Ninth National Image-Guided Therapy Workshop

March 14 & 15, 2017
Bethesda, MD

ncigt.org

Workshop Chairs
Tina Kapur, PhD
Kristy Brock, PhD
Kevin Cleary, PhD
Keyvan Farahani, PhD
Steven Krosnick, MD
## Day One - Tuesday, March 14, 2017

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<td>Session Chairs: Kevin Cleary, PhD, <em>Children’s National Health System</em> &amp; Tina Kapur, PhD, <em>Brigham and Women’s Hospital and Harvard Medical School</em></td>
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<td>1:00 PM</td>
<td>Image-Guided Interventions in AMIGO</td>
<td>Clare Tempany, MD, <em>Brigham and Women’s Hospital and Harvard Medical School</em></td>
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<td>Center for Image Guided Cancer Therapy at MD Anderson</td>
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<td>Jeff Siewerdsen, PhD, <em>Johns Hopkins University</em></td>
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<td>Ergonomic Surgical Goggles for Molecular Fluorescence-Guided Cancer Resection</td>
<td>Samuel Achilefu, PhD, <em>Washington University at St. Louis</em></td>
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<td><strong>SESSION TWO: Perspectives from NCI, NIBIB</strong></td>
<td>Session Chairs: Maie St. John, MD, PhD <em>University of California, Los Angeles</em> &amp; Zion Tse, <em>University of Georgia</em></td>
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<td>Image-Guided Cancer Interventions at the National Cancer Institute</td>
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<td>Research Funding Opportunities at the National Institute of Biomedical Imaging and Bioengineering</td>
<td>Steven Krosnick, MD, <em>National Institute of Biomedical Imaging and Bioengineering</em></td>
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<td><strong>SESSION THREE: Individual Interactions with NIH Programs Staff</strong></td>
<td>Session Chairs: Maie St. John, MD, PhD <em>University of California, Los Angeles</em> &amp; Zion Tse, <em>University of Georgia</em></td>
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<td>One-on-one interactions between individual investigators and NIH Program Directors will take place in four 20 minute sessions (4:40-5:00, 5:00-5:20, 5:20-5:40, 5:40-6:00)</td>
<td>NCI Program Directors: Keyvan Farahani, PhD, Pushpa Tandon, PhD, Houston Baker, PhD NIBIB Program Directors: Steve Krosnick, MD, Randy King, PhD, Richard Baird, PhD, Todd Merchak (SBIR)</td>
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<td>8:30-9:30 AM</td>
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<td>Session Chair: Sarah Frisken, PhD, <em>Brigham and Women’s Hospital and Harvard Medical School</em></td>
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<td>8:30 AM</td>
<td><strong>Building Value in Your Startup</strong></td>
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<td>Neil Glossop, PhD, <em>Medical Device Entrepreneur</em></td>
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<td>8:50 AM</td>
<td><strong>Image-Guided Interventions as a Business: Cash Cow or Cooked Goose?</strong></td>
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<td>Greg Sorensen, MD, <em>IMRIS, Inc.</em></td>
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<td><strong>SESSION FIVE: Poster Session &amp; Coffee Break</strong></td>
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<td>10:30-11:30 AM</td>
<td><strong>SESSION SIX: Novel Techniques for Living Tissue Microscopy and Spectroscopy</strong></td>
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<td>Session Chair: Milind Rajadhyaksha, PhD, <em>Memorial Sloan Kettering Cancer Center</em></td>
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<td>10:30 AM</td>
<td><strong>Peri-operative Confocal Imaging-guided Treatment of Basal Cell Carcinomas</strong> for Mohs Surgery, Laser Ablation</td>
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<td>Milind Rajadhyaksha, PhD, <em>Memorial Sloan Kettering Cancer Center</em></td>
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<td>10:50 AM</td>
<td><strong>Multimodality Molecular Imaging of Surgical Tissue for Breast Cancer Margin Assessment</strong></td>
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<td>Nathalie Agar, PhD, <em>Brigham and Women’s Hospital and Harvard Medical School</em></td>
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<td>11:10 AM</td>
<td><strong>Stimulated Raman Scattering Microscopy Provides Rapid Intraoperative Histology for Accurate Diagnosis of Pediatric Brain Tumors</strong></td>
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<td>Todd C. Hollon, MD, <em>Department of Neurosurgery, University of Michigan Health System</em></td>
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<td>Session Chair: Jagadeesan Jayender, PhD, <em>Brigham and Women’s Hospital and Harvard Medical School</em></td>
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<td>1:00 PM</td>
<td><strong>MRI Compatible Robotics for In-bore Interventions</strong></td>
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<td><em>Kevin Cleary, PhD, Children’s National Hospital</em></td>
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<td><strong>Mixed Reality Navigation for Laparoscopic Surgery</strong></td>
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<td>*Jagadeesan Jayender, PhD, <em>Brigham and Women’s Hospital and Harvard Medical School</em></td>
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<td>Towards Precise Freehand MRI-guided Cellular Therapeutic Targeting for Amyotrophic Lateral Sclerosis</td>
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<td>Towards Cooperative Control of MRI-guided Pelvic Needle Placement Procedures</td>
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<td>Robot-Assisted Less-Invasive Treatment of Osteolysis using a Continuum Manipulator</td>
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<td>Bimanual Autonomous Anastomosis of the Vaginal Cuff using the Smart Tissue Autonomous Robot (STAR) and Near-Infrared 3D Tracking System</td>
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<td>Folate Targeted Intraoperative Imaging of Pulmonary Tumors</td>
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<td>Monitoring Cryoablation using Short TI Inversion Recovery Ultrasound Echo Time (STIR-UTE) MRI</td>
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<td>Patient-Mounted Flexible Needle Guide Template for MRI Transperineal Prostate Focal Laser Ablation</td>
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# Poster Presentations - March 15, 2017

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<td>Oliver Bruns, Thomas Bischof, Jessica Carr, Rakesh Jain and Moungi Bawendi</td>
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<td>Biomechanical Planning for Robot-Assisted Augmentation of Osteoporotic Femurs.</td>
<td>Amirhossein Farvardin, Mahsan Bakhtiarinejad, Gang Zhu, Ryan Murphy, Ehsan Basafa, Harpal Khanuja and Mehran Armand</td>
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<td>Application of 5-Axis Cranial Implant Laser Cutting System for Single-stage Cranioplasty.</td>
<td>Joshua Liu, Jerry Fang, Ryan Murphy, Chad Gordon and Mehran Armand</td>
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<td>Maintaining C-arm to Patient Registration for Orthopedic Procedures using RGBD Augmented C-arm.</td>
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<td>Ryan Murphy, Robert Grupp, Russell Taylor, Javad Parvizi and Mehran Armand</td>
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<td>Time Sequence Recording for Navigated Medical Procedures.</td>
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<td>Lesion Modeling and Visualization for Image-guided Cardiac Ablation Interventions.</td>
<td>Cristian A. Linte, David R. Holmes iii and Dieter Haemmerich</td>
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<td>Visual and Haptic Simulator for Cardiac Electrophysiology Procedures.</td>
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<td>CT/MR-Compatible Laryngoscopy System for Image-Guided Trans-oral Surgery.</td>
<td>Xiaotian Wu, Joseph Paydarfar and Ryan Halter</td>
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<td>MRI-Conditional Soft Robotic Gastrointestinal Endoscope Tip Design.</td>
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<td>Kareem Elfatairy, Christopher Filson, Omer Kucuk, Peter Rossi and Sherif Nour</td>
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<td>Three-dimensional Image Guidance of Transcranial Focused Ultrasound In Vivo.</td>
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<td>Phase I Trial of Convection Enhanced Delivery of IL-13 Pseudomonas Toxin in Diffuse Intrinsic Pontine Glioma Patients.</td>
<td>Aria Jamshidi, Prashant Chittiboina, Kathy Warren and John Heiss</td>
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<td>Everette Burdette, Goutam Ghoshal, Patrick Roady, Laurie Rund and Larry Schook</td>
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<td>Classification of Clinical Significance of Multi-parametric MRI Prostate Findings using Convolutional Neural Networks.</td>
<td>Alireza Mehrtash, Alireza Sedghi, Mohsen Ghafoorian, Clare Tempany, Parvin Mousavi, Purang Abolmaesumi and Andriy Fedorov</td>
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<td>Christian Herz, Peter Behringer, Kemal Tuncali, Clare Tempany and Andriy Fedorov</td>
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<td>Image-Based Known-Component Registration for Surgical Guidance.</td>
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<td>John Snell, Changzhu Jin and Neal Kassell</td>
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Zhuo Zhao, Sheng Xu, Bradford J. Wood and Zion Tse.


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PET-MR of 89Zr-Iron Oxide Nanoparticles for Targeted Magnetic Drug Therapy In Vivo. Caroline Jordan, Mariam Aboian, Kiel Neumann, Carol Stillson, Teri Moore, Wesley Kuo, Joshua Fisher, Youngho Seo, Henry Vanbrocklin, Mark Wilson, Alastair Martin and Steven Hetts.

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Automatic Brain Tumor Segmentation using Stochastic Multiresolution Texture Features and Random Forest. Zeina Shboul, Linmin Pei, Syed Reza and Khan Iftekharuddin.

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ABSTRACTS FOR ORAL PRESENTATIONS
Title: Stimulated Raman scattering microscopy provides rapid intraoperative histology for accurate diagnosis of pediatric brain tumors

Authors: Todd Hollon1, Mia Garrard1, Balaji Pandian1, Spencer Lewis1, Hugh L. Garton1, Cormac Maher1, Karin Muraszko1, Sandra Camelo-Piragua2, Daniel Orringer1

Affiliations: 1University of Michigan, Department of Neurosurgery; 2University of Michigan, Department of Pathology

Purpose: Accurate intraoperative histopathologic diagnosis is essential for optimal surgical management of pediatric brain tumors. Standard intraoperative histology suffers from intensive tissue preparation and processing artifact. Stimulated Raman scattering (SRS) microscopy uses the intrinsic biochemical properties of fresh surgical specimens to provide label-free histologic images, named stimulated Raman histology (SRH). We aim to evaluate the ability of SRH to reveal the histopathologic features of pediatric brain tumors for accurate intraoperative diagnosis.

Methods: Pediatric and young adult brain tumor patients (≤26 years) were prospectively enrolled over 18 months. Fresh surgical specimens were imaged intraoperatively using the first clinical fiber-laser-based SRS microscope. Reviewers evaluated SRH images for histopathologic features and diagnostic accuracy was calculated. An automated SRH image quantification system and ensemble machine learning method was developed to rapidly differentiate normal versus lesional tissue and low-grade versus high-grade pediatric brain tumors.

Results: A total of 30 patients were enrolled; histopathologic diagnoses included pilocytic astrocytoma/low-grade glioma(9), ganglioglioma(6), medulloblastoma(4), primitive neuroectodermal tumor(2), ependymoma(2), diffuse intrinsic pontine glioma(1), germinoma(1), and normal specimens(5, epilepsy surgery). SRH provided rapid (< 2.5 min) histologic images with sub-micron resolution for all specimens without tissue processing artifact. SRH was able to preserve both cytologic and histoarchitectural features within the same field of view. Diagnostic histopathologic features (e.g. pilocytic processes, small round blue cell morphology, etc.) were evaluated in 1,851 400µm x 400µm fields of view from the above listed tumor types. SRH provided diagnostic features in 32/33 (97%) fresh surgical specimens. Using high-throughput digital image processing software, SRH segmentation and feature extraction was used to develop a random forest machine learning strategy for automated image analysis. Cellularity, immune cell infiltration, and nuclear morphology parameters were able to predict normal versus lesional tissue and low-grade versus high-grade tumors with greater than 95% accuracy on out-of-bag cross-validation.

Conclusion: SRS microscopy provides rapid intraoperative histology for accurate diagnosis of common pediatric brain tumors. Our results give insight into how SRH can be used to improve the surgical care of pediatric brain tumor patients.

Funding Source(s): National Institute of Biomedical Imaging and Bioengineering (R01EB017254), University of Michigan-Michigan Translational Research and Commercialization for Life Sciences Program (U-M MTRAC), and the Michigan Institute for Clinical and Health Research (2ULITR000433)
Title: Mixed Reality Navigation for Laparoscopic Surgery

Author: Brian Xavier, Franklin King, Ahmed Hosny, David Black, Steve Pieper, Jagadeesan Jayender

Affiliation: Surgical Planning Laboratory, Radiology, Brigham and Women’s Hospital

Purpose: The role of mixed reality that combines augmented and virtual reality in the healthcare industry, specifically in modern surgical interventions, has yet to be established. In laparoscopic surgeries, precision navigation with real-time feedback of distances from sensitive structures such as the pulmonary vessels is critical to preventing complications. Combining video-assistance with newer navigational technologies to improve outcomes in a simple, cost-effective approach is a constant challenge.

Methods: This study aimed to design and validate a novel mixed reality intra-operative surgical navigation environment using a standard model of laparoscopic surgery. We modified an Oculus Rift with two front-facing cameras to receive images and data from 3D Slicer and conducted trials with a standardized Ethicon TASKit surgical skills trainer.

Results: Participants were enrolled and stratified based on surgical experience including residents, fellows, and attending surgeons. Using the TASKit box trainer, participants were asked to transfer pegs, identify radiolabeled pegs, and precisely navigate through wire structures. Tasks were repeated and incrementally aided with modalities such as 3D volumetric navigation, audio feedback, and mixed reality. A final task randomized and compared the current standard of laparoscopy with CT guidance with the proposed standard of mixed reality incorporating all additional modalities. Metrics such as success rate, task time, error rate, and user kinematics were recorded to assess learning and efficiency.

Conclusions: A mixed reality surgical environment incorporating real-time video-assistance, navigational, and radiologic data with audio feedback has been created for the purpose of better enabling laparoscopic surgical navigation with early validations demonstrating potential use cases.

Funding Sources: This project was supported by the National Center for Research Resources and the National Institute of Biomedical Imaging and Bioengineering of the National Institutes of Health through Grant Numbers P41EB015898 and P41RR019703.
Towards Precise Freehand MRI-guided Cellular Therapeutic Targeting for Amyotrophic Lateral Sclerosis
Rui Li¹, Sheng Xu², Bradford J. Wood², Drs. Peter Choyke², Baris Turkbey², John Oshinski³, Zion Tsz Ho Tse¹,⁴
¹ Engineering, University of Georgia, Athens, GA; ²National Institutes of Health, Radiology and Imaging Sciences, Center for Interventional Oncology; ³ Radiology and Imaging Sciences, Emory University, Atlanta, GA; ⁴3T Technologies, LLC

Purpose We hypothesized that cellular therapeutics could be percutaneously delivered to the ventral horn of the spinal cord for Amyotrophic Lateral Sclerosis under MRI guidance using a minimally invasive needle guidance platform which provides a simple and efficient workflow for spinal interventions without the need of active navigation and motorized equipment.

Methods The needle guidance platform is comprised of a needle holder (Fig. 1) and an MRI visible grid. The needle holder, modified from SeeStar®, AprioMed Inc., provides two degrees of freedom for remote center motion, consisting of a MRI visible base ring maker, skin entry point marker and a needle guide, all of which are 3D-printed and filled with gadolinium contrast agent. Targeting angles and skin entry points were planned in the OncoNav planning software using intraoperative MRI. The needle was adjusted freehand using a smartphone-based protractor.

Test 1: The feasibility of the platform for MRI-guided targeting was tested with a phantom which utilized an boiled egg and an coagulated target within the yolk.

Test 2: The platform was tested in a CIRS abdominal tumor phantom.

