AD_________________
(Leave blank)

Award Number:
W81XWH-05-1-0072

TITLE:
Washington DC Area Computer Aided Surgery Society Monthly Meetings

PRINCIPAL INVESTIGATOR:
Kevin R. Cleary, Ph.D.

CONTRACTING ORGANIZATION:
Georgetown University
Washington, DC 20057

REPORT DATE:
March 2009

TYPE OF REPORT:
Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: (Check one)

_X_ Approved for public release; distribution unlimited

___ Distribution limited to U.S. Government agencies only; report contains proprietary information

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. Agency Use Only (Leave blank)

2. Report Date
March 21, 2009

3. Report Type and Period Covered (i.e., annual 1 Jun 00 - 31 May 01)
Final 22 Feb 2005-21 Feb 2009

4. Title and Subtitle
Washington DC Area Computer Aided Surgery Society Monthly Meetings

5. Award Number
W81XWH-05-1-0072

6. Author(s)
Kevin R. Cleary, Ph.D.

7. Performing Organization Name (Include Name, City, State, Zip Code and Email for Principal Investigator)

Georgetown University
37th & O Streets, N.W.
Washington, DC 20057
Contact E-Mail: cleary@georgetown.edu

8. Performing Organization Report Number (Leave Blank)

9. Sponsoring/Monitoring Agency Name and Address

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. Sponsoring/Monitoring Agency Report Number (Leave Blank)

11. Supplementary Notes (i.e., report contains color photos, report contains appendix in non-print form, etc.)

12a. Distribution/Availability Statement (check one)
_X_ Approved for public release; distribution unlimited
___ Distribution limited to U.S. Government agencies only - report contains proprietary information

12b. Distribution Code
(Leave Blank)

13. Abstract *(Maximum 200 Words)* *(abstract should contain no proprietary or confidential information)*

Since its inception in 1999, the Washington, D.C., Area Computer-Aided Surgery Society (WashCAS) has become the major vehicle in the Washington/Baltimore area for exploring the issues in the emerging field of computer aided surgery and related technologies.

The key accomplishments of the society to date are:

1. Has held meetings every other month since 1999, featuring many of the world's leading experts on computer-assisted surgery and related topics.
2. Has brought together representatives from national funding agencies including NIH, NSF, NRL, the Navy Medical Center, Walter Reed, and Fort Detrick. Participating universities have included Georgetown, George Washington, George Mason, Catholic, and Johns Hopkins, among others.
3. While the great majority of the meetings have been held at the National Library of Medicine, we have also held meetings at Georgetown, George Washington, and the University of Maryland.
4. Established a web site (www.washcas.org) to disseminate information, including abstracts of all the talks to date and links to local research groups.

14. Subject Terms (keywords previously assigned to proposal abstract or terms which apply to this award)
Computer aided surgery, societies, organizations

15. Number of Pages (count all pages including appendices)
13

16. Price Code (Leave Blank)

17. Security Classification of Report	18. Security Classification of this Page	19. Security Classification of Abstract	20. Limitation of Abstract
Unclassified	Unclassified	Unclassified	Unlimited

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89)
Prescribed by ANSI Std. Z39-18
298-102

1 Table of Contents

2 Introduction

The Washington, D.C., Area Computer Aided Surgery Society (WashCAS) has become the major vehicle in the Washington/Baltimore area for exploring the issues in the emerging field of computer aided surgery and related technologies. The society was founded with the intent to bring together physicians, scientists, and engineers to discuss computer applications in surgery, including image-guided surgery, medical robotics, medical imaging, surgical simulation, teleradiology, and other related topics. Meetings with keynote speakers are held every other month.

The Society was founded in the summer of 1999 and has held 39 meetings to date, with an average of 40 attendees at each meeting. Attendees have included representatives from university, commercial, and government entities (including USUHS, MRMC, WRAMC, NIH, FDA, and NLM). Since the fall of 2000, the society has been funded by the Telemedicine and Advanced Technology Research Center (TATRC) of the U.S. Army Medical Research and Material Command (USAMRMC). This funding has allowed us to recruit internationally known speakers as well as provide food before the meetings (an essential element since most people come directly from the office for the 7 pm talks).

