Annual Meeting. CT Screening: Medico-Legal and Regulatory Issues (San Diego, CA, May 2003).

5. U.S. Food and Drug Administration, Center for Devices and Radiological Health. Off-Label Use and the Potential Legal Exposure for Healthcare Professionals (Rockville, MD, May 2003).

6. General Electric Global Research. Off-Label Use and Legal Exposure: An Examination of CT Screening (Niskayuna, NY, June 2003)

7. Society of Interventional Radiology. Stroke Consensus Conference. Off-Label Use of Medical Products (Chicago, IL, June 2003).

8. Society of Interventional Radiology. Stroke Consensus Conference. Informed Consent and Off-Label Use of Medical Products (Chicago, IL, June 2003).

9. Coverage and Analysis Group, Centers for Medicare and Medicaid Services. CIMIT Health Policy Internship: Project Presentations (Baltimore, MD, July 2003).

10. Whitehead Institute Scientific Retreat. Academia, Industry and the Bayh-Dole Act: An Implied Duty to Commercialize (Waterville Valley, NH, September 2003).

Technology Assessment
Program Director: Scott Gazelle, M.D., Ph.D., MGH

Executive Summary

The Technology Assessment and Outcomes Analysis Program is divided into a Core and one major Outcomes Project. The Program Core functions to: 1) assist the Operations Group with resource allocation decisions by performing preliminary analysis of technologies identified in requests for funding; 2) provide scientific direction, project coordination and administrative support to the Outcomes Research Project; and 3) provide consultation and guidance to CIMIT investigators and collaborators regarding issues such as project feasibility, study design, optimal endpoint determination and data analytic or statistical methods. Work is progressing in all three areas.

The single major Outcomes Research Projects is related to one of CIMIT's major focus areas: Operating Room of the Future.

TECHNOLOGY ASSESSMENT PROGRAM CORE

The Technology Assessment and Outcomes Analysis Program Core supports CIMIT research, administrative and clinical activities using a variety of analytic techniques to investigate specific technology related questions as well as broader national health policy issues. Projects may range from examining the potential cost-effectiveness of a new technology under consideration for CIMIT funding, to determining the optimal point of intervention in any one of a number of broad disease areas.

With CIMIT support and guidance, we have succeeded in establishing a large and capable group of investigators. These investigators have developed a rich network of collaborations throughout CIMIT. We have collaborated and/or consulted with other CIMIT investigators on issues such as project feasibility, study design, endpoint determination, and approaches to data analysis. We have also assisted with primary data collection and analysis. This work complements other more traditional laboratory and/or clinical research being carried out by individual CIMIT investigators or within the context of major CIMIT Programs.

The Program Core will continue to support the entire CIMIT scientific and administrative community, as well as the two Technology Assessment and Outcomes Analysis Program Research Projects (see below). The Program Core will help CIMIT focus resource allocation for the development of innovative medical technologies that can result in improved patient care; provide advice on and perform studies to assess the effectiveness, cost and cost-effectiveness of new technologies under development; and demonstrate the value of these new technologies to the public, physicians, payers, industry, and legislators so as to facilitate their appropriate dissemination and implementation.

Specific Aim 1: Provide consultation and guidance to CIMIT investigators and collaborators regarding issues such as project feasibility, study design, optimal endpoint determination and data analytic or statistical methods.

Progress/Plan Specific Aim 1

The original mission of the CIMIT Technology Assessment and Outcomes Analysis Program was to develop a world class program in technology assessment and outcomes analysis that would support all research, education, and clinical activities of the CIMIT Consortium. Our major CIMIT

research effort is now directed primarily towards one specific Outcomes Project (Operating Room of the Future), as described above. However, we continue to be available to collaborate with CIMIT investigators on issues such as project feasibility, study design, endpoint determination, and approaches to data analysis. These collaborations over the past three years shaped the major research focus of the Program, and laid the groundwork for the Operating Room of the Future Outcomes Projects.

As projects are funded and move from the conceptual stage through the various stages of development, we work with investigators to accurately and expeditiously evaluate the capabilities and potential impact of the new technologies on health outcomes and costs, particularly as the magnitude of the expenditures required for widespread clinical implementation increases. Specifically, we will develop plans for and carry out rapid and accurate analyses of effectiveness, cost and cost-effectiveness. The results of these analyses can then be used to demonstrate the value of specific technologies to the public, physicians, payers, industry, and legislators, in order to facilitate appropriate dissemination and implementation.

Specific Aim 2: Provide scientific direction, project coordination and administrative support to major Technology Assessment Program Research Projects.

Progress/Plan Specific Aim 2

As part the larger Technology Assessment and Outcomes Analysis Program, we are conducting one specific research project: the Operating Room of the Future Outcomes Project. This is the continuation of an ongoing research effort which involves collaboration with leaders of the corresponding major CIMIT research focus area. The Technology Assessment Program Core provides scientific direction, project coordination, and administrative support to this project. The specific Outcomes Project is are described elsewhere in this report, but is summarized briefly in the following paragraphs.

In the Operating Room of the Future Outcomes Project, we have developed, verified, and begun to and utilize a discrete event simulation model in order to evaluate the OR of the Future as it is developed and utilized. The model is a comprehensive, robust and expandable model of the entire surgical suite, and will be used in order to better understand the optimal approach to integrating ORF activities. We have also worked with the ORF Project team to plan and conduct additional studies related the actual ORF, now that it is operational.