Results: The needle was guided to the predefined targets at the egg yolk in Test 1 (Fig. 2), and the tumors in the abdominal phantom (Fig. 3), with the targeting error of <5mm.

Conclusions The needle guidance platform successfully allowed for precise freehand MRI-guided needle targeting.

Figure 1 illustrates the needle holder, modified from SeeStar device to make it MRI visible, including (b) skin entry point marker, and (c) a needle guide, both of which are made MRI visible with lumen filled with gadolinium contrast agent.

Figure 2 shows the MRI images of the egg anatomy with a target tumor at the center, needle insertion in the saggital, coronal and transverse planes. (c) shows the anatomy cross section compared to (b). (f) shows the cross section of the base ring and skin entry marker in an MRI image.

Figure 3 illustrates the MRI-guided target performed on an abdominal phantom, (b) its MRI image, showing the tumor target and needle trajectory.
Towards Cooperative Control of MRI-guided Pelvic Needle Placement Procedures

Gregory S. Fischer¹,², Marek Wartenberg¹, Nirav Patel¹, Junichi Tokuda², Clare Tempany², Nobuhiko Hata²

¹Worcester Polytechnic Institute, MA, USA, ²Brigham and Women’s Hospital, MA, USA

Purpose: Often needle-based percutaneous pelvic interventions require multiple insertion attempts to reach sufficient targeting accuracy due to needle placement errors in the soft tissue. Simply following a pre-planned open-loop trajectory for needle insertion does not account for target shift during tissue deformation or unmodeled needle deflection caused by layers of biological structures with various mechanical properties. Repeated insertions lead to lengthened procedure time, increased cost, and unnecessary discomfort to the patient. In our previous work we reported live intraoperative needle tracking via interactively updated MRI with control of the scan plane geometry in real-time to maintain needle visibility. This, coupled with in-bore robotic manipulation of a bevel tipped needle, enables active compensation of the needle path in real-time. As an alternative to autonomous insertion where the physician is not directly in the loop or teleoperation which removes the physician from the procedure site, we have developed a cooperatively controlled robotic needle driver, seen in Fig. 1. This fully actuated shared control system inserts the needle of a biopsy gun under user initiated force-based admittance control based on sensors integrated into the body of the needle driver, while rotation of the needle is used to employ autonomous closed-loop control of needle steering to ensure the planned target is reached despite unmodeled deformations of the needle or tissue.

Methods: We have also previously shown a 4-DOF robotic system to assist in guiding needles for MR-guided prostate biopsy, currently in clinical trials. That system aligns a needle guide in the 2-D plane and provides the physician with the depth to insert the needle by hand. The cooperative needle driver presented herein mounts to the base of that robot in place of the current manual needle guide and is suitable for the MR environment. This driver can hold the same biopsy gun used in clinical trials and maintains an almost identical workflow because the cooperative aspect requires the physician perform the insertion directly at the procedure site. The advantage of cooperative control is the admittance based continuous insertion also collects needle force and brings movement into a robot workspace allowing for incorporation of virtual fixtures and tissue modeling. Registered intraoperative images become 3D volumes where voxels can be assigned gradient values according to mechanical properties of the tissues they represent. Using the aforementioned live needle tracking, steering can be done autonomously using closed-loop control during continuous cooperative insertion.

Results: This robotic needle driver was built completely in house, along with the custom control system seen in Fig. 2. Both are suitable for the MR environment as the robot has no ferromagnetic material and the control boxes are aluminum and well-shielded.

Conclusions: Continuous insertion and live needle tracking with active compensation can reduce targeting errors leading to fewer insertions per target. The presented cooperatively controlled needle driver is built on the base of a clinical system with intentions of this becoming the next step forward. The robot is being evaluated in the MR environment for effect on SNR images, capturing and reflecting needle forces in heterogeneous layered phantoms, as well as needle steering under continuous cooperative insertion. Using this control architecture provides an environment for integrating the robotic accuracy of teleoperation, virtual fixtures and tissue models while leaving ultimate control of the procedure to the physician.

Funding Sources: Supported by NIH R01CA111288, R01EB02 0667, and P41EB015898.
Robot-Assisted Less-Invasive Treatment of Osteolysis Using a Continuum Manipulator
Farshid Alambeigi1, Shahriar Sefati1, Ryan J. Murphy2, Paul Wilkening1, Russell H. Taylor1, Harpal Khanuja3, and Mehran Armand1,2,3

1. Laboratory for Computational Sensing and Robotics, Johns Hopkins University, Baltimore, MD, USA
2. Johns Hopkins University Applied Physics Laboratory, Laurel, MD, USA
3. Department of Orthopedic Surgery, Johns Hopkins Medical School, Baltimore, MD, USA

Purpose
We are developing a robot-assisted surgical workstation including continuum dexterous manipulators (CDM) attached to a positioning robot with accompanying tools and sensors for minimally-invasive treatment of osteolysis. The CDM is driven using an actuation unit and is positioned in the workspace by a robot such as a UR5 (Universal Robots, Inc.). To treat osteolysis (Fig.1), the CDM operates through the screw holes of a well-fixed acetabular implant. Large-deflection shape sensors track the shape of the CDM. Furthermore, we developed 2D-3D registration techniques to update the pose of the CDM with respect to the lesion using x-ray images during the surgery. We propose a cooperative control algorithm to position the CDM with the UR5 using feedback from the FBG shape sensors and x-ray images, when necessary.

Method
In this study, we formulated the concurrent control of our robotic system using an iterative constrained damped least square optimization solved for multiple constraints defined in the task and/or joint space of the robot. To ensure patient safety during the procedure, several constraints bound the movement of the system. We used FBG sensor feedback to estimate the CDM shape and control it using an adaptive Jacobian formulation.

Results
The 2D-3D registration approach showed joint angle error of 0.15±0.29 degree. The FBG sensor assembly tracked the shape of the CDM within 3.3% error. To evaluate performance of the proposed method, we generated an arbitrary 3D-path representing the boundary of an osteolytic lesion. Using the shape sensor feedback, we demonstrated concurrent control of the UR5 and CDM along the desired path with less than 1 mm error.

Conclusions
The components of the proposed framework demonstrate feasibility for real-time control of the CDM. Further research will investigate integrating system components and evaluating its overall performance in cadavers with artificial (osteolysis-like) lesions behind the well-fixed acetabular implants.

Funding Source(s) Research supported by NIH/NIBIB grant R01 EB016703.
Bimanual Autonomous Anastomosis of the Vaginal Cuff using the Smart Tissue Autonomous Robot (STAR) and Near-Infrared 3D Tracking System

J Opfermann, S Leonard, R Decker, C Bayne, A Broch, A Krieger
Sheikh Zayed Institute for Pediatric Surgical Innovation, Children’s National Health System, Washington, DC

Purpose: Vaginal cuff closure is a challenging task during laparoscopic hysterectomy. Even in robotic cases, suturing is technically demanding, as inconsistent suture placements can cause rupture, complications, and reoperation. We present a novel surgical robot and imaging system, STAR, capable of performing autonomous anastomosis of the vaginal cuff. Previously, STAR demonstrated a more consistent bowel anastomosis when compared to expert surgeons [1]. We hypothesize the integration of two surgical arms with STAR’s imaging system will enable autonomous vaginal cuff closure in an in-vivo porcine model.

Methods: STAR’s vision system consists of registered and calibrated color, NIR, and plenoptic 3D cameras (Fig 1a). This setup was evaluated previously for accuracy in dynamic surgical environments including occlusion [2]. For this task, STAR’s robotic arms were equipped with mechanized surgical tools (Fig. 1b), and programmed with collaborative, laparoscopic motion, to apply sutures (white robot), and manage suture (orange robot). The vaginal cuff was prepared by laparoscopic dissection, and suspended by transabdominal stay sutures (Fig. 1c). STAR’s vision system generated a surgical plan to suture the vaginal cuff informed by number, location, and ideal suture spacing (Fig. 1d). STAR was used to autonomously close the vaginal cuff.

Results: STAR’s vision system successfully tracked target tissue with an accuracy of 1.61 mm, degrading to 1.71 mm when occluded. STAR’s universal grasper had positional resolution of 0.001°, pitch from 0-70°, and independent 360° rotation of the distal tip. After successful integration of these two systems, STAR completed autonomous laparoscopic closure of the vaginal cuff using barbed suture and three stitches (n=1) (Fig.1e). Average stitch spacing was 2.75±0.43mm with rupture force greater than 10N. Total anastomosis time was 5.43min.

Conclusions: STAR’s vision system enables automated soft tissue surgeries by overcoming the challenge of occlusion in the surgical environment. Results from this acute study indicate STAR’s collaborative, laparoscopic approach can create consistent anastomoses with rupture force exceeding clinical requirements. While additional development and testing are necessary, this case study illustrates feasibility of autonomous robotic surgeries.

Funding Source(s):
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Figure 1: (a). Vision system showing NIR, plenoptic, and color cameras with NIR light. (b). Multilateral STAR with collaborative suturing (white), and suture management (orange) robots. (c) Laparoscopic image of staged vaginal cuff (d). STAR’s three dimensional image and suture plan (e). Excised vaginal cuff showing consistent suture spacing.

Feasibility of Real-time Adapptive Treatment Planning for MR Guided High Dose Rate Interstitial Brachytherapy

RA Cormack¹, CV Guthier¹, EJ Schmidt², AN Viswanathan³

¹Department of Radiation Oncology, Dana-Farber Cancer Institute/Brigham and Women’s Hospital, Boston MA. ²Department of Radiology, Brigham and Women’s Hospital, Boston MA ³Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins Medicine, Baltimore MD

Purpose Brachytherapy is a crucial component of radiation therapy of gynecologic cancers. For large tumors, interstitial high dose rate (HDR) brachytherapy is used to provide coverage of the tumor by ionizing radiation. Magnetic resonance guidance of needle placement provides visual evaluation of the implant. While real-time quantitative dosimetric guidance of brachytherapy is used in permanent brachytherapy implants, the practice has not been feasible in an interventional MR environment. This work presents technological advances that make real-time treatment planning feasible in a timeframe relevant to an MR guided interstitial implant.

Methods Actively tracked brachytherapy needle obturators, in addition to facilitating MR visualization of needle placement, provide a means of needle digitization concurrent with needle placement.¹ The MR tracked needle positions are measured in MR coordinates and may be directly used for brachytherapy treatment planning using the interventional MR images for definition of anatomic structures. A generalization of a new optimization algorithm² provides HDR treatment plans that respect normal tissue tolerances. An HDR needle selection algorithm has been developed that provides a population of needle configurations providing quantitative evaluation of dose distributions achievable with the current needle configuration and the potential dosimetric benefits of adding needles to the implant. The needle geometries and anatomy contours of MR guided implants of gynecologic tumors were analyzed to evaluate the clinical relevance of the optimization algorithms.

Results Twenty implants [target volume (mean 63 cc max 237 cc), needles quantity(mean 18 max 39)] were used to evaluate the utility of the algorithms. For a needle configuration, the dwell time optimizer found a plan that respected normal tissue tolerances while achieving target coverage with dose distributions judged to be comparable to clinical plans. Time for dose optimization showed a mean of 1.6 seconds. For a given contoured anatomy, and set of template holes, the needle selection algorithm can provide a menu of plans demonstrating the dosimetric outcomes achievable as a function the number of needles used in under 30 seconds. This speed makes it feasible to add these functions to an MR guided implant, which take from ~1 to 2 hours or more.

Conclusions HDR optimization and needle selection algorithms have evolved to the point where dosimetric based decision support can be provided in a time frame relevant to MR guided interstitial implants. In conjunction with real-time actively tracked MR catheter digitization, these algorithms enable in-procedure dosimetric feedback to the clinician about the quality of the achieved implant and should lead to improved dosimetric coverage for interstitial gynecologic implants. The approach may be generalized to prostate implants with real time catheter reconstruction. Dosimetric guidance will be evaluated in a clinical study and future work will generalize the algorithm to support needle selection in robot assisted implants.

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Folate Targeted Intraoperative Imaging of Pulmonary Tumors
Sunil Singhal, MD, Hospital of the University of Pennsylvania

Introduction: Each year, nearly 100,000 patients proceed to the operating room for pulmonary resection, though identification of pulmonary nodules can frequently be challenging. We hypothesize that targeted intraoperative molecular imagining can improve identification of pulmonary nodules at the time of surgery.

Methods: OTL38 is a near-infrared imaging agent that targets FRα, a receptor upregulated by 10,000-fold in 85-90% of patients with pulmonary adenocarcinoma. After extensive preclinical testing, 100 patients with a lung nodule suspicious for a pulmonary adenocarcinoma were enrolled in a clinical trial. Prior to surgery, patients were systemically administered OTL38 (0.0025mg/kg) by intravenous infusion. During surgery, tumors were imaged in situ and ex vivo. Tumor fluorescence was quantified using tumor-to-background ratio (TBR).

Results: In human patients receiving OTL38 prior to resection, we observed only 8 Grade 1 toxicities comprised of itching and rashes. We identified 90% of pulmonary nodules, and the mean tumor size was 2.5 cm (range 0.5-10.5cm). 22% of the fluorescent nodules measured less than 1cm. Mean TBR of fluorescent tumors was 3.2 (range 1.7-4.6). Tumor size did not correlate with TBR (p>0.05). In several patients, intraoperative imaging identified synchronous subcentimeter nodules which were not detected by pre-operative CAT or PET scanning. Furthermore, intraoperative imaging identified tumors that were close to the surgical margins requiring a larger resection.

Conclusion: Our clinical trial showed targeted molecular imaging with OTL38 is safe and has only minor Grade I toxicities. In addition, this study showed that the optical contrast agent is capable of detecting subcentimeter pulmonary nodules in humans. Our group is initiating a multicenter, Phase II study to better understand the implications of intraoperative molecular imaging using OTL38. To date, this is the largest clinical trial in intraoperative imaging of solid tumors in the United States.
Monitoring Cryoablation using Short TI Inversion Recovery Ultrashort Echo Time (STIR-UTE) MRI

Tokuda J1, Tuncali K1, Seethamraju RT2, Fairhurst J1, Tempany CM1, Schmidt EJ1

1Department of Radiology, Brigham and Women’s Hospital, MA, USA, 2Siemens Healthcare, Boston, MA, USA.

Introduction. Percutaneous cryoablation is a well-established tumor treatment option that avoids surgical morbidity and complications [1]. While MRI is recognized as a useful tool for monitoring the boundary of the ice ball, the signal void on conventional MRI sequences (with TE>1ms) does not differentiate between tissue temperatures below 0 °C, making it difficult to confirm tissue necrosis, as the critical temperature to induce cellular death is -10°C to -80°C [2]. To delineate the volume cooled to below the critical temperature, MRI-based temperature mapping of frozen tissue using ultrashort TE (UTE) imaging was proposed [3]. However, clinical application might not be straightforward, especially in regions with physiological motion or cryo-probe-related susceptibility artifacts, as the methods rely on multiple-echo images to obtain R2* values. In this study, we propose an alternative approach to delineate the area below the critical temperature using short TI inversion recovery (STIR) UTE and demonstrate it in the prostate and kidney using a STIR 3D PETRA sequence [4].