The vast majority of the meetings have been held at the National Library of Medicine (NLM) on the NIH main campus. NLM has a first-class conference room at the Lister Hill Center. These facilities have been made available to us at no charge and this has enabled us to extend our initial funding several years. The primary source of society information is the website at www.washcas.org. The society is run by volunteers, and no salary support has been charged to the grant. In short, we believe the government has received excellent value for the funds expended.

The society organizers are:

- President: James Burgess, MD, Allegheny General Hospital
- Treasurer: Kevin Cleary, PhD, Georgetown University
- Secretary: Gabor Fichtinger, PhD, Johns Hopkins University
- Local host: Terry Yoo, PhD, National Library of Medicine

3 Report Body

This report covers the period from 22 February 2005 to 21 March 2009. The award number is W81XWH-05-1-0072.

As stated in the reporting requirements on the USAMRMC web site, the report body is to “describe the research accomplishments associated with each task in the statement of work”. Since this award supports the WashCAS meetings, there are no research accomplishments to report. Instead, we provide a list of the meetings to date in Table 1.

Table 1. WashCAS Seminar Speakers

Date	Speaker	Title
17 Feb 2009	Lance Liotta	Individual Therapy, the Promise of Systems Biology Medicine
20 May 2008	Sangtae Kim	The R&D Crisis in the Pharmaceutical Industry: A Personal Perspective
18 Mar 2008	Jaydev Desai	Smart Device Technology for Orthopaedic Surgery
15 Jan 2008	Lutz Nolte	Robust Computational Methods for Multimodality Assessment of Organ Structure and Function
13 Nov 2007	Dimitris Metaxas	Producing an Entire Patient Specific Surgical Tool Kit in under One Hour
18 Sept 2007	Joel Salz	Middleware Support and Collaborative Multi Center Translational Research
20 Mar 2007	Warren Grundfest	Percutaneous Infrared Endoscopic Imaging of the Cardiovascular System
30 Jan 2007	Tony Chan	The Mathematics and Physical Sciences Directorate at NSF Initial Reflections and Possible Connections with NIH
14 Nov 2006	Reuben Mezrich MD	The Quick Kill: Stimulating Innovation
19 Sep 2006	Gabor Szekely	Realistic simulation of Inteventions for Surgical Skill Training
16 May 2006	Guido Gerig	Mapping the Trajectory of the Early Developing Brain: Challenges and Rewards
21 Mar 2006	Elliot McVeigh	Real-time MRI Guided Cardiac Interventions
17 Jan 2006	Jonathan Lewin	Advances in Interventional and Intra-Operative MRI
15 Nov 2005	James Williams	Closed Loop Image-Guided Intervention
15 Sept 2005	Terry Peters	Towards Image-Guidance for Interventional Cardiac Procedures
15 Mar 2005	Andrew Maidment	Imaging Over Seven Orders of Magnitude
18 Jan 2005	John Wong	Methods and Challenges of Image-Guided Adaptive Radiation Therapy
16 Nov 2004	Tim Salcudean	Modeling of Mechanical Properties of Tissue Using Ultrasound
21 Sept 2004	Karl Heinz Hohne	Volume Models for Anatomy Teaching and Surgery Simulation
18 May 2004	Phil Corcoran	Robotic Cardiothoracic Surgery
16 Mar 2004	Bill Lorensen	Inside Insight: A Behind the Scenes Look at the Insight Toolkit
20 Jan 2004	Chris Johnson	Biomedical Computing and Visualization
20 Nov 2003	Robert Maciunas	Overview of Image-guided Neurosurgery
16 Sept 2003	Calvin Maurer	Image Registration, Segmentation, and Visualization for Surgical Planning and Guidance
29 July 2003	Pierre Vieyres	Mobile Tele-Echography using an Ultra-Light Robot
20 May 2003	Peter Basser	Diffusion Tensor Imaging
21 Jan 2003	Kenneth Salisbury	Enhancing Surgery Through Robotics and Automation
19 Nov 2002	Carl Jaffe	Frontiers in Vascular Imaging
17 Sept 2002	Mandayam Srinivasan	Haptics and Surgical Simulation
16 Apr 2002	Michael Ackerman Brett Peterson	Health Information and the Next Generation Internet Network Enhanced Collaboration in Biomedical Technology Centers
19 Feb 2002	Allison M. Okamura	Vision Assisted Control for Manipulation
11 Dec 2001	Lawrence J.	Human Performance Considerations in Medical Systems