Specific Aim 3: Assist the CIMIT Operations Group with resource allocation decisions via preliminary analysis of technologies identified in requests for funding.

Progress/Plan Specific Aim 3

The Technology Assessment Program Core is available to work with the Operations Group in order to review specific proposals under consideration, collect and provide relevant data to the Operations Group concerning costs, disease burden, etc., and perform economic and/or outcomes analyses of the technologies or programs under consideration. Thus far, however, no requests for analyses related to this aim have been received. Our work with the Operations Group has thus been limited to providing input and guidance on general issues related to our areas of expertise. We look forward to working together with the Operations Group in coming months in order to help to focus resource allocation for the development of innovative medical technologies that are most likely to result in improved patient care and healthcare outcomes.

List of Personnel Receiving Pay

Principal Investigator	Project Title
Bouma, Brett	Spectrally Encoded Confocal Microscopy
Chan, Raymond	Robust elastography for IVUS and OCT- based imaging of strain in the vulnerable atherosclerotic plaque
Cohen, Richard	Continuous Cardiac Output Monitoring for Combat Casualty Care
Dawson, Steve	Medical Simulation
De Boer, Johannes	Early diagnosis of Osteoarthritis by polarization sensitive Optical Coherence Tomography
Dubowsky, Steven	Electrostrictive Polymer Artificial Muscle (EPAM) Devices for Magnetic Resonance Imaging (MRI)
Ellsmere, James	Image-guided endoscopy: LapUS Project
Ferrigno, Massimo	Field Cooling of Injured Soldiers
Grant, Aaron	Radio Frequency Impedance Mapping for Medical Imaging
Guttag, John	Patient Centric Networking and Applications
Isaacson, Keith	Measuring impact of a passive wireless tracking system
Langer, Robert	New Degradable Polymeric Materials for Localized Gene Transfer
Rattner, David	Learning Predictive rules from medical data
Redmond, Robert	Photochemical Tissue Bonding: Enabling Studies and Application to Microsurgical Reconstruction of Peripheral Nerves
Shortkroff, Sonya	Nanofibrous scaffolds for cartilage regeneration
Sims, Nathaniel	Untethered Monitoring
Tearney, Guillermo	Speckle imaging for plaque characterization

Animal and Human Use Tracking Sheets

Animal Protocols

PI	PROTOCOL TITLE	Approval from DoD Contracting
Cohen, Richard	Method for Determination of Cardiac Output from Pressure Waveforms anywhere in Arterial Tree	6/26/03
Ellsmere, James Rattner, David	Ultrasound guidance for minimally invasive abdominal surgery	1/8/03
Ferrigno, Massimo	Field Cooling of Injured Soldiers	3/7/03
Frangioni, John	Molecular imaging of rodents	5/2/03
Gold, Herman Thompson, Craig	Evaluation of myocardial regeneration by percutaneous cellular cardiomyoplasty	5/2/03
Hamblin, Michael	Treatment of Vulnerable Atherosclerotic Plaques with Macrophage-Targeted Photodynamic Therapy	4/22/03
Levine, Robert	Ischemic Mitral Regurgitation: From Mechanism to Therapy	6/26/03

PI	PROTOCOL TITLE	Approval from DoD Contracting
Redmond, Robert	Photochemical Tissue Bonding: Enabling Studies and Application to Microsurgical Reconstruction of Peripheral Nerves	4/22/03
Shortkroff, Sonya	Nanofibrous scaffolds for cartilage regeneration	5/2/03
Slocum, Alexander Agnihotri, Arvind	External Mitral Annuloplasty	4/22/03
Tawakol, Ahmed Fischmann, Alan	External imaging of experimental atherosclerosis with radiolabled peptides	3/7/03
Torchiana, David	Expandable Intravenous Access	Pending submission to DoD
Troulis, Maria	Minimally Invasive Approach to Reconstruction of the Midfacial Skeleton	3/4/03

Human Protocols

PI	Project Title	DoD Approval Date *
Bouma, Brett	Diagnosis of Pancreatic Cysts	1/7/03
Bouma, Brett	Spectrally Encoded Confocal Microscopy	1/7/03
Bueno, Rafael	Development of a gene ratio-based test kit for dianosis of lung cancer	4/22/03
Chan, Raymond	Robust elastography for IVUS and OCT- based imaging of strain in the vulnerable atherosclerotic plaque	5/2/03
Cooper, Jeff	Development of realistic-simulation-based training systems for personnel using the OR suite and new technology	
Davis, Cristina	Detection of Pentane in Patient Breath using Planar FAIMS	
De Boer, Johannes	Early diagnosis of Osteoarthritis by polarization sensitive Optical Coherence Tomography	4/22/03
Greenman, Robert	Magnetic Resonance Imaging of Carotid Plaques at 3 Tesla	
Jaklitsch, Michael	Prostate Cancer	
Rattner, David	Learning Predictive rules from medical data	11/6/02
Rattner/ Kaebling	Learning Predictive rules from medical data	11/6/02
Shrinivasan, Mandayam	High frequency ultrasound (50MHz) imaging and characterization of skin lesions in vivo	
Tearney, Guillermo	Speckle imaging for plaque characterization	1/7/03
Vacanti, Joseph	Tissue Engineering and Organ Fabrication	6/26/03

*** Those without a date are still in process at home institution or at DoD**