Methods. This approach relies on studies that showed that soft-tissue T1 is strongly dependent on temperature and Larmor frequency [5]. It was shown that T1 drops sharply below -5°C (from ~300 to ~90msec at 1.5T), reaches a minimum at -40°C, and then gradually grows at lower temperatures. If the tissue’s T1 at the critical temperature is known, the region below this critical temperature can be delineated with a STIR sequence, since regions with longer T1s will have hypointense pixel magnitude. In addition, since T2* values below 0°C are <100 μs, STIR must be combined with UTE. To accentuate the frozen-region contrast (create an “ice image”), signal from unfrozen (>0°C) tissue is saturated by using short T1s, short spoke repetition-time $T_{R_S}$, and short total repetition-time/pass $T_{R_0} = (T_1 + T_2 * N + W)$, where N is the number of radial-spokes/pass, and W is the recovery time. $(T_1/T_{R_0}/T_{R}/TE1/=80/400/1.6/0.07ms; N=40, 15000 spokes, matrix =128x128x128, pixel size 3.4375x3.4375x3.4375mm³, FOV=330mm³, TA=90 sec/vol). The method was applied to patients undergoing MRI-guided prostate and kidney cryoablations in a 3T MRI (Verio 3T, Siemens). Prostate cryoablation was performed using two 17G probes (Ice Seeds, Galil Medical Inc) with two 11-minute freezing / 5-minute thawing cycles, whereas the kidney cryoablation was performed using three 17G probes (Ice Rods, Galil Medical Inc) with 17-minute freeze, 10-minute thawing, and 14.5-minute freezing. In both cases, STIR UTE images were acquired at the end of each freezing cycle.

Results. Figures 1, 2 show T2-weighted (T2-w) TSE and STIR UTE images at the corresponding slices. Entirely within the T2-w designated signal voids (<0°C), the STIR UTE images show rings with ~20% hyper-intensity, surrounding central lower-intensity regions.

Discussion. STIR UTE provided positive contrast in the frozen tissue, and potentially provides an alternative approach to MR-based cryoablation monitoring. However, we could not clearly delineate the area below the critical temperature (-40°C) with STIR UTE, because PETRA did not allow setting TI below 80 ms, although the central lower-intensity regions may correspond to regions at very low temperatures.

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Patient-Mounted Flexible Needle Guide Template for MRI Transperineal Prostate Focal Laser Ablation

Rui Li\textsuperscript{1}, Sheng Xu\textsuperscript{2}, Bradford J. Wood\textsuperscript{2}, Peter Pinto\textsuperscript{2}, Peter Choyke\textsuperscript{2}, Baris Turkbey\textsuperscript{2}, Zion Tsz Ho Tse\textsuperscript{1,3}
\textsuperscript{1}The University of Georgia, College of Engineering, Athens, GA; \textsuperscript{2}National Institutes of Health, Bethesda, MD; \textsuperscript{3}3T Technologies, LLC

Purpose
We hypothesized that a 3D-printed flexible needle guide template, mounted on the patient’s perineum as a MRI visible grid, could assist visualization and targeting during the workflow for MRI-guided focal laser ablation (FLA) procedure. This abstract focuses on a preliminary evaluation of the design.

Methods (Fig.1)
Flexible patient-mounted MRI visible grid was 3D-printed and filled with gadolinium contrast agent for MRI visualization (a-b). A needle guide was designed to provide selectable insertion trajectories of 0, 15, 30 and 45 degrees relative to the head-foot direction. The needle guide was then placed on the corresponding MRI grid position according to the OncoNav planning software (c-d).

Test 1: Tangerine targeting (Fig.2)
Test 2: Prostate phantom targeting (Fig.3)
OncoNav was used to determine the needle trajectory, skin entry point, and the insertion depth performed manually.

Results
Test 1 (Fig.2): A tangerine was placed in the MRI with the grid attached. A virtual tumor was predefined as a target (a-b). MRI images were acquired to visualize the insertion trajectory.
Test 2 (Fig.3): The needle successfully targeted 4 out of all 4 tumors (error of <4.5mm).

Conclusion
A patient-mounted flexible template which consists an MRI grid and a needle guide was developed to assist MRI-guided prostate FLA procedures.
Visualizing Surgical Margins During Robot-Assisted Procedures with Multi-Electrode Endoscopic Devices

Ryan Halter1,2, Aditya Mahara1, Ethan Murphy1, Shadab Khan4, Elias Hyams2,3, Jason Pettus2,3
1Thayer School of Engineering (Dartmouth College), 2Geisel School of Medicine (Dartmouth College),
3Dartmouth-Hitchcock Medical Center, 4Boston Children’s Hospital/Harvard Medical School

Purpose Positive surgical margins (PSMs) following cancer resection surgery result in an increased incidence of cancer recurrence. Intraoperative frozen section (IFS) analysis is the primary approach used to evaluate margin status during surgery. Unfortunately, this approach typically takes more than 20 minutes to perform, requires the surgeon to mentally register the histological findings with the intraoperative scene, and in robot-assisted procedures, such as radical prostatectomy, would require the robot to be de-docked to extract the tissue for analysis. An endoscopic device outfitted with sensors capable of classifying tissue pathology in real-time would enable a streamlined approach to intraoperative surgical margin assessment and help to reduce the incidence of post-surgical cancer recurrence.

Methods A flexible endoscopic probe with a 10 mm diameter multi-electrode sensor head was designed for introduction through a 12 mm auxiliary port during robot-assisted radical prostatectomy (RALP). The probe is capable of sensing the electrical properties of the tissue bed following prostate resection. Multiple electrode combinations are used to sense the electrical properties in different regions under the probe head. Electrical properties were recorded from the peri-prostatic tissue bed in 11 men undergoing a RALP. Multiple strategies for visualizing and interpreting the data were implemented including electrical impedance tomography (EIT), electrical impedance mapping, and SVM-based tissue classification. These strategies were implemented for real-time intraoperative deployment and were validated on ex vivo benign and malignant prostate.

Results While no positive surgical margins were found in this initial cohort of patients, the electrical property sensing endoscopic device was successfully deployed in 11 RALP procedures. The additional time required to probe the bladder neck and pelvic floor around the urethral stump was < 5 minutes. EIT provides the best resolution (<1mm), but requires the longest time to provide feedback to the surgeon (~24 seconds per probed site). The SVM-based approach provides a low-resolution, single point classification, but has a classification accuracy of 81% (based on ex vivo tissue studies) and can be computed in < 1 second once the model has been trained.

Conclusions Surgical margin assessment during robot-assisted procedures is possible using endoscopic probes outfitted with multiple sensors. One such embodiment of this type of probe includes the use of a dense electrode array designed to gauge the electrical properties of tissue. These devices can be used to produce an image of the electrical properties of the sensed tissue or to classify the entire region probed as being benign or having some foci of cancer. Since a surgeon is typically limited to resecting additional tissue specimens >5mm in length, a simple machine learning based classification may be sufficient for these endoscopic devices.

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ABSTRACTS FOR POSTER PRESENTATIONS
**Next-generation in vivo optical imaging with short-wave infrared quantum dots**

Oliver T. Bruns\(^1\), Thomas Bischof\(^1\), Jessica Carr\(^1\), Rakesh K. Jain\(^2\) and Mouni G. Bawendi\(^1\)

\(^1\)Department of Chemistry, MIT, 77 Massachusetts Ave., Cambridge, MA 02139 (USA)
\(^2\)Steele Lab, MGH and Harvard Medical School, 100 Blossom St., Boston, MA 02114 (USA)

**Purpose:** The short-wavelength infrared region (SWIR; 1000—2000 nm) provides several advantages over the visible and near-infrared regions for in vivo imaging. The general lack of autofluorescence, low light absorption by blood and tissue, and reduced scattering can render a mouse translucent when imaged in the SWIR region. Despite these advantages, the lack of a versatile and functional emitter platform has prevented its general adoption by the biomedical research community.

**Methods:** Here we introduce a class of high-quality SWIR-emissive indium arsenide-based quantum dots (QDs) for the next generation of in vivo SWIR imaging.

**Results:** Our QDs exhibit a dramatically higher emission quantum yield (QY) than previously described SWIR probes, and are readily modifiable for various functional imaging applications. In addition, narrow and size-tunable emission allows for multicolor imaging in the SWIR region. To demonstrate the capabilities of this SWIR quantum dot imaging platform, we quantify the metabolic turnover rates of lipoproteins in several organs simultaneously in real time, measure the heartbeat and breathing rates in awake and unrestrained mice, and generate detailed three-dimensional quantitative flow maps of brain vasculature by intravital microscopy.

**Conclusions:** In conclusion we show that the improved optical properties and functional coatings of SWIR QDs enable multiple biological imaging applications with an unprecedented combination of deep penetration, high spatial resolution, and fast acquisition speed.

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**Reference:** Bruns et al. *Next-generation in vivo optical imaging with short-wave infrared quantum dots* Nature Biomedical Engineering accepted
Biomechanical Planning for Robot-Assisted Augmentation of Osteoporotic Femurs
Amirhossein Farvardin¹, Mahsan Bakhtiarinejad¹, Gang Zhu¹, Ryan Murphy¹,², Ehsan Basafa¹, Simon Mears³, Harpal Khanuja³, and Mehran Armand¹,²,³
¹ Department of Mechanical Engineering, Johns Hopkins University, MD, USA
² Johns Hopkins University Applied Physics Laboratory, MD, USA
³ Department of Orthopaedic Surgery, Johns Hopkins University, MD, USA

Purpose Laboratory experiments have shown that the femoral bone augmentation with PMMA bone cement can be an effective alternative interventional approach in patients with severe osteoporosis. However, because of complexities of cement diffusion inside the cancellous bone, it is essential to conduct detailed surgical planning, execution, and monitoring to avoid complications such as thermal necrosis due to leakage of the PMMA. The femoral bone augmentation is still in pre-clinical stages partly due to absence of the technique that delivers the appropriate amount of augmentation material precisely to the planned location.

Methods An image-guidance system for femoral bone augmentation surgery that implements a novel concept of intraoperative feedback was designed and tested on three cadaver experiments. The system consists of surgical planning using hydrodynamics-based bone cement diffusion model, surgical navigation involving 2D/3D registration of preoperative CT scans to the augmented hip bone, real-time tracking, a handheld motorized bone cement delivery device, and an intraoperative monitoring system of the cement shape from X-ray images (Fig. 1). Current system advancements include automated positioning of the drill and injection system using a six degree of freedom robotic arm (UR10, Universal Robots Inc.) (Fig. 1).

Results The proposed system was implemented as an integrated workstation for surgical planning and navigation. Through cadaver experiments with manual bone drilling, it was determined that an average of 9.5 mL of bone cement is sufficient to increase the yield load of the specimen by 52%.

Conclusions Successful integration of cement flow modeling, X-ray imaging and robotically-controlled cement injection was achieved to enable us to conduct minimally-invasive femoral bone augmentation surgery. Three cadaver studies had shown that the developed system offer significant advantages in surgery. Our future research will focus on streamlining the surgical protocol and advancing to clinical trials.

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Application of 5-Axis Cranial Implant Laser Cutting System for Single-stage Cranioplasty

Joshua Liu¹, Jerry Fang¹, Alex Mathews¹, Ryan J. Murphy², Chad Gordon³, Mehran Armand¹,²
¹Laboratory for Computational Sensing and Robotics, Johns Hopkins University, MD, USA
²Johns Hopkins University Applied Physics Laboratory, MD, USA
³Department of Plastic and Reconstructive Surgery, Johns Hopkins University, MD, USA

Purpose: Cranioplasty is a procedure for skull reconstruction after removal of lesions such as tumors. Recent approaches involve the use of customized cranial implants (CCIs) created from a CT scan of the patient skull. A challenge in performing cranioplasty with the CCI is that the actual implant size/shape is unknown until the tumor is removed. We propose a robotic laser cutting system that has the capability of modifying CCI profiles during the single-stage cranioplasty. The goal is to achieve higher quality fit of the implant for both plain and complex craniofacial deformities.

Methods: The procedure flow is shown in Fig. 1. A 3D infrared structure sensor, manufactured by Occipital, is utilized to scan the defect region. Post data processing is applied on the scanned image to achieve accurate identification of the defect wall. The cutting path is computed from the defect contour, registered to the CCI, and converted into G-code to be used by the laser cutting system. The custom-built laser system features five-axis laser cutting capability that enables three-dimensional modification. Components include a Cartesian linear stage for 3 Degrees-Of-Freedom (DOF) linear motion and a rotary table for 2 DOF rotary motions. Linux CNC – open source software that controls CNC machining – reads the G-code and instructs the laser system to move accordingly.

Results: The average registration error between the skull surface-model constructed with the structure camera to the model constructed from the CT of the skull was 0.4 mm. The contour and edge of the defect wall were generated from the defect region. The implant profiles were modified by the laser cutting system and the results was compared against conventional manual approach. The maximum overlay distance for the two approaches were 1.47 mm and 2.0 mm, respectively. The maximum gap distance was 1.05 mm and 3.89 mm respectively.

Conclusion: Preliminary results indicate a superior fit with only mm size gaps between the implant and the remaining skull. Further controlled experiments are required to isolate the sources of error for improving the system performance.

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Maintaining C-arm to patient registration for orthopedic procedures using RGBD augmented C-arm

Javad Fotouhi1, Bernhard Fuerst1, Alex Johnson2, Russell Taylor1, Greg Osgood2, Nassir Navab1,4, Mehran Armand1,2,3

1 Johns Hopkins University, Baltimore, MD, USA
2 Johns Hopkins Hospital, Department of Orthopedic Surgery, Baltimore, MD, USA
3 Johns Hopkins University Applied Physics Laboratory, Laurel, MD, USA
4 Technical University of Munich, Munich, Germany

Purpose: In many orthopedic and trauma interventions pre-operative CT scans are available, but the translation to the surgical scenario using 2D/3D registration is difficult. We propose an opto/X-ray system which enables fast and automatic re-initialization of the registration after the C-arm is moved. This approach allows the surgeon or medical staff to frequently reposition the C-arm and maintain an approximation of the 2D/3D relationship prior to acquiring X-ray images.

Methods: The spatial relation between the C-arm and the pre-interventional data is estimated using the optical data acquired from an RGBD camera mounted near the detector plane of the C-arm. We use a pre-calibrated C-arm view (estimated by a pre-interventional 2D/3D registration with manual interaction) to establish the basic relationship of the patient CT and the C-arm. Thereafter, the relative poses of the C-arm at different arrangements are estimated using RGBD Simultaneous Localization and Mapping (SLAM) system, and transferred to the C-arm coordinate frame based on the pre-calibration of the RGBD and C-arm imaging devices. We use this tracking to re-initialize the intensity-based 2D/3D registration at different C-arm poses.

Results: To evaluate the vision-based tracking system and the registration outcome in a realistic surgical conditions, dry pelvic-femur phantom is encased in gelatin and partially covered with drapes. A target registration error of 11.83 mm is measured using several landmarks attached to the bone after re-initialization. The re-initialization outcome is then used as input to an intensity-based 2D/3D registration. This yielded 75% success rate for the registration, where a registration attempt is considered successful only if the target registration error after re-initialization is lower than 2.5 mm. Registration with random initialization yielded only 23% success rate. Fig.1 demonstrates the spatial relation of pre- and intra-interventional data at different stages.

Conclusions: Re-initialization using RGBD SLAM provides a reliable initialization within the capture range of the 2D/3D intensity-based registration. This allows to maintain the registration of pre- and intra-interventional data throughout the orthopedic procedure with no manual interaction. Therefore, the workflow remains intact.