	Hettinger	
23 Oct 2001	King Li	Biomedical Imaging in the New Millennium
17 July 2001	Robert Galloway Jr.	Advances in Technology-Guided Therapy at Vanderbilt
15 May 2001	Elizabeth Bullitt	Patient-Specific Vascular Models for Surgical Applications
20 Mar 2001	Charles Richardson	Fused Deposition Modeling for Surgical Support
16 Jan 2001	Michael Miller	Computational Anatomy
14 Nov 2000	James Duncan	Use of Geometrical and Physical Models in Image Analysis
19 Sept 2000	Ron Kikinis	Surgical Planning Laboratory
18 July 2000	Richard Swaja	Bioengineering, Bioimaging, and Bioinformatics at the NIH
30 May 2000	Larry Clarke	New Resources Within NIH/NCI for Imaging Technology
28 Mar 2000	Brian Athey	Visualization & Manipulation of Visible Human Datasets
18 Jan 2000	Richard Bucholz	Computer Aided Surgery to Information Guided Therapy
16 Nov 1999	Clay Easterly	The Virtual Human Initiative
13 Sept 1999	Russell Taylor	Computer-Integrated Surgery

3.1 Abstracts

Provided within this section is a concise reproduction of abstracts for selected talks held during the period of February 22, 2005 to March 21, 2009. The abstracts present a clear indication of the caliber of subject matter presented over the course of the past several years.

3.1.1 Individualized Therapy, the Promise of Systems Biology Medicine

Lance Liotta, MD, PhD
Professor of Life Sciences, George Mason University

Systems biology is the integration of molecular information across cells, tissues, and organ systems. Nanotechnology, laser microdissection, mass spectrometry, and molecular profiling technology offers powerful methods for discovering biomarkers predictive of early stage disease, monitoring the ongoing flow of information within cells and tissues, and revealing the disease associated alterations in cellular communication networks. Suppression of aberrant signaling is the goal of molecular targeted therapies of the future. A goal of functional proteomics is to develop "circuit maps" of protein signal pathways regulating proliferation, apoptosis, and differentiation in normal cells and diseased cells. Protein microarray technology provides a means to profile cellular signaling pathways in a manner not achievable by gene arrays. It is now possible to procure a biopsy, microdissect the cancer cells, and map the functional state of key signal pathways within a patient's tumor cells. The ultimate goal is tailored combination therapy which provides higher individual efficacy with lower toxicity. The speaker will review new systems medicine technology, provide examples of clinical research studies, and describe new ongoing clinical research trials testing the application of proteomic signal pathway profiling to individualized therapy.

3.1.2 Percutaneous Infrared Endoscopic Imaging of the Cardiovascular System

Warren Grundfest, MD
Professor, Department of Bioengineering, UCLA

Real-time imaging through blood is theoretically feasible using infrared imaging technologies. Using Mie optical scattering theory and experimentation we determined that infrared light in the range of 1550-1650nm would permit imaging through blood. We designed and built a catheter-based, infrared optical imaging system using an Indium-Gallium-Arsenide 320x256 pixel focal plane array. Subtraction of background noise, removal of the fiberoptic pixel pattern, and image enhancement are accomplished using standard digital signal processing techniques. Frame rates of 15 frames per second are used, and stop-frame imaging helps to identify intracardiac structures. These IR angioscopes were tested in 35 canine and 40 porcine models. Imaging through human blood was considered based on results of animal experimentation. After obtaining FDA approval in-vivo applications were examined in human clinical trials. In the first 50 patients studied intracardiac images revealed the ability to identify the coronary sinus, the eustacian ridge, the fossa ovalis, the tricuspid valve, and other intracardiac and vascular structures. In some patients tissue detail was resolved to 100 microns, but useful images could not be obtained in some patients. Additional technical improvements will be required for routine clinical use. Early experience shows that IR endoscopy can be used to define intracardiac and vascular anatomy and guide interventional procedures.