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Figure 1. Overlay of digitally reconstructed radiographs and C-arm X-ray images are shown after (a) random initialization, (b) re-initialization using RGBD SLAM, and (c) registration using the re-initialization.
Intraoperative 3D Fragment Tracking of Periacetabular Osteotomy using Single-Plane X-ray Images

Ryan J. Murphy¹, Robert Grupp², Russell H. Taylor², Javad Parvizi⁴, Mehran Armand¹,³
¹ Johns Hopkins University Applied Physics Laboratory, Laurel, MD
² Department of Computer Science, Johns Hopkins University, Baltimore, MD
³ Department of Mechanical Engineering, Johns Hopkins University, Baltimore, MD
⁴ Orthopaedic Surgery, Rothman Institute of Thomas Jefferson University, Philadelphia, PA

Purpose
Periacetabular osteotomy (PAO) is a joint-preserving surgical procedure used to treat developmental dysplasia of the hip by reorienting the hip joint. Conventional surgery relies on x-ray images for feedback, thereby limiting relevant information to a single 2D plane. Optical navigation systems have been used to provide 3D information, but rely on an external tracker and reference. We developed a preliminary system capable of quantitative 3D tracking of the osteotomized fragment using only x-ray images. We investigate two different approaches for tracking the osteotomized fragment: with and without fiducials attached to the patient.

Methods
We developed two approaches to estimate the fragment repositioning: 1) a fiducial-based approach and 2) a fiducial-less approach (Fig. 1). In the fiducial-based approach, we attach a set of four reference fiducials (metallic BBs) to the fragment intraoperatively. The locations of these BBs are not known a priori. Intraoperatively, the fiducials are identified on a set of x-ray images pre- and post-osteotomy; from each set of images, we estimate the 3D position of the BBs. Using the estimated positions, we compute the rigid transformation of fragment motion. In the fiducial-less approach, we register a partially known fragment to a set of post-osteotomy images. This approach assumes some a priori knowledge about the acetabular fragment to within 1 cm of each cut plane. We tested the fiducial-based approach on a cadaveric specimen and the fiducial-less approach through simulation.

Results
The cadaveric study showed the fiducial-based approach recovered the fragment transformation within 2.2 degrees and 3.2 mm. In simulation, the fiducial-less approach achieved a mean rotational error of 2.3 (± 2.3) degrees and translational error of 0.8 (± 0.5) mm in the anterior pelvic plane. The mean registration time was 7.1 (± 1.0) seconds.

Conclusions
Both the fiducial-based and fiducial-less approach to fragment tracking are viable alternatives to optical navigation. Integrating these techniques into our surgical system may offer surgeons a more intuitive and effective way for performing PAO. Further studies are required to understand the advantages and disadvantages of the presented approaches.

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Time sequence recording for navigated medical procedures
Andras Lasso¹, Tamas Ungi¹, Longquan Chen², Junichi Tokuda², Gabor Fichtinger¹
¹Laboratory for Percutaneous Surgery, Queen’s University, Kingston, ON, Canada
²Surgical Planning Laboratory, Brigham and Women’s Hospital, Boston, MA, USA

Purpose Medical interventions often use real time data acquisition and visualization methods for navigating needles or surgical tools. Time sequence data recording has been implemented in some navigation applications for some tools, but a generally usable method for recording time series was missing. We implemented a general-purpose recording solution in a widely used open-source medical imaging software platform, 3D Slicer. We tested the software in ultrasound-guided needle interventions training, and in a teaching course for surgical navigation.

Methods We implemented the Sequences extension for the 3D Slicer (www.slicer.org) application that is freely available from the 3D Slicer Extension Manager. The Sequence Browser module of this extension allows any data node to be registered with a sequence for both saving and for reloading data as it changes in time. The implementation allows recording of not only tracking or medical imaging data, but all data that changes in time. With the time browser not only the position and image data can be reviewed, but also the display settings and visualization options, like virtual camera orientation synchronized in time.

Results We have successfully tested the Sequences extension in two applications. Trainee skill evaluation was computed from recordings of simulated ultrasound-guided needle insertions, and trainees could review the procedure from multiple angles for faster learning. The second application is an online teaching course (www.SlicerIGT.org) on how to implement surgical navigation systems (Figure 1).

Conclusions The Sequences extension can record and replay all data changes in time, which allows offline procedure analysis, performance evaluation, and serves as a teaching tool.

Figure 1. Skull CT registration tutorial for neurosurgical navigation using Sequences and SlicerIGT extensions. A: Sequence browser toolbar allows to replay the recorded experiment and pause it at any time. B: Video image shows the picture corresponding to the current time point. C: Tracked objects and models are shown in the 3D viewer synchronously.

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Lesion Modeling and Visualization for Image-guided Cardiac Ablation Interventions

Cristian A. Linte\textsuperscript{1}, David R. Holmes III\textsuperscript{2} and Dieter Haemmerich\textsuperscript{3}

\textsuperscript{1}Biomedical Engineering & Imaging Science, Rochester Institute of Technology, Rochester NY
\textsuperscript{2}Biomedical Imaging Resource, Mayo Clinic, Rochester MN
\textsuperscript{3}College of Medicine, Medical University of South Carolina, Charleston, SC

\textbf{Purpose:} Image-guided cardiac ablation therapy has evolved as the preferred treatment strategy for cardiac arrhythmias. However, treatment success for atrial fibrillation (AF) still experiences a high recurrence rate, with 20–40\% of patients requiring repeat procedures. The high rate of recurrence has been attributed primarily to the delivery of sub-optimal lesions as a result of current image-guided ablation systems lacking intra-operative monitoring capabilities during therapy delivery. While some crude lesion representations are available in the form of colored glyphs indicative of the catheter location, they provide no meaningful (Fig. 1) information on the geometry or quality of the lesions.

\textbf{Methods:} We model the tissue response to RF energy during ablation via a coupled resistive-conductive heat transfer process. The model was implemented on a two-compartment computational domain consisting of tissue and blood extracted from cardiac CT or MRI images. The model uses the image voxels as computational elements and computed tissue temperature estimates in response to the ablation parameters, exposure, electrode-tissue contact and tissue properties. The model-predicted ablation lesion comprises all voxels exposed to 55°C for 5 s or as irreversibly injured tissue (Fig. 2).

\textbf{Results:} Our model accurately predicted the end-ablation temperature at 1 and 3 mm from the ablation catheter. In addition, we also investigated the lesion geometry (i.e., volume) in response to the electrode-tissue contact assessed according to the electrode penetration depth (Fig. 3).

\textbf{Conclusions:} This work builds the foundation to provide, for the first time, real-time visualizations of the ablation lesions that quantify the extent of induced tissue injury. These visualization paradigms that enable the characterization of the ablation lesion geometry and quality and its visualization in real time will help clinicians better plan, guide, and optimize ablation therapy, enabling higher treatment efficacy.

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\textbf{Fig. 1:} Left atrial EAM showing the ablated sites as strings of white markers that render no quantitative lesion quality information (left); VisiTag navigation showing the EAM and ablated sites displayed as colored markers dependent on the user-defined contact force and ablation time.

\textbf{Fig. 2:} Illustration of model-predicted lesion and induced tissue injury. Note the irreversible core lesion (yellow) surrounded by the reversible lesion penumbra (white).

\textbf{Fig. 3:} End-ablation tissue temperature at 1 and 3 mm from electrode tip. Preliminary study showing model-predicted lesion dimensions vs.
Ultrasound-Triggered Release from Red Blood Cells for Image-Guided Drug Delivery.
Johnny L. Chen\(^3\), Adam J. Dixon\(^3\), Justin M. Farry\(^3\), Ali H. Dhanaliwala\(^3\), Zhongmin Du\(^3\), John A. Hossack\(^3\), Alexander L Klibanov\(^1\)\(^2\)
\(^1\)Cardiovascular Division, Department of Medicine, \(^2\)Cardiovascular Research Center, \(^3\)Department of Biomedical Engineering, University of Virginia, Charlottesville VA 22908

**Purpose.** Targeted drug delivery aims to create a design that would maximize accumulation and retention of a selected functional drug in the area of disease (e.g., in the tumor node) yet minimizing systemic toxicity. Red Blood Cells (RBCs), operating as drug carriers, provide excellent drug loading capacity and circulation time; however, unmodified RBCs cannot release the drug locally as a result of external stimuli. We have prepared acoustically active RBCs (aaRBCs) by attaching them to perfluorocarbon nanodroplets, so that a focused ultrasound pulse breaks the RBC membrane and thereby selectively releases the entrapped content.

**Methods.** Nanodroplets were prepared by sonication of perfluoropropane or perfluorobutane in aqueous saline, followed by repeated Nuclepore filtration under pressure. Nanoparticles were stabilized with a monolayer of DSPC, PEG stearate and distearoyl trimethylammonium propane, with Dil red fluorescence dye for shell labeling if desired. Purified murine or human RBCs were repeatedly washed with PBS and incubated with nanodroplets; electrostatic interaction was used for binding of positively charged nanodroplets with negatively charged RBCs. Nanodroplets that were not attached to RBCs were removed by differential centrifugation. Targeting was achieved by co-incubating the RBCs with cyclic RGD-PEG3400-DSPC micelles, so that the lipid anchor was embedded in RBC plasma membrane. For dye or magnetic nanoparticle entrapment, hypo-osmotic loading was applied, followed by isotonic rescaling with glucose-containing buffer to maintain RBC stability.

Ultrasound-triggered release was tested by subjecting aaRBCs to a single 10 MHz pulse (10 cycles, 11 MPa peak negative acoustic pressure). Video microscopy was applied to monitor dye release in response to ultrasound treatment in real time. Photoacoustic imaging of ICG dye-loaded aaRBCs was performed in a channel phantom with a Verasonics Vantage triggered from a tunable (710 - 850 nm) pulsed (20 Hz, 5 ns) laser (2 mJ/cm\(^2\) fluence), in a nontargeted control study, or following the application of a neodymium magnet. Radiolabeling of aaRBCs was performed by Cr-51; after centrifugal wash, labeled aaRBCs were administered intravenously in C57BL/6 mice; blood samples were taken repeatedly until 2 h time point, when the animals were euthanized. Organ biodistribution pattern was established using a gamma counter.

Testing of peptide-RBC targeting was performed via a solid phase binding assay, on a layer of recombinant \(\alpha_V\beta_3\) or control albumin-only polystyrene dish.

**Results.** Entrapped calcein dye released from stored aaRBC very slowly (under 10% per day); ICG was also reliably encapsulated. Doxorubicin load reached 0.2 pg per particle. Under video microscopy, we observed rapid calcein loss from aaRBC upon ultrasound triggering: liquid perfluorocarbon nanodroplet phase converts to gas microbubble; rapid compression and expansion of the microbubble in the ultrasound field results in aaRBC rupture and release of contents. Fluorescence spectroscopy quantification indicated that ~50% of entrapped dye was released upon insonification. Radiolabeled aaRBCs demonstrated excellent circulation time and minimal uptake by non-target organs (~90% in the bloodstream 2 hours after i.v. administration). 60-fold target-to-control specificity ratio was demonstrated in a solid-phase RBC binding assay on a \(\alpha_V\beta_3\) layer. Magnetic targeting of nanoparticle-loaded aaRBCs was also observed.

**Conclusions.** Acoustically active RBCs prepared by conjugation of perfluorocarbon nanodroplets to RBCs become triggered delivery/release systems. These particles remain in the bloodstream and can effectively entrap fluorescent dyes, as well as doxorubicin, and retain entrapped material for many hours. Upon a short pulse of focused ultrasound, entrapped material is rapidly released from aaRBCs.

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Visual and Haptic Simulator for Cardiac Electrophysiology Procedures
Brian Boland¹, Kent Ronald Nilsson², Sheng Xu³, Bradford J. Wood⁴, Zion Tse Ho Tse¹
¹Engineering, The University of Georgia, Athens, GA, USA, ²Athens Regional Medical Center, University of Georgia & Georgia Regents University Medical Partnership, GA, USA, ³National Institutes of Health, Radiology and Imaging Sciences, Center for Interventional Oncology

Purpose: Radiofrequency ablation (RFA) of cardiovascular structures to treat arrhythmia is an electrophysiology (EP) procedure requiring the operator to manipulate ablation catheters to specific arrhythmic sources identified in the electroanatomical map [1]. Integrating imaging and catheter tracking [2] allows physicians to guide catheters to the desired location and assess the efficacy of the RFA treatment [3] by maintaining consistent catheter-tissue contact force, which is critical for successful ablation procedures. Currently, difficulties in navigating the catheter based on imaging are common due to visual-motor disorientation. Thus, a low-cost haptic system is proposed, involving a procedural simulation device which integrates force and 3D MRI-cardiovascular visualization models for catheter operation training.

Methods: A cardiovascular structure model, reconstructed from STL files of cardiac MR images (NIH 3D Print Exchange), was imported into a 3D environment (Fig. 1). A modified 3D Touch Stylus haptic platform was used to graphically display the position and geometry of the catheter tip as an overlay on the cardiovascular structure. The catheter’s motion was tracked in seven degrees of freedom for RFA procedures with targets located at the left pulmonary arteries (Fig. 3). The user encounters resistive force indicating that the catheter is making contact with cardiovascular tissue [4]. The simulation system includes a foot pedal which is used to control RFA duration.

Results: For this study, we compare performance indices for RFA procedures both with and without the haptic feedback assistance. Based on preliminary analysis, the haptic feedback from the device is useful in aiding movement accuracy even in small environments.

Conclusions: The presented simulator could be a cost-effective haptic visual platform for EP RFA training. The proposed system is designed for simulating RFA procedures, although the simulator could be easily modified to provide simulation training for biopsies, brachytherapy, and other types of ablation including cryo-, microwave, and laser ablation. Further software development is critical in providing more intuitive options for the training simulator, and further research is currently ongoing.

Funding Sources: This study was supported in part by the National Institutes of Health (NIH) Bench-to-Bedside Award, the NIH Center for Interventional Oncology Grant, the National Science Foundation (NSF) I-Corps Team Grant (1617340), NSF REU site program 1359095, the UGA-AU Inter-Institutional Seed Funding, the American Society for Quality Dr. Richard J. Schlesinger Grant, the PHS Grant UL1TR000454 from the Clinical and Translational Science Award Program, and the NIH National Center for Advancing Translational Sciences.
CT/MR-Compatible Laryngoscopy System for Image-Guided Trans-oral Surgery
Xiaotian Wu¹, Joseph A. Paydarfar²,³, and Ryan J. Halter¹,²
¹Thayer School of Engineering (Dartmouth College), ²Geisel School of Medicine (Dartmouth College), ³Dartmouth-Hitchcock Medical Center

Purpose
The trans-oral approach to head and neck cancer resections have decreased surgical morbidity due to its minimally invasive nature. However, assessing the extent of the tumor and locating key anatomical structures beneath the visible mucosal surface remain challenging. Surgical navigation could potentially be of benefit; the placement of necessary surgical retractors and laryngoscopes deforms the tumor and critical anatomy which limits the utility of preoperative imaging. Intraoperative imaging is hindered by metal artifacts caused by instrumentation. To get a good visualization of the intra-operative anatomical state, we designed a CT/MR-compatible laryngoscopy system, allowing for intra-operative imaging. This will open up the possibility for intra-operative image-guidance for trans-oral procedures. Furthermore, the system enables us to study the typical deformations that occur due to instrumentation during laryngoscopy in order to generate a predictive model of tissue deformation in the future.

Methods
A custom polymer laryngoscope was designed and 3D-printed based on a standard Lindholm metal operating laryngoscope. A complementary non-metal suspension system was built to secure the laryngoscope for suspension laryngoscopy. Eight patients scheduled to undergo diagnostic laryngoscopy were recruited to this study. A preoperative CT scan with contrast was obtained with patient in repose prior to any instrumentation and an intraoperative CT scan with contrast was obtained after the placement of the laryngoscopy system. Deformation and displacements of key anatomical structures (mandible, hyoid, and tongue) were quantified.

Results
No intra- or post-operative complications were noted during this study. Intraoperative CT scans with our system showed clear improvement in image quality as compared to those acquired with the traditional metal laryngoscope. Key anatomical structures were visualized successfully (Fig. 1). Mean center displacements for the mandible and hyoid were 12.2mm (±3.8mm) and 13.7mm (±2.6mm) respectively. Mean tongue surface fiducial displacement for each patient was 25.7mm (±4.6mm).