3.1.3 The Mathematics and Physical Sciences Directorate at NSF Initial Reflections and Possible Connections with NIH

Tony Chan, PhD
Assistant Director and head of the Directorate for Mathematics and Physical Sciences, National Science Foundation

Dr. Chan will share the experience of his first 100 days in office, describing his transmogrification from academic director to NSF Directorate head. In his talk, Dr. Chan will address his hopes and the direction he has tried to foster at NSF, as well as how that perspective of NSF may have changed now that he has had time to acclimate to the Federal system. As his current research is funded by a combination of NSF, NIH, and

ONR, Dr. Chan recognizes that there are opportunities for coordination and cooperation among agencies to promote cross-disciplinary research. At the end of his remarks, he plans to open a continuing conversation on how NSF and NIH could participate in future cross-agency, interdisciplinary initiatives.

3.1.4 The Quick Kill: Stimulating Innovation

Reuben Mezrich, MD, PhD, FACR
Professor and Chairman, Department of Radiology, University of Maryland School of Medicine

The goal of all of us involved in research is finding new ideas, making new discoveries and then developing them into practical products or processes. The main job of the members of the technical staff was to invent and innovate. The main job of the administration was to provide the resources and the environment in which we could do this job. The main tool that the administration used to support our efforts at innovation was the "Quick Kill". The underlying understanding was that most new ideas failed. At the RCA Labs the expectation was that 80% of all ideas would fail and the administration would manage to that expectation. If in any year more than 80% of new ideas failed they were being too aggressive, if less than 80% failed they were not being aggressive enough. The "Quick Kill" was used to weed out the failures. Twice each year we would all gather together for an award ceremony where those ideas that hadn't quite made it were celebrated – nice plaques were distributed – but these were known as the "kiss of death" awards. The project was terminated, but no one was fired. The next morning the boss would ask…"what's your new idea". The sin was not failing, the only sin was not having new ideas. Among the many ideas that came out of the Labs was color television, the LCD display, the CMOS transistor and on and on. The environment at the Labs was an effective stimulant to innovation.

Unfortunately we now live in an environment, especially in government funded research, where failure isn't tolerated. All research, almost by design, must succeed, but such research, almost by definition, will not be innovative, and in fact won't achieve the goals most of us really want. I will review this situation and then try to illustrate, by example, what we are doing at the University of Maryland Department of Radiology to stimulate innovation.

3.1.5 Realistic Simulation of Interventions for Surgical Skill Training

Gabor Szekely, PhD
Swiss Federal Institute of Technology

Virtual reality based simulation of medical procedures has become a rapidly developing research area during the past decade. A large number of academic and commercial systems have been developed, offering the possibility for training and planning procedures for a very wide spectrum of applications. Nevertheless, until recently the realistic simulation of complete interventions in real-time, as necessary for advanced skill training, has been impossible due to numerous technological barriers. Thanks to significant advances in algorithmic and hardware development during the past few years, high fidelity training simulation is today within reach, at least for some selected interventions especially in minimally invasive surgery. The talk will analyze recent results with special emphasis on anatomical scene generation, modeling and simulation of tissue behavior and development of virtual surgical instruments. The power of these techniques will be demonstrated on a simulator system allowing the training of diagnostic and therapeutic hysteroscopic interventions.

3.1.6 Mapping the Trajectory of the Early Developing Brain: Challenges and Rewards

Guido Gerig, PhD
Taylor Grandy Professor of Computer Science and Psychiatry, University of North Carolina at Chapel Hill

Imaging studies of early brain development get increasing attention as improved modeling of the pattern of normal development might lead to a better understanding of origin, timing and nature of morphologic differences in neurodevelopmental disorders and brain disease. UNC has collected one of the largest samples of longitudinal MRI/DTI of neonates and infants up to age 5 years (N>300) to model the trajectory of early brain development using structural MRI (sMRI) and diffusion tensor imaging (DTI). Studying MRI of this age group involves two major challenges, successful high quality MRI scanning of non-sedated infants and image analysis methods that can cope with very low contrast-to-noise ratio, small brain size, variability of brain shape and size, and locally varying contrast changes due to a continuous change of early myelination.

We will discuss the challenge of scanning children in this age group but then focus on image analysis aspects, since standard methodology developed for adult MRI is inadequate for images of this age group This will include new tissue segmentation for partially myelinated white matter, parcellation of full brain into major lobar and subcortical structures, and computational anatomy tools for building age specific atlases and for modeling local growth throughout the whole volume. Shape analysis of multi-object complexes, here the set of subcortical structures, is demonstrated to describe major changes due to longitudinal growth and cross-sectional group differences. White matter development is assessed by novel region-based statistical analysis of diffusion tensor imaging (DTI) and tools for quantitative analysis of major fiber tracts.

We will present latest results on lateralization, gender differences, very early trajectory of cortical gray matter growth, and the development of white matter as seen most rapidly in the first year of development but still very significant between 2 and 4 years. Measuring the early trajectory of growth via structural MRI and DTI will likely provide a vastly improved understanding of early brain development.

3.1.7 Real-time MRI Guided Cardiac Interventions

Elliot McVeigh, MD
Principal Investigator, National Heart, Lung, and Blood Institute, National Institutes of Health

Interventional cardiac MR (CMR) has been undergoing rapid development because of the availability of MR compatible interventional catheters, and the increased performance of the MR systems themselves. Much of this development has benefited from the previous groundbreaking work in MRI guided surgical technologies; however, intravascular techniques do not carry the requirement for an open access scanner, and hence higher imaging performance during procedures can be achieved. Now, with the availability of a short, relatively open cylindrical scanner, high imaging performance is also available to guide direct surgical procedures.

One of the principal enabling technologies for guiding interventional procedures in the beating heart is real-time imaging. The obvious trade-off is between spatial resolution and temporal resolution, but this should be fully adjustable on an interactive system. With the development of multiple receiver systems, image acquisition can be accelerated using surface coil arrays.

3.1.8 Middleware Support and Collaborative Multi Center Translational Research

Joel Salz, MD
Emory University

I will describe biomedical grid middleware designed to facilitate multi-center translational research efforts that involve sharing many different types of biomedical data such as biomedical imagery, high throughput molecular data, electrophysiology data, tissue data and clinical information. The centerpieces of the infrastructure I will describe is a growing middleware suite consisting of caGrid 1.1, the caBIG in vivo imaging extensions and caGrid derived infrastructure developed as part of the Cardiovascular Research Grid. I will provide a brief summary of the middleware architecture, outline some applications that employ the middleware, and describe ways in which cooperative groups and collaborative translational research efforts can take advantage of this infrastructure. Finally, I will outline some of the future challenges we expect to face as the Biomedical Informatics community attempts to scale biomedical grid infrastructure to support increasingly large and diverse biomedical communitie

3.1.9 Robust Computational Methods for Multimodality Assessment of Organ Structure and Function

Dimitris Metaxas, PhD
Rutgers

We present a novel computational approach to assessing organ structure and function based on the use of various modalities for cardiac and cancer applications. Our methods are based on the integration of novel deformable models, statistical methods and medical domain knowledge capable of dealing with complex segmentation, registration and classification problems in the above medical domains. These mature methods are now capable of reliably addressing the above problems and be used by physicians efficiently.

In the first part of the talk we will describe a complete system for the segmentation, reconstruction and classification of the cardiac motion from MRI tagged data and Ultrasound data. We also show for the first time how to register and compare ultrasound and MRI-tagged data for a variety of pathologies. In the second part of the talk we will present segmentation, reconstruction and registration methods for lung cancer from CT data, as well as the registration of fluorescence and planning CT data for improved lung cancer radiotherapy applications.

These methods are based on collaborative research with NYU medical school, Columbia Medical School, MSKCC, and UMDNJ/Robert Wood Medical School.