Conclusions
Our MR/CT-compatible laryngoscopy system allowed for intraoperative imaging to visualize and quantify anatomical deformations due to instrumentation. The data obtained from this work can serve as validation for biomechanical models and registration algorithms. 3D-printing of laryngoscopes has tremendous benefits in image guidance for trans-oral surgeries and opens up possibilities of patient-specific designs to improve surgical instrumentation.

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MRI-Conditional Soft Robotic Gastrointestinal Endoscope Tip Design
Rudy Montayre¹, Austin Taylor¹, Kent Ronald Nilsson², Zion Tsz Ho Tse¹

¹College of Engineering, The University of Georgia; ²Athens Regional Medical Center, Athens, GA

Purpose: Soft robotics is a new and unique system for designing and creating a new generation of medical devices [1]. Soft robotic 3D printed endoscope tips can be controlled and driven using only tubing and air pressure. We are attempting to create a new kind of gastrointestinal endoscope tip made from flexible resin material. We hypothesized that gastrointestinal endoscope tips could be fabricated from MRI-conditional soft robotic actuators with high dexterity due to the flexibility of the material, allowing a high degree of maneuverability.

Methods: Using SolidWorks, we designed an actuator that manipulates bending in one direction to best quantify bending. The actuator was printed using Formlabs Flexible Resin (FLFLGR02) with the Form 2 printer at 0.1 mm. An endoscope was designed, combining three actuators and a central lumen for insertion of a camera/catheter (Fig 1). The flexible resin is meant to simulate 80A rubber, which has shown true to the actuator’s flexibility, rigidity, and ability to maintain its original shape after undergoing several dozen inflations. The flexible resin is relatively inexpensive in comparison to the price of the several parts of metallic endoscopes. The material cost for each 3D printed endoscope is less than $10.

Results: The end of the endoscope tip bends farther from the flat side as the added air pressure increases (Fig 2). As pressure is increased from 5 - 20 psi, the bending data follows a steady curve (Fig 3). This relationship between the bending and air pressure demonstrates the controllability of the 3D printed tip bending by varying air pressure. The 3-actuator endoscope tip is flexible and can bend in any direction by controlling the pressure input in multiple inlets.

Conclusions: The soft robotic gastrointestinal endoscope tip is inexpensive, non-magnetic, can be 3D-printed, and its bending is manipulated by changes in air pressure. This design can be scaled to fit various MRI-compatible medical devices.


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**MRI Negative Areas May Harbor Clinically Significant Prostate Cancer: Utility of Direct MRI-Guided Biopsy**

Authors: Kareem K. Elfatairy, Christopher P. Filson, Omer Kucuk, Peter J Rossi, Viraj A Master, Sherif G. Nour

*School of Medicine-Emory University*

**Purpose:**

Multiparametric prostate MRI has been shown to have a high negative predictive value for clinically significant cancers in studies using standard TRUS or MRI/US fusion biopsies. With the current tendency for a complete shift of paradigm towards a targeted-only biopsy approach, we sought to investigate the outcomes of added random biopsies from MRI negative (MRI -ve) areas in the setting of direct in-bore MRI guided biopsies (MRGB).

**Methods**

27 patients with 43 sampled MRI -ve areas were included. MRI -ve areas defined as those having PI-RADS (V2) category 1 or 2 lesions with no definite focal targets.

All patients had mpMRI with our institutional protocol (T2, DWI and DCE) and transrectal in-bore MRGB using 3T magnet. Areas with no definite focal targets were selected on random basis. Clinically significant cancers (CSC) were defined as those with Gleason score (GS) ≥7 ‘Pathology Grade Group 2 or higher’. The pathology results were referenced to MRGB. Results were evaluated for 1) spectrum of pathological outcomes; 2) presence of cancer, its grade and volume; and 3) NPV for all prostate cancers as well as for CSC. Descriptive statistical analysis was done using SPSS (version 23, IBM) for Microsoft Windows.

**Results**

22 patients (81.5%) were diagnosed with prostate cancer either with MRI visible targets (MRI-Tr) alone (13/22), TRUS biopsy (TRUS-Bx) alone (4/22), both MRI-Tr and TRUS-Bx (4/22) and MRGB of MRI -ve areas only (1/22). MRI -ve areas showed higher grade than MRI-Tr in one patient (MRI-Tr =4+3=7 vs MRI -ve areas =4+4=8) (4.5%) and diagnosed cancer not detected through biopsied MRI-Tr in one patient (3+3=6). Out of 43 biopsied MRI -ve areas, there were 7/43 (16%) malignant lesions (false negative mpMRI). NPV of mpMRI for all cancers was 84%, and for CSC was 90.7%. Most of MRI -ve areas with malignant pathology results had CSC (4/7, 57%) (Figure 1). In cases that had MRI-Tr, most of MRI -ve areas having cancers were contralateral to those MRI-Tr (3/5, 60%). The median cancer core % length was 40 % (range 5-90%). After retrospective assessment of images of cases with CSC from MRI -ve areas, the samples from two cases (GS 4+3 =7 and 4+4 =8) appeared to have been contaminated from nearby high grade lesions.

**Discussion and Conclusion:**

MRI -ve areas on 3T prostate mpMRI demonstrated a high negative predictive value for CSC. With existing imaging capabilities, an extended biopsy approach including sampling of areas without visible MRI abnormalities may still need to be considered prior to prostate cancer management decisions, particularly those involving focal therapy or nerve sparing surgery.

**Funding source:** None
Purpose: Transcranial focused ultrasound (tFUS) is being investigated for a range of applications for the treatment of brain disorders, including epilepsy and stroke. Both thermal and nonthermal bioeffects of tFUS have been exploited, but the closed-loop spatiotemporal control of tFUS-tissue interactions is the key to the reliable application of tFUS in applications such as neuromodulation. Real-time transcranial imaging of tFUS effects at the target brain tissue with sufficient spatial and temporal resolution will be necessary to achieve this goal. We have developed a dual-mode ultrasound array (DMUA) system for the image-guided monitoring and control of tFUS beams in vivo small-animal model. Three-dimensional DMUA imaging is used for guiding the tFUS application based on identifying the bregma and lambda suture lines. The purpose of this study is to establish the feasibility of precise spatiotemporal control of tFUS application at subtherapeutic levels in the small-animal model.

Methods: Sprague Dawley rats (275 – 300 g) were anesthetized fixed to a stereotaxic stage in a prone position in accordance with IACUC approved protocol. A 3.5-MHz DMUA prototype was used to image and generate subtherapeutic tFUS beams at selected locations with respect to the bregma and median suture lines based on brain atlas. Previous studies have demonstrated that the size of the tFUS focal spot was 300 X 500 X 2000 um³. We have also demonstrated the use of DMUA imaging for evaluating temperature changes at frame rates up to 500 frames per second during the application of tFUS. Ultrasound thermography data were used as feedback to control the tFUS-induced temperature rise at the target to a specified set point. Real-time display of the spatiotemporal temperature maps were generated to provide immediate visual feedback of temperature rise at the target and the intervening tissues, including the skull.

Results: The figure below gives an example result showing the 3D guidance imaging with the suture lines clearly visible on the C-mode DMUA image of the skull. The bregma suture line (at 12 mm) was used as a reference for multiple tFUS applications (bregma - 2mm, -4mm and -6mm). The figure to the right shows an example of closed-loop control of tFUS-induced temperature at 4° set point (calibrated based on ex vivo measurements with reference thermocouple). The heated region is shown to be highly localized at the target location with an axial extent of less than 2mm. The line profile demonstrates the stability of the control in the presence of pulsation and gasping due to the high frame rate of data collection.

Conclusions: DMUA 3D image guidance, together with ultrasound thermography, proved very useful in demonstrating spatiotemporal control of tFUS in vivo.

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Title: Phase I Trial of Convection Enhanced Delivery of IL-13 Pseudomonas Toxin in Diffuse Intrinsic Pontine Glioma Patients

Authors: Jamshidi, A, Chittiboina, P, Warren, K, Heiss, J

Affiliation: Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, Bethesda, Maryland

Purpose: Pre-clinical and clinical studies of IL13 Pseudomonas exotoxin demonstrated anti-tumor activity and a favorable risk-benefit profile as an anti-tumor agent for high-grade gliomas. In this phase I clinical trial report, we analyze the imaging findings and discuss the safety and efficacy of IL13-PE38QQR administration via intratumoral CED (convection enhanced delivery) in pediatric patients with DIPG

Methods: Five consecutive patients who had failed standard treatment for recurrent or progressive DIPG were enrolled. The anti-tumor agent, IL13-PE38QQR was co-infused with a surrogate marker of its distribution, Gd-DTPA. This was a Phase I single institution, open label, dose escalation, safety and tolerability study of IL13-PE38QQR infused via CED into pediatric patients with DIPG. IL13-PE38QQR was administered to regions of tumor confirmed by radiographic findings. Escalating dose levels were evaluated: cohort 1 = 0.125 micrograms/ml, cohort 2 = 0.25 micrograms/ml. Real-time MRI was performed during infusions, and imaging results were analyzed.

Results: Five patients (3 males, 2 females; mean age at initial infusion 13.0 ± 4.7 years; range 5–17 years) underwent 7 intratumoral infusions into DIPGs. Brainstem infusions were clearly identified on T1- weighted MR images at 1-mM (1 infusion) and 5-mM (6 infusions) coinfused Gd-DTPA concentrations. While the volume of distribution (Vd) increased progressively with volume of infusion (Vi) (mean volume 2.63 ± 0.8 ml; range 1.1–3.7 ml), final Vd:Vi ratios were significantly reduced with lower Gd-DTPA concentration (Vd:Vi for 1 mM of 1.6 compared with a mean Vd:Vi ratio for 5 mM of 2.6 ± 1.3) (p = .11). A total of 5 serious adverse events occurred: elevated creatine kinase levels (2), renal calculi (1), somnolence (1), suspected aspiration/hospitalization (1). Only one serious adverse event was definitely attributed to the study procedure. All serious adverse events resolved. In total, there were 54 non-significant adverse events. The infusions at the doses administered were associated with mild and usually temporary exacerbation of tumor-related dysfunction of brainstem cranial nerves and swallowing. The majority of adverse events were grade 1 (54%) or 2 (43%), with 14 of these 38 events remaining unresolved four weeks after treatment.

Conclusions: While clinically relevant Vds can be achieved by convective delivery, specific tissue properties can affect distribution volume and pattern, including Gd-DTPA concentration, preferential flow patterns, and infusion rate. Understanding of these properties of CED can enhance its clinical application. Direct brainstem infusion of IL-13PE in our patients with DIPG did not arrest disease progression. All five patients had evidence of interval disease progression by three months post-operatively. No patient had radiographic or clinical evidence of acute or long-term toxicity. The failure of the agent to have a positive effect on performance status, overall survival or progression of disease is likely multifactorial. We were unable to effectively infuse the entire volume of the tumor bed with the exotoxin. A more reliable way to cover the entire mass with infusate would involve a multi-catheter approach, targeting the anterior-posterior and medial-lateral borders of the tumor. Further, intra-tumoral delivery may have been more effective if an agent were used that could trigger a cascade of anti-tumor responses resulting in immune-activation and bystander effects on the surrounding mass.
Title
Image-guided catheter-based ultrasound thermal ablation of tumors in genetically engineered oncogenic pigs

Author(s)
E. Clif Burdette¹, Goutam Ghoshal¹, Patrick Roady², Laurie Rund², Larry Schook²

Affiliation(s)
Acoustic MedSystems, Inc.¹, University of Illinois, Urbana-Champaign²

Purpose
Induce tumor growth in genetically engineered oncogenic pigs and assess the treatment efficacy of 3D spatially-registered image-guided needle based ultrasound thermal therapy.

Methods
A transgenic ‘oncopig’ line encoding a Cre recombinase inducible transgene encoding KRAS<sup>G12D</sup> and TP53<sup>R17H</sup>, a commonly mutated oncogene and tumor suppressor, respectively, in human cancers was created. Treatment of cells derived from these oncopigs with adenoviral vector encoding Cre (AdCre) led to KRAS<sup>G12D</sup> and TP53<sup>R17H</sup> expression, which rendered the cells transformed in culture and tumorigenic when engrafted into immunocompromised mice. Finally, injection of AdCre directly into these oncopigs led to the rapid and reproducible development of soft tissue sarcomas in the muscle. Ultrasound imaging was used to monitor the growth of these tumors. Once the tumor reached approximately 2cm by 3cm, it was treated with catheter based therapeutic ultrasound energy for thermal therapy. Sectored tubular transducers were used to precisely deliver thermal energy to the treatment region. Ultrasound image guidance combined with 3D EM tracking were used to place the applicator in the target region.

Results
The tumors were successfully grown in the muscle within two weeks of injecting the AdCre virus into the oncopigs. Skin incision less than 1cm length was sufficient to provide for insertion of catheter under image-guided ultrasound for ablating the muscle tumors. The tumors were treated for 6-9 minutes at 7 Watts acoustic power. Thermocouples inserted into the tumors showed temperature range of 55-65°C during the treatment. Histopathology analysis showed complete ablation of the tumor using single applicator configuration.

Conclusion
The results suggest catheter-based therapeutic ultrasound can be used to perform fast volumetric ablation of the tumors. The tracked ultrasound image guidance is important to guide and precisely place the catheter at the target region.

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The Impact of Deviations between Accumulated and Planned Dose in Luminal NTCP models

Molly McCulloch, M.S., 1,3,7 Daniel G Muenz, M.S., 2 Matthew J. Schipper, Ph.D., 2,3 Michael Velec, Ph.D., 4,6 Laura A. Dawson, M.D., 4,5,6 Kristy K. Brock, Ph.D. 7

1Department of Nuclear Engineering and Radiological Sciences, 2Department of Biostatistics, and 3Department of Radiation Oncology, Univ. of Michigan, Ann Arbor, MI; 4Radiation Medicine Program, Princess Margaret Hospital, University Health Network, Toronto, ON, Canada; 5Department of Radiation Oncology and the 6Institute of Medical Science, Univ. of Toronto, ON, Canada; 7Department of Imaging Physics, The University of Texas MD Anderson Cancer Center

Purpose – To analyze the potential impact of differences between planned and accumulated dose on normal tissue complication probability (NTCP) models, for the development of the model from patient data and for use of the models for patient specific assessment.

Methods – Thirty patients, 15 with metastatic cancer and 15 with primary cancer (and underlying liver cirrhosis), who were previously treated with 6 fraction SBRT for liver disease and underwent dose accumulation were assessed retrospectively. For the stomach and duodenum of each patient, a Lyman-Kutcher-Burman (LKB) NTCP model was built with (α/β) = 2.5 and n = 0.09. The linear quadratic equivalent dose at 2Gy per fraction (LQED2) and generalized equivalent uniform dose (gEUD) were calculated for both the planned and accumulated dose. An NTCP was calculated from the gEUD for each organ, each patient, and each scenario (planned and accumulated). New NTCP models were also estimated based on this data for stomach, stomach and cirrhosis, and duodenum for both planned and accumulated doses. Stomach models were developed for the cirrhosis and non-cirrhosis cohorts to reflect the differences in the TD50 values.

Results – 58.3% of patients have accumulated dose that deviates more than 5% from the planned dose, and 66.6% of patients had deviations greater than 5% between NTCP based on accumulated dose and NTCP based on planned dose. The percent change in NTCP per percent change in dose is greater for duodenum than for stomach, and there is not a significant difference for this metric between patients who had cirrhosis versus patients who did not for either organ. As doses increases, the gradient deviates more from the mean planned dose over accumulated dose. NTCP based on accumulated dose deviates greatly from NTCP based on planned dose for duodenum (errors in the probability of toxicity of up to 22%), but only slightly for stomach (errors in the probability of toxicity of up to 6%). NTCP models for duodenal toxicity showed attenuation in the fitted curves using planned dose, meaning that the models fit to planned dose can overestimate toxicity risk for low doses, but underestimate toxicity risk for high doses.

Conclusion – If deviations between planned and accumulated dose are not taken into account, errors of up to 22% in the probability of toxicity can occur. Building NTCP models based on accumulated dose impacts both the derived probability as well as the model itself. With the advances in technology used for image guided cancer therapy, there exists the potential to rebuild NTCP models to more accurately predict toxicity to patients, where accumulated dose can be considered in the models that undergo liver cancer radiation treatment, as well as other cancers that lead to luminal GI toxicity.
Tracking the arcuate fasciculus for neurosurgical planning through regions of peritumoral edema using a free water model in two-tensor unscented Kalman filter tractography

Shun Gong¹,², Fan Zhang¹, Isaiah Norton¹, Walid I. Essayed¹, Prashin Unadkat¹, Laura Rigolo¹, Yogesh Rathi¹, Lijun Hou², Alexandra J. Golby¹, Lauren J. O'Donnell¹
¹Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA
²Department of Neurosurgery, Shanghai Institute of Neurosurgery, Shanghai Changzheng Hospital, 415 Fengyang Road, Shanghai 200003, China

Purpose The usage of diffusion imaging tractography for neurosurgical planning is increasing, with the aim of enhancing neurological function recovery and precisely removing lesions in brain tumor patients. However, peritumoral edema poses a challenge that limits fiber tracking. The purpose of this study is to investigate a free water model of edema in the two-tensor unscented Kalman filter tractography (UKFt) algorithm to track the arcuate fasciculus (AF) in brain tumor patients with peritumoral edema.

Methods We retrospectively evaluated 26 consecutive brain tumor patients who had undergone diffusion MRI and T2-weighted images acquired presurgically at Brigham and Women's Hospital. To evaluate the presence of edema, we segmented edematous brain regions using T2-weighted images. Then fiber tractography was performed using UKFt with and without a free water model. An automated white matter fiber tract identification approach was applied to delineate the AF. Results from tractography with and without the free water model were compared quantitatively according to the volume of the voxels occupied by the AF. Paired t-tests were then used to compare the AF volumes between the two tractography results.

Results 17 of 26 patients had peritumoral edema, resulting in a total of 19 of 28 tumor hemispheres that contained edema (2 patients had tumors in both hemispheres). We focused on the AFs located in the tumor hemispheres. The AF volume in the tumor hemispheres of patients with edema was significantly larger using the free water model (p<0.0001), while it was not significantly larger in patients without edema (p=0.1471). The result from one patient is shown in Fig. 1.

Conclusions In general, the free water model can provide the ability to trace a larger volume of AF in UKFt in the setting of peritumoral edema in brain tumor patients. This initial study demonstrates that biophysical models of edema have potential to increase the sensitivity of tractography in regions of peritumoral edema.

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Classification of Clinical Significance of Multi-parametric MRI Prostate Findings Using Convolutional Neural Networks

Alireza Mehrtash¹,², Alireza Sedghi³, Mohsen Ghafoorian¹,², Clare M. Tempany¹, Parvin Mousavi³, Purang Abolmaesumi¹, Andriy Fedorov¹

¹Brigham and Women’s Hospital, ²University of British Columbia, ³Queen’s University, ⁴Radboud University

Purpose In 2016, prostate cancer was the most common type of cancer in men and was the second leading cause of cancer mortality among men. Multi-parametric magnetic resonance imaging (mpMRI) is being used widely to detect and characterize the prostate cancer. In this work, we present a fully automated CAD system for classification of the prostate lesions based on pathology results. The method was developed as part of the SPIE-AAPM-NCI Prostate-X challenge (https://spie.org/conferences-and-exhibitions/medical-imaging/prostatex-challenge).

Methods We used 5-fold cross-validation on 201 subjects for training and tuning of our convolutional neural network (CNN) based model. 3-dimensional patches of size of 40×40×40 mm centered at findings served as inputs to CNN. Data augmentation was necessary to create more training examples and balance the data. As illustrated in Figure 1, the training data was imbalanced in terms of positive and negative samples and the location of the finding. Data augmentation was used to create training/validation dataset with 10,000 training and 2,000 validation examples. Our CNN architecture included multiple streams of 3d convolutional layers with different types of inputs. The T2 structural streams used (12, 64, 64) inputs consisting of 12 convolutional layers with combinations of (1, 3, 3) and (3, 3, 3) filter sizes. DCE-MRI and DWI modalities with input sizes of (12, 32, 32) had 9 convolutional layers with the same combinations of filter sizes as the T2 stream. Max-pooling layers of size 1x2x2 were applied in selected middle layers. At the end of each stream we flattened the output of the last layer of convolutional layer and connected it to a fully connected dense layer with a single output. The neurons of this layer were concatenated with the zonal information of the finding and then applied to another three fully connected layers. For training the network, we used the stochastic gradient descent algorithm with the Adam update rule, mini-batch size of 64 and a binary cross-entropy loss function. Leaky rectified linear unit (Leaky-RELU) function was used as the nonlinearity element. We initialized the CNN weights randomly from a Gaussian distribution using the He method. To limit overfitting, we used the batch normalization, drop-out and L2 regularization. Cross-validation was used on different combinations of input channels and number of filters for convolutional layers.

Results Network was tested using 206 findings from 140 patients. ADC, maximum b-value and Ktrans images in combination with zonal information of the lesion resulted in the best accuracies on the training data. For test data prediction, we ensemble the prediction of the best 4 out of the 5 models. The result reported in the Prostate-X challenge (AUC=0.80) was the average probability of clinical significance computed on each of the top four selected models. This result is comparable with experienced human reader AUC values which are 0.79 and 0.83 for PI-RADS v1 and PI-RADS v2 respectively [1]. Funding Sources: NIH Grant No. P41EB015898.

**SliceTracker: An open source 3D Slicer extension for supporting transperineal in-bore MRI-guided targeted prostate biopsy**

Christian Herz, Peter Behringer, Kemal Tuncali, Clare Tempany, Andriy Fedorov
Brigham and Women's Hospital (BWH), Harvard Medical School (HMS), Harvard University, Boston, Massachusetts, United States of America

**Purpose** Prostate Cancer (PCa) is one of the most common causes of cancer deaths in the USA. Transperineal MRI-guided targeted prostate biopsy (tpMRgBx) has a high rate of detecting significant PCa and is well tolerated among patients and clinicians (1, 2). tpMRgBx includes the following steps: biopsy planning, correlation with the patient’s coordinate system, targeting, segmentation, deformable registration and evaluation. Until recently, tpMRgBx procedure, as implemented at our institution, relied on custom, closed source software tools developed over a decade ago. Our goal was to develop a free open source extension for the 3D Slicer platform to support tpMRgBx continuing earlier work in (3), and perform its comparison with the previously used approach.

**Methods** Two approaches were compared retrospectively by analyzing timestamps on the data collected during the past procedures (n=20 for each approach), and measuring the time from receiving the initial intra-procedural image to the time when re-identified targets become available to the operator.

**Results** SliceTracker combines all of the steps of tpMRgBx into one single workflow. Automation of the segmentation and registration tools were improved, and overall the workflow was simplified for improving user experience, reducing possibility of error, and streamlining the process of training for the new operators of the tool. The extension is available in the currently maintained 3D Slicer version 4.7, and is accompanied by a test dataset for training, and a detailed user manual. SliceTracker has been used to support tpMRgBx procedures since September 2016 in the total of 50 procedures to date. The time to provide target locations to the operator was significantly lower for SliceTracker (p<0.01) as compared to the previous implementation: median time was reduced from 6.6 min (range 4.6-32.7 min) to 3.6 min (range 1.4-17.7 min) (see Fig.1).

**Conclusions** The results show an improvement regarding the availability of the re-identified target(s) in nearly half the time as compared to the original implementation. SliceTracker successfully replaced the old approach in our center. The source code and manual are available at https://github.com/SlicerProstate/SliceTracker.

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ROS-IGTL-Bridge: An Open Network Interface for Medical Robotics Research

Tobias F¹, Krieger A², Leonard S³, Patel NA⁴, Tokuda J⁵

¹Gottfried Wilhelm Leibniz Universität Hannover, Hannover, Germany, ²Children’s National Health System, Northwest, Washington, DC, ³Johns Hopkins University, Baltimore, MD, ⁴Worcester Polytechnic Institute, Worcester, MA, ⁵Bingham and Women’s Hospital and Harvard Medical School, Boston, MA

Introduction. With the growing interest in advanced robotics in medicine, such as autonomous assistance [1], medical robotics research is becoming dependent on a broader range of technologies beyond robotics, such as medical imaging. Given the range of technologies used, and the fact that clinical translation of robotic systems often requires numerous iterations of prototyping and testing, effective use of existing engineering resources is becoming essential. While open software platforms, such as Robot Operating System (ROS) [2] in robotics and 3D Slicer [3] in medical imaging, have been successful in facilitating resource sharing within their research field, there is no single platform that can support the range of technologies beyond the field. We propose a new open network bridge interface that integrates two platforms, namely the ROS and 3D Slicer, to address this emerging engineering demand.

Methods. A ROS node named “ROS-IGTL-Bridge” was implemented (Fig. 1). It establishes a TCP/IP network connection between the ROS environment and 3D Slicer using the OpenIGTLInk protocol [4]. The node exports ROS messages to the external software over the network and vice versa simultaneously, allowing seamless data sharing between the ROS-based devices and the medical image computing software based on 3D Slicer. It supports data types essential for surgical planning, navigation, and robot control, including transforms, images, videos, point clouds, and 3D surface model. To test the feasibility of the proposed software, we evaluated the performance of network communication between ROS and 3D Slicer using a mock image-guided surgical robot system.

Results. Performance tests demonstrated that the bridge could stream transforms, strings, points, and images at 30 fps in both directions successfully. The data transfer latency was less than 1.2 ms for transforms, strings, and points, and 25.2 ms for color VGA images. A separate test also demonstrated that the bridge could achieve 900 fps for transforms. Additionally, the bridge was demonstrated in two representative systems: a mock image-guided surgical robot setup consisting of 3D Slicer, and Lego Mindstorms with ROS as a prototyping and educational platform for IGT research (Fig 2); and the smart tissue autonomous robot (STAR) surgical setup [1] with 3D Slicer (Fig. 3). Thanks to the ROS-IGT-Bridge, these robotic systems benefit from the rich image computing and visualization features offered by 3D Slicer.

Discussion. The study demonstrated that the bridge enabled cross-platform resource sharing between ROS and 3D Slicer. The setup will allow rapid and seamless integration of advanced image-based planning/navigation.

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Fig. 1. A representative architecture of robotic systems based on ROS and 3D Slicer integrated by the proposed ROS-IGTL-Bridge.

Fig. 2. A robotic arm built with Lego Mindstorms is following a trajectory on the 2D phantom (a) that was previously planned in 3D Slicer (b) after a successful image-to-patient registration.

Fig. 3. Picture of porcine bowel staged for anastomosis (left), current STAR suture plan (middle), and suture plan using 3D Slicer enabling 3D adjustments (right).
Image-Based Known-Component Registration for Surgical Guidance

A Uneri,¹ J Goerres,¹ T De Silva,¹ MW Jacobson,¹ MD Ketcha,¹ G Kleinszig,² S Vogt,² J-P Wolinsky,³ and JH Siewerdsen¹,³

¹Department of Biomedical Engineering, Johns Hopkins University, Baltimore, MD USA
²Siemens Healthcare XP Division, Erlangen, Germany
³Department of Neurological Surgery, Johns Hopkins Medicine, Baltimore, MD USA

Purpose: Intraoperative imaging provides direct up-to-date visualization, which allows the surgeon to track instruments and implants in relation to changing anatomy. In spinal and pelvic procedures, for example, fluoroscopic imaging is used in guiding K-wires and assessing screw placement for providing fixation. Recognizing the value of accurate guidance within the context of complex 3D anatomical structures, this work aims to provide high-precision navigation, using the 2D images already acquired within the standard workflow, and a 3D-2D image registration method that exploits prior knowledge of the patient and known components such as surgical instruments.

Methods: The proposed method—known-component registration (KC-Reg)—is a cascaded approach, in which: i) the anatomy is localized within the imaging system using patient-specific preoperative CT, amounting to a fully automatic “tracker registration” that uses anatomical features as “registration fiducials”; and ii) the components are localized relative to the anatomy using instrument shape models, thus achieving “tool tracking” without the need for externally affixed markers. Experiments emulating lumbar spine and pelvic fixation procedures were performed, wherein different shape models representing rigid (screw), composite (screw with polyaxial cap), and deformable (K-wire) instruments were used to solve for component pose and shape parameters. Multiple components were simultaneously registered, where complications due to overlaps in projection views were mitigated by adding 3D collision constraints to the optimization. Geometric accuracy, sensitivity to dependencies (e.g., number of views, dose), and factors relating to workflow were evaluated in phantoms, cadaver specimens, and more recently in preclinical studies.

Results: Using radiographs that would be acquired within a standard surgical procedure, KC-Reg could guide the bending K-wires (used to make pilot holes) with a target registration error (TRE) of 1.5±0.9 mm at the tip and 0.6±0.2° deviation in approach. Following placement of 10 pedicle screws, components were simultaneously solved for, yielding TRE 1.1±0.1 mm and 0.7±0.4°. Finally, registering screws in clinical data yielded TRE 2.7±2.6 mm and 1.5±0.8°, where higher errors may be attributed to lack of exact component specifications from vendor and approximation of projective geometry due to lack of an encoded C-arm.

Conclusions: KC-Reg offers to extend the means for high-precision surgery to a broader scope of surgeries in which conventional surgical tracking techniques have not seen wide adoption. The approach integrates naturally to the existing surgical workflow, and does not require preoperative placement of extrinsic fiducials, manual patient registration, or calibration of instruments. In addition to instrument navigation, it allows intraoperative assessment of the final implanted construct.

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A Visualization Platform for Transcranial Focused Ultrasound Patient Screening, Planning and Case Review

John W Snell, PhD1, Jin Changzhu, MS1,2, Neal F. Kassell, MD1

1Focused Ultrasound Foundation, Charlottesville, VA
2Jeju National University, Korea

Purpose

Transcranial focused ultrasound procedures involve complex and unintuitive interaction between transducer geometry, skull characteristics and acoustic physics. An interactive visualization system can enhance understanding and workflow efficiency by making these interactions visible and manipulable in real time.

Methods

A platform portable software application has been developed in Java and OpenGL which models the geometry of the transcranial transducer and the relative position and orientation of the brain and skull from patient MR and CT datasets. Transducer element beam paths are computed incorporating detection of skull surfaces, refractions and phase correction for a specifiable intracranial target. This geometric simulation can be used to produce a three dimensional map of the treatment envelope in terms of the number of elements with incident angle below the critical angle. Additionally the beam paths can be used to interactively compute the skull density ration (SDR) and other skull characteristics which are currently used for patient selection. A fast, qualitative preview of the pressure field around the focus can be interactively visualized using the simulated beam paths and an idealized beam profile function. Treatment exports of clinical cases can be loaded into the system for interactive case review including MR thermometry.