3.1.10 Smart Device Technology for Orthopaedic Surgery

Lutz Nolte, PhD
University of Bern

In the past few years a novel area of research and development - Computer Assisted Orthopaedic Surgery (CAOS) - has been established. Its primary goal is to provide a direct link between preoperative planning and intraoperative surgical action. Key elements to this link are surgical trackers allowing precision image-interactive surgical procedures. Trackers can be either freehand based on optoelectronic or electro-magnetic concepts or robots operating in semi-constraint (surgeon-driven) or autonomous modes. Associated surgical modules have emerged from the laboratory and are being clinically used in various orthopaedic subspecialties on a routine basis, such as joint replacements, spinal and trauma interventions, etc. In combination with advanced intraoperative imaging devices, fast and reliable percutaneous registration and referencing techniques as well as virtual und augmented realities the "transparent patient" may soon become reality. Part of such a scenario the development of new surgical devices, i.e. instruments and implants should be seen. In this field a rather conservative attitude of orthopaedic device manufacturers and surgeons can be identified. This is in contrast to related pure technological areas, where a quantum leap of innovation has been observed in the past decades. In particular there have been groundbreaking developments in fields such as mechatronics, micro-sensor and actuator technology, microelectronics, systems technology, etc. In addition, material science research has brought forward revolutionary options for technology developers. A vast number of corresponding laboratory prototypes have emerged into successful engineering products in large scale markets, such as consumer electronics, automotive industry, etc. Transfer of these engineering technologies into the medical arena may provide novel opportunities for medical applications. In the future they hold potential to further optimize the treatment loop, i.e. the way we diagnose, plan, simulate, execute, document and evaluate a surgical procedure. In this presentation an overview is given of the state of the art in research and development on smart surgical device technology, i.e. instruments and implant involving advanced sensor and actuator technology. Special focus is on their use in orthopaedic interventions.

3.1.11 Medical Robotics Research at Robotics, Automation, Manipulation, and Sensing (RAMS) Laboratory

Jaydev Desai
University of Maryland

In this talk, I will discuss the various areas of research being pursued in the RAMS Laboratory. These areas include:

- Haptic (sense of touch) interfaces for applications in Robot-assisted Surgery – We will describe the design, development, and implementation of a 7 degree-of-freedom (DOF) haptic feedback interface developed in the laboratory
- Reality-based soft-tissue modeling for Surgical Simulation – Modeling basic surgical skills such as probing and cutting soft-tissue
- Model-based teleoperation in Robot-assisted surgery – Design and development of a model based controller for the Mitsubishi PA-10 robot arm and interfacing it with an automated laparoscopic tool and the 7 DOF haptic feedback interface
- Cell manipulation and Force feedback interfaces for Cellular Surgery – interface and human factors studies to understand the role of force feedback at the micro-scale

Towards the end of the talk, I will also briefly present on our recent effort in:

- Developing a teleoperated force-feedback interface system for a 1 DOF robot for radiofrequency ablation (RFA) under continuous Magnetic Resonance Imaging (MRI). The procedure was initially performed on a breast phantom model.
- Developing an initial prototype of a meso-scale robot for applications in neurosurgery.

4 Key Research Outcomes

This section is intended to provide a bulleted list of key research accomplishments. Since this is not a research grant, instead we list some of the accomplishments of the WashCAS organization.

- Has held meetings every alternate month since 1999, featuring many of the nation's leading experts on computer aided surgery and related topics.
- Has brought together representatives from national funding agencies including NIH, NSF, NRL, the Navy Medical Center, Walter Reed, and Fort Detrick. Participating universities have included Georgetown University, George Washington University, George Mason University, Catholic University, and Johns Hopkins University among others.
- While the great majority of the meetings have been held at the National Library of Medicine, we have also held meetings at Georgetown University, George Washington University, and the University of Maryland.
- Established a web site (www.washcas.org) to disseminate information, including abstracts of all the talks to date and links to local research groups.

5 Reportable Outcomes

This section provides a list of reportable outcomes.

The major reportable outcome is the archive of WashCAS talks over the past three years. This are listed on the WashCAS web site at:

http://www.washcas.org/events.html

In addition, many of the talks have been recorded by the National Library of Medicine and are available on their web site at:

http://collab.nlm.nih.gov/webcastsandvideos/washcas/washcas.html

6 Conclusions

The Washington Area Computer Aided Surgery Society (WashCAS) has become the major vehicle for interaction among researchers in this field and related fields in the Washington-Baltimore area. This would not have been possible without the funding provided by this award. The society has held meetings every alternate month since 1999, with an average attendance of 40 people per seminar. Based on input from the participants, the organizers plan to continue in this manner, and welcome suggestions from all concerned parties as to how the society can best achieve its mission to promote the field. As of the writing of this report (February 2009) we are planning to transition WashCAS to WashSys. This new organization WashSys will focus on Systems Biology and the new advances in this field.