Results

The visualization tool has been successfully used to communicate the basic concepts and challenges of transcranial focused ultrasound to lay people as well as to assist with pre-surgical visualization and planning in a few clinical cases. SDR calculations have be validated against a small set of cadaver skulls and a larger validation with clinical cases is pending. The tool may play a valuable role in patient selection once validated.

Conclusions

Visual computing provides valuable insight for better understanding, planning and evaluation of transcranial focused ultrasound procedures. It is also intended to use the software as a visual front end to various full wave acoustic simulation packages. The Foundation plans to make the software available to the community as open source.

Funding Source

Focused Ultrasound Foundation, Charlottesville, VA
Cortical Parcellation Prediction of Neurosurgical Patients with Brain Tumors from Diffusion MR Images using a Data-driven Cortical Atlas Generation Method

Fan Zhang1, Pegah Kahali1, Yannick Suter1, Isaiah Norton1, Laura Rigolo1, Peter Savadjiev1, Yang Song2, Yogesh Rathi1, Weidong Cai2, William M. Wells III1, Alexandra J. Golby1, Lauren J. O'Donnell1

1Brigham and Women's Hospital, Harvard Medical School, Boston MA, USA
2School of Information Technologies, University of Sydney, Sydney NSW, Australia

Purpose: Identification of critical brain anatomy is crucial for maximizing neurosurgical tumor resection. Our goal is to investigate novel brain cortical models that may generalize to brain tumor patients to aid in neurosurgical planning, a task that currently requires expert image processing and interpretation. Computational cortical parcellation has been conducted using sulcal/gyral landmark approaches, but such methods cannot generally be applied to data of neurosurgical patients with brain tumors. In this work, we present a method to segment cortical regions using brain connectivity via white matter.

Methods: The method begins with learning a cortical atlas from a healthy population of 10 subjects from the Human Connectome Project (https://db.humanconnectome.org). A group-wise fiber tractography registration and clustering is conducted to learn common white matter connectivity across multiple healthy subjects. We then apply spectral embedding to generate a novel atlas that represents a common cortical surface model associated with connectivity and cortical parcellation information from the healthy population. Application of the atlas to patient data is performed for cortical parcellation prediction.

Results: We tested the method using a diffusion MRI, structural MRI, and fMRI dataset from 5 neurosurgical patients with brain tumors. We compared the predicted cortical parcels to the functional ground truth from subject-specific functional MRI activation areas. The result from one patient is shown in Fig. 1. In general, we obtained good prediction results, with 10 of 13 activations overlapping an anatomically corresponding prediction.

Conclusions: In this study, we have demonstrated an automated group-wise white matter connectivity-based pipeline for cortical parcellation prediction in brain tumor patient data. These preliminary results show the potential of joint modeling of multimodal data (such as structural connections, surfaces of brain regions, image data, and/or functional activations) to improve understanding of critical, individualized brain functional anatomy.

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Real-Time, Tracked, Mobile Augmented Reality Display for Surgical Navigation: Usability Study on Simulated Patients
Zachary Baum, Tamas Ungi, Andras Lasso, Gabor Fichtinger
Laboratory for Percutaneous Surgery, Queen’s University, Kingston, Canada

Purpose Navigation using medical image guidance is applied in clinical practice for various needle interventions. Commonly, images are acquired throughout the needle insertion process to track progression of the needle path. This process may lead to patient discomfort from procedure length, and the possibility of multiple needle insertions. Augmented reality (AR) image overlay systems have been proposed to limit the number of images required, the number of failed insertions, and patient discomfort. Though not translated to clinical settings due to a lack of portability and robustness, overlaying a single image slice on a patient makes it simpler for clinicians to navigate to targets and insert needles correctly. We present a lightweight, robust, system for intraoperative AR guidance.

Methods Our AR image overlay system can be handheld or mounted to a table at the patient bedside to allow operators to navigate scanned patient images. We built software on the open-source 3D Slicer and PLUS platforms and used optical tracking to acquire real-time position of the image overlay system. The system provides operators with an augmented intraoperative view by overlaying preoperative images directly onto patients (Figure 1). Physicians were asked to navigate patient images using this system, and plan needle insertions using the overlay (Figure 2).

Results Five physicians responded to a series of questions to assess handheld and table-mounted forms of the image overlay system by rating them on a Likert scale. Responses showed that the participants felt it was simple to learn how to use the system, and that it was simple to understand where the projected image was located on the patient. Participants also indicated that there was an increase in how demanding the handheld version of the system was to use over the table mounted version. Additionally, participants felt they could position themselves more comfortably and navigate images more easily using the table-mounted system.

Conclusions Participants identified the image overlay system as being simple to use and understand. Results show promise for use in clinical interventions. Further assessment of the image overlay system in a real-world clinical setting represents next steps in our research.

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Mapping lung ventilation trough stress maps derived from biomechanical models

G. Cazoulat¹, M. Matuszak¹, S. Jolly¹, D. Owen¹, J. Balter¹, K. Brock²
¹ Department of Radiation Oncology, University of Michigan
² The University of Texas MD Anderson Cancer Center

**Purpose:** A promising way of improving the outcomes of lung cancer radiotherapy is to minimize the irradiation of highly functioning parts of the lungs by incorporating ventilation imaging into the dose optimization process. The standard ventilation imaging used in this context is the single-photon emission tomography for ventilation (SPECT-V). However, its reliability is still not well evaluated and its use represents additional cost and time in a treatment protocol. CT-ventilation imaging, a recent modality in which a map of the ventilation function is calculated from the standard planning 4DCT, may be a viable alternative. Existing CT-ventilation image analysis methods are based on deformable image registration (DIR) between temporal phases of the 4DCT, followed by the measure of local volume changes (Jacobian determinant of the displacement field) or by the measure of fraction of air changes (in Hounsfield Units (HU)). As a new metric for CT-ventilation imaging, we propose in this study to generate stress maps in the lungs with Morfeus, a biomechanical model-based registration method.

**Methods:** Six patients who had lung cancer radiotherapy were retrospectively analyzed. Each patient had a planning 4DCT and SPECT-V scans. For each pair of inhale and exhale images in the 4DCT, Morfeus automatically: (i) modelled the lungs and body into tetrahedral meshes; (ii) determined boundary conditions on the chest wall and vessel tree; (iii) assigned to each tetrahedral element a Young’s modulus between 1 and 20kPa as a function of the Hounsfield Units in the CT image; (iv) computed the displacements and maximum principal stress for each element; and (v) resampled the stress values on the grid of the CT to obtain a map of the ventilation function. The Spearman correlation coefficient between the stress maps and the reference SPECT-V was computed.

**Results:** The mean±SD (min-max) Spearman correlation coefficient between the calculated stress maps and the SPECT-V was r=0.58±0.13 (0.35-0.73). This correlation was found significantly higher (p < 0.001) than with previously published metrics, respectively the Jacobian (r = 0.40±0.13 (0.17-0.56)) or the change in HU (r=0.37±0.17 (0.24-0.62)).

**Conclusions:** The proposed biomechanical model of the lungs generates stress maps which present a good correlation with SPECT-V. Those stress maps thus appear to be a promising surrogate to SPECT or previously proposed CT-ventilation metrics for incorporation into advanced treatment planning strategies.

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Mixed Reality for Dose Monitoring
Molly Flexman, Ashish Panse, Ayman Alalao, Christopher Martel, Atul Gupta
Philips Research North America, Philips ImCS R&D, Philips Image Guided Therapy

Purpose
The hybrid operating room (OR) and the catheterization lab (cath lab) make use of interventional x-ray which is an imaging modality that uses ionizing radiation. It has been shown that staff awareness of personal radiation dose can lead to workflow changes, potentially reducing radiation dose to both the patient and the staff. Currently, real-time information about dose to the staff is communicated via a screen that cannot always be seen by everyone in the room and may not be noticed by the x-ray operator. A method to use mixed reality with head mounted displays to present real-time dose information to the staff, is described here.

Methods
Products such as DoseAware (Philips, Best, NL) and RaySafe (Fluke Biomedical, Everett, WA) provide real-time x-ray dose monitoring. They consist of wearable real-time dosimeter badges that wirelessly connect to a display showing the instantaneous and cumulative dose for each person wearing a badge. The display is not always visible to all staff during a procedure, a problem that is addressed by some users by mounting additional displays in multiple places throughout the procedure room. Figure 1(a) shows a real time dosimeter badge with the dose information display. Unique markers were affixed to the dosimeter badge for each user. These markers were detected by the Microsoft HoloLens using marker detection library Vuforia by PTC, to determine the location of the user. A holographic sphere was placed at an offset position \((x,y,z) = (50, 50, 50)\) cm with respect to the detected marker position for proper overlay next to the staff wearing the badge. The sphere modulates size to holographically depict upon the staff member their unique real-time dose, larger the size, more the dose, and progressively changes color according to a predefined color map that corresponds to the cumulative dose to the patient. Figure 1(b) shows an image taken from the Hololens showing the orange holographic sphere next to a user wearing a dosimeter badge enhanced with a marker.

Results and Conclusion
It is shown that mixed reality is a very promising platform to present information to the user in a non-obstructing manner without having the user look away from the important tasks at hand. The addition of mixed reality is expected to further enhance the staff’s ability to alter behavior to reduce their radiation exposure beyond the 35% reduction shown by the existing product. (Ref: http://radfys.gu.se/digitalAssets/1335/1335207_examensarbete-tm.pdf). As mixed reality headset technology improves, it will allow enhanced integration of information into the procedure room. Mixed reality can alleviate the burden currently placed on 2D displays that are already overloading staff with information and also remove additional room displays restoring valuable real-estate back to the OR and cath lab.
Electromagnetically Tracked Needle Clip: An Enabling Design to Turn Generic Needles into Precise Image-guided Therapy Tools
Zhuo Zhao¹, Sheng Xu², Bradford J. Wood², Zion Tsz Ho Tse¹,³
¹Engineering, The University of Georgia, Athens, GA; ²National Institutes of Health, Radiology and Imaging Sciences, Center for Interventional Oncology; ³3T Technologies, LLC

Purpose: Miniature electromagnetic (EM) sensors can be embedded in needles to track needle location during needle insertions guided by ultrasound (US) or computed tomography (CT) imaging [1]. The most competitive EM tracked needles on the market are costly with restricted selections of needle sizes and types, which limit the clinical applications [2]. We hypothesized that a disposable and inexpensive clip which can be mounted on 16–22 gauge needles could allow for EM needle tracking in CT or US image-guided procedures. This study aimed to evaluate the accuracy and feasibility of the EM needle clip (Fig.1).

Methods: The EM needle clip contained two miniaturized EM solenoids, fabricated in-house, and positioned perpendicularly to each other for six degrees of freedom tracking. The solenoids were connected to Aurora system through minimal coaxial cables with serial programmable ROM. The Aurora system was used to generate magnetic field and collect position information (Fig.2a). Both the-positional template test (n=20) and spinal phantom test (n=20) were used to evaluate the accuracy (Fig.2b-c). The actual positions were measured using a MicroScribe G2X Digitizer (error<0.23mm).

Results: Fig. 3 shows the axial and radial targeting accuracy of the EM needle clip in the template and spinal phantom tests, respectively. The errors were less than 1 mm in both direction, resulting in targeting accuracy on par with the commercial EM tracked needle (~0.7mm).

PET-MR of $^{89}$Zr-Iron Oxide Nanoparticles for Targeted Magnetic Drug Therapy In Vivo

Caroline D. Jordan, PhD$^1$, Mariam Aboian, MD PhD$^1$, Kiel D. Neumann, PhD$^1$, Carol Stillson$^1$, Teri Moore$^1$, Wesley Kuo MS$^1$, Joshua Fisher MS MPH$^1$, Youngho Seo, PhD, Henry F. VanBroocklin, PhD$^1$, Mark W. Wilson, MD$^1$, Alastair J. Martin, PhD$^1$, Steven W. Hetts, MD$^1$

1. Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA

**Purpose:** Targeted drug delivery using magnetic nanoparticles (1,2) could reduce systemic toxicity of transarterial chemoembolization by conjugation to a chemotherapeutic drug, which is then extracted via the temporary deployment of an intravenous magnetic filtration device (3) downstream of a tumor. Current in vitro methods use $^{89}$Zr-iron oxide nanoparticles (IONPs, Fe$_3$O$_4$) to measure particle capture (4) and accurate quantification of the drug distribution is necessary to show efficacy in vivo. Prior work demonstrated intrahepatic fusion of magnetic-targeted carrier-Doxorubicin via susceptibility artifact under MRI (5). The recent development of new imaging methods, such as PET/MR, provides a unique opportunity to simultaneously acquire and compare several multiparametric techniques. Our goal was to test the feasibility of using PET-MR to quantify the biodistribution of $^{89}$Zr-IONP in the liver in vivo.

**Methods:** *In vivo experiment:* Under IACUC approval, we performed a preliminary in vivo experiment by injecting 2.33 mCi radiolabeled $^{89}$Zr in 100mg IONP in 10mL saline (10,000 mg/L) in the common hepatic artery of a single swine. A 3T PET-MR hybrid system (Signa, GE Healthcare, Milwaukee, WI) was used for the simultaneous acquisition of a 10 minute time-of-flight PET acquisition and a breath-held 3D multi-echo GRE sequence (SWAN) with 9 echoes, $\Delta TE = 3.0\text{ms}$, and $TE = [13.0−37.0]\text{ms}$, TR = 55.7 ms, and an upper anterior array coil. We imaged the animal before the injection, infused over a 5-minute period outside the scanner room, then imaged again after 5 minutes. *Post-processing:* To obtain the $T_2^*$ maps, we performed a mono-exponential fit of the magnitude images, then took the inverse pixel-wise. Mean ± standard deviation of selected ROIs were calculated.

**Results:** *In vivo experiment:* Infusion of the $^{89}$Zr-IONPs in the common hepatic artery resulted in substantial changes in the posterior hepatic lobe before and after injection (Fig. 1). A manually drawn ROI resulted in mean $T_2^*$ prior to infusion of 23.8 ± 10.6 ms and a mean ROI of the 3D volume resulted in a PET SUV of 19.5 g/ml after infusion, while there was not sufficient signal to acquire a $T_2^*$.

**Conclusions:** Substantial uptake was observed in the liver in a preliminary in vivo experiment after injection of magnetic nanoparticles, indicating that PET-MR may be feasible for in vivo radiolabeled IONP injections. A preliminary in vivo study demonstrated proof of principle for assessing magnetic nanoparticle tracking.

Image-Guided Radiation Therapy using Combined MRI and Ultrasound


*GE Global Research, Niskayuna, NY and **University of Wisconsin-Madison

Purpose
A novel approach providing image guidance with good soft-tissue contrast during radiation therapy procedures is presented. Our approach matches four-dimensional ultrasound data of a patient’s respiratory state acquired during radiation treatment to simultaneously acquired, pre-procedural ultrasound and MR images. Hence, during the treatment stage, the matched MR images representing the current respiratory state of the patient is used for visualizing and tracking the tumor target relative to the LINAC beam. This improves the overall dose conformity to the tumor target and permits reduced treatment margins placed around the tumor.

Methods
There are two primary requirements to accomplish the guidance. First, an electronically-steered e4D ultrasound transducer that can operate in an MRI scanner as well as in a high radiation dose environment. Second, a rapid, feature recognition and tracking algorithm that can perform at real-time imaging rates to match respiratory states from a pre-procedural acquisition.

An e4D transducer with 18,000 elements was tested in a 3T MRI scanner (GE MR750) to investigate interactions between the ultrasound (GE Vivid VE9) and MR systems. As the e4D ultrasound probe also included beam forming and data acquisition electronics (FPGA and ASICs) in the transducer housing, sufficient electromagnetic interference (EMI) shielding was needed to avoid errant signals from fast switching electric fields from both the MRI gradient and radiofrequency (RF) fields corrupting the ultrasound control lines/signals. Similarly, ultrasound probe shielding was necessary to prevent the MRI system from picking up emissions from the ultrasound electronics. The VE9 system was placed outside of the scan room with long ultrasound control cables passing through the MRI scan room penetration. The ultrasound probe was placed in an aluminum box and positioned at different locations within the magnet bore. Images were observed for artifacts during simultaneous MR (fast gradient echo and fast spin echo) and ultrasound acquisition.

Results
Shielding of the ultrasound probe housing and cable successfully reduced and minimized system-to-system interactions (Fig. 1). The resulting MR and ultrasound images were relatively artifact-free in the initial component testing. The block matching algorithm demonstrated computation rates of between 73-234 fps per fiducial marker for 2D tracking. With 3D tracking, the computation rates will be reduced but should still be above the 4D ultrasound acquisition rate of 10 fps, allowing several fiducial markers to be tracked simultaneously.

Conclusions
The progress reported moves the project towards a truly functional e4D imaging system that is able to acquire simultaneous MR and ultrasound images. With a fast fiducial marker tracking algorithm, real-time tracking tumor target motion using MRI without the need for expensive MR-LINAC systems can be realized.

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References
Reflectance confocal microscopy imaging for detection of cancer margins during Mohs micrographic surgery of non-melanoma skin cancers: feasibility of a peri-operative imaging algorithm

Eileen Flores, Oriol Yelamos, Miguel Cordova, Kivanc Kose, William Phillips, Anthony Rossi, Kishwer Nehal, Milind Rajadhyaksha
Memorial Sloan Kettering Cancer Center (MSKCC), New York, NY, USA

Purpose Conventional surgical (wide) excision and Mohs micrographic surgery (MMS) of skin cancers currently rely on pathology for confirmation of clearance. However, the preparation of pathology is time-consuming (hours to days) and labor intensive. Reflectance confocal microscopy (RCM) imaging shows promise for detection of residual cancer directly on patients for potentially guiding surgical treatment of skin cancers. Recent technological advancements such as the introduction of the handheld version of the reflectance confocal microscope, video acquisition and video-mosaicking have improved RCM as an emerging tool to evaluate residual cancer margins during routine surgical procedures such as MMS. Detection of residual non-melanoma skin cancer (NMSC) tumor during MMS is feasible, as demonstrated by the introduction of real-time perioperative imaging on patients in our surgical setting. Our study tests feasibility of a new video-mosaicking algorithm for peri-operative RCM imaging of NMSC cancer margins on patients during MMS.

Methods We report progress and image analyses on forty-five patients, who presented for treatment of basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) with MMS at the MSKCC Dermatology service. The first 10 patients were used as a training set to establish an RCM imaging algorithm, which was implemented on the remaining test set of 35 patients. RCM imaging, using 35% AlCl₃ for nuclear contrast, was performed pre- and intra-operatively with a handheld microscope (Vivascope 3000, Caliber ID, Rochester, NY). Imaging was performed in quadrants in the wound, to simulate the Mohs surgeon’s examination of pathology. Videos were taken at the epidermal and deep dermal margins. Our Mohs surgeons assessed all videos and video-mosaics for quality and correlation to histology.

Results Peri-operative RCM imaging using our video-mosaicking algorithm is feasible. Imaging time ranged from 5-10 minutes, depending on the size and location of the lesion, during the Mohs procedure. According to our Mohs surgeons (co-authors AR and KN), RCM videos and video-mosaics of the epidermal and dermal margins were found to be of clinically acceptable imaging quality, in terms of resolution, contrast and visualization of nuclear detail (91% pre-operatively, 83% intra-operatively). Figure 1 is an example of pre-operative RCM video-mosaic showing epidermal disarray, an inherent feature in SCC. Pre-operative RCM and histology correlation was observed in thirty-two (91%) of 35 lesions with biopsy-proven NMSC. The presence of residual BCC/SCC tumor and normal skin features could be detected intra-operatively, using 35% AlCl₃. Visualization of nuclear and cellular morphology of residual BCC/SCC tumor and normal skin features could be detected in the peripheral and deep dermal margins. We observed correlation between the RCM videos/video-mosaics and the corresponding histopathology for presence of tumor in ten (77%) of 13 wounds and absence of tumor in nineteen (86%) of 22 wounds that showed normal skin. Figure 2 is an example of intra-operative RCM and histology confirmation of residual BCC tumor. In three wounds, the presence of residual tumor was not detectable in the corresponding RCM videos/video-mosaics.

Conclusions Peri-operative RCM imaging shows promise for improved and faster detection of residual cancer margins directly on patients and guiding MMS in the surgical setting. Testing of alternate contrast agents and improvements in our video-mosaicking algorithm are ongoing and will be necessary to improve sensitivity and specificity.

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Reflectance confocal microscopy (RCM) imaging is advancing into routine clinical practice for noninvasive diagnosis and margin delineation of skin cancers. Recently, reimbursement codes for RCM imaging of skin were granted by the Centers for Medicare and Medicaid Services. However, high resolution microscopic imaging is inherently limited to small fields of view (FOVs), typically on the order of a 1mm². By contrast, pathologists, typically use a wide range of magnifications (2X to 10X) and FOVs (100 mm² to 1 mm²). To increase the FOV for clinical confocal microscopy, mosaicking approaches - acquiring a sequence of images and stitching them together - have been developed. Mosaicking with existing reflectance confocal microscopes is performed in a highly controlled manner in vivo using pre-defined raster scan paths over relatively small areas. However, a new generation of smaller and handheld confocal microscopes offer the freedom to image larger areas using arbitrary, freehand, interactively chosen paths. Imaging larger areas more quickly is possible by acquiring videos instead of still images. However, a video, simply by itself, is merely a time sequence of small FOVs and therefore does not display the spatial distribution of tissue morphologic patterns over large areas, as is necessary for pathology-like examination. We are developing novel video-mosaicking approaches to bring a solution to this problem, by stitching consecutive frames of a video to display morphologic patterns over larger areas of interest. Testing has been performed on about 100 melanocytic and non-melanocytic skin lesions in dermatology service at MSKCC.

We present 2 exemplar applications; (i) prediction of surgical margins of lentigo maligna (LM) and lentigo maligna melanoma (LMM) lesions using video-mosaicking and (ii) detection of sites to biopsy in recurrent extramammary Paget disease (EMPD). In both cases, the sub-clinical sub-surface focal areas and the spread of the lesions cannot be determined with required accuracy through traditional clinical examination and dermoscopy. Therefore, clinicians rely on invasive “scouting” biopsies to determine the focal areas and spread of such lesions. RCM video-mosaicking potentially offers a non-invasive alternative for delineating such lesions.

In the LM/LMM study, we imaged 10 patients with a radial video-mosaicking approach prior to staged excision. Initially, the clinical margins were determined with dermoscopy and Wood’s lamp (ultraviolet light). We assessed the sub-surface spread beyond the clinical margins using video-microscopy and video-mosaicking. LM or LMM positive areas, when detected in any particular quadrant, were further imaged radially outwards to further determine the subsurface extensions and the potential surgical margins. Patients then underwent routine staged excision blinded to the RCM video-mosaicking results. Comparing the radial extent (millimeters) needed to be excised to achieve histological clearance after surgery, in 23 quadrants we saw no difference between RCM-predicted values and values after surgery. RCM underestimated in 14 quadrants, and overestimated in 3 quadrants. Overall, from our random effects regression model, controlling for patient age and previous surgery, surgical margins were on average, 0.80 mm larger than the RCM prediction (95% CI: 0.67- 0.92, p<0.001).

In our EMPD study, we interrogated the concerning lesion areas in 5 patients (overall 22 suspicious areas), 2 of which were imaged using video-mosaicking. RCM in 19 out of 22 regions were successively diagnosed (10 true positive and 9 true negative) and only 3 areas were misdiagnosed (3 false negative). The false negatives occurred at the margins of EMPD close to previous biopsies. Videomosaicking seemed to improve the detection accuracy, reduce sampling bias, and improve the precision of targeted biopsies, thus reducing the number of biopsies to render a correct diagnosis.

As illustrated through these examples, our video-mosaicking approach can allow healthy tissue sparing by reducing unnecessary biopsies in clinically uncertain areas. This is particularly important in cosmetically-sensitive areas such as the face or the genitalia. Predicting surgical defects with our approach may enable surgeons to plan surgical reconstructions in advance and eventually guide surgery when the technique is validated in larger studies. In addition, knowing the surgical defect in advance can provide patients with realistic, visual information about potential post-surgical defects. Although our implementation is specific for RCM imaging of skin, our video-mosaicking algorithm could be readily adapted for widespread use with other optical microscopic approaches for living tissue, such as confocal fluorescence endoscopy, optical coherence tomography, multiphoton microscopy and photoacoustic microscopy.

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*Shared first authorship
Clearance of Cisplatin from Physiologic Solutions with DNA-based ChemoFilter

Department of Radiology and Biomedical Imaging, University of California San Francisco, California

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Purpose: ChemoFilter is a novel medical device that limits systemic toxicity of chemotherapeutics by filtering non-target drug from blood that could be described as intra-vascular dialysis. This method has a potential to prevent toxicity associated with treatment of multiple cancers including primary liver cancer, liver metastases, and head and neck cancer. We report two novel methods to filter cisplatin from solution that use either cisplatin's intrinsic DNA binding activity or an ion exchange mechanism. We also show that ChemoFilter can be used for combinations of drugs that simulate clinical administration of chemotherapeutic cocktails.

Materials and Methods: Cisplatin and doxorubicin clearance experiments were carried out in deionized water and phosphate buffered saline under experimental and physiological conditions (single chamber non-linear flow and closed circuit flow model). Ion exchange resins with different properties and genomic DNA were used for clearance of doxorubicin and cisplatin. Optimum packaging method for DNA was determined using polyester and nylon mesh using different design parameters.

Results: Strong cation ion exchange resin effectively clears up to 40% of pure cisplatin from single chamber non-linear flow model within 1 minute of reaction time in deionized water. There is no clearance of cisplatin in solutions with high sodium chloride concentrations, such as phosphate buffered saline. Clinical grade cisplatin that contains high concentration of sodium chloride is also not cleared by strong cation ion exchange resin. In contrast, genomic DNA clears up to 50% of cisplatin from a 0.05 mg/ml cisplatin solution within 1 minute of reaction in water and phosphate buffered saline at room temperature and 50C. Similar clearance rates are observed in flow model with 150 ml/min rate of flow. Cisplatin clearance in phosphate buffered saline is lower as compared to doxorubicin clearance with ion exchange resin and genomic DNA.

Conclusion: ChemoFilter is a novel endovascular device that was previously shown to be highly effective for clearance of doxorubicin from physiologic solutions. We now demonstrate that genomic DNA can be used to clear a commonly used chemotherapeutic cisplatin. We also show that ion exchange resin method is not effective for cisplatin in physiologic solutions.
Basal Cell Carcinomas Margins Delineation for Laser Ablation Therapy Guidance with Combined Optical Coherence Tomography - Reflectance Confocal Microscopy Imaging

*Physical Sciences, Inc., Andover, MA 01810
**Memorial Sloan Kettering Cancer Center (MSKCC), NY

Purpose: The purpose of this research is to develop and test the feasibility of a high-resolution combined optical coherence tomography (OCT) and reflectance confocal microscopy (RCM) imaging approach for accurately detecting the presence and then delineating the lateral and depth margins of basal cell carcinomas (BCCs), to potentially guide laser ablation therapy. Compared to traditional Mohs surgery, laser ablation can be particularly effective for minimally invasive removal of superficial and early nodular BCCs. Skin can be vaporized in μm-thin layers in a highly controlled manner, with minimal damage to the surrounding normal tissue. However, the lack of pathological feedback results in variable efficacy and limited cure rate. The high-resolution OCT/RCM imaging approach may address this limitation by detecting the presence or clearance of residual BCCs directly on the patient, and provide immediate pathology-like feedback.

Methods: OCT and RCM were combined into a single instrument to provide cross-sectional images, simultaneously in real-time, with structural-level resolution in deeper skin (reticular dermal layers), to depths of at least 1 mm, as well as en face images with nuclear-level resolution in superficial skin (epidermal layers and papillary dermal layers, including dermal-epidermal junction), to depths of about 200 μm. A preliminary feasibility study on 15 patients was recently performed at MSKCC.

Results: Figure 1 shows an example case. The cross-sectional and enface OCT images (lower left) allow for lateral and depth delineation of the BCC tumor (seen as hypoechoic areas), while the RCM image (lower right) confirms the diagnosis and presence of BCC, based on the appearance of tumor nests (dark nodal areas surrounded by bright stroma (whiter rim)) with increased nuclear density, palisading and clefting, and with increased vasculature and blood flow. Histology (upper right) confirms OCT/RCM findings. Several more cases will be presented, demonstrating the capability of the OCT/RCM technology for detecting BCCs and delineating margins and thus its potential suitability for laser ablation therapy guidance.

Conclusions: Combined noninvasive OCT/RCM imaging may enable in situ delineation of lateral margins and spreading depth of superficial and early nodular BCCs. In the long-term, this approach can serve for guiding laser ablation therapy, which could potentially replace Mohs surgery. Since superficial and early nodular BCCs constitute about 40% (600,000 cases per year) of Mohs surgical cases, laser ablation would be a good alternative to Mohs surgery for these cases.

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Automatic Brain Tumor Segmentation using Stochastic Multiresolution Texture Features and Random Forest
Zeina A. Shboul, Linmin Pei, Syed S. Reza, Khan M. Iftekharuddin
Vision Lab, Department of Electrical and Computer Engineering
Old Dominion University, Norfolk, VA 23529

Purpose: This work discusses ongoing works in our group (with NCIGT and clinical collaborators at CHOP, UCSD, and Iowa) on the effectiveness of using the stochastic multiresolution texture features along with random forest clustering in brain tumor segmentation and prediction. Because medical images have a degree of randomness associated with its spatial intensity distribution, we use fractal texture modeling in order to measure the surface roughness in MR images. We extract spatially varying texture features such as piecewise triangular prism surface area (PTPSA) and multifractional Brownian motion (mBm) along with other intensity features and then use these features for random forest (RF) classification of multiple abnormal tissues in brain MRI.

Methods: We develop methods for multiclass (edema, necrosis, enhance tumor, and non-enhance tumor) brain tumor segmentation in multimodality MRI (T1, T1C, T2, and FLAIR). The stochastic multiresolution texture (mBm, PTPSA) and regular texture (texton) and intensity features captures both global and local characteristics of different tissues. We then fuse all features to obtain a 3D feature matrix use them for RF Classification.

Figure 1. General Flow Diagram for Multiclass Abnormal Brain Tissue Segmentation

The RF classifier is trained on a set of training dataset with known tissue (class) label to build the RF training model. Then we use this model to predict the class for test dataset. Figure 1 shows the complete pipeline for the brain tumor segmentation method.

Results: We evaluate our abnormal tissue segmentation method by performing two studies using BRATS-2013 and BRATS-2014 datasets. The first study uses 213 cases from BRATS-2014 and 20 cases from BRATS-2013, respectively. We trained RF classifier using BRATS-2013 cases and test using BRATS-2014 cases. The average scores varies from 63% - 76% using Dice overlap metric for tumor core and complete tumor, respectively.

In the second study, we perform threefold cross-validation with 213 cases randomly selected from the BRATS-2014. The average classification scores using the proposed method varies from 73% - 87% using Dice overlap metric for tumor core and complete tumor, respectively. These results show that our segmentation method is very promising, and offer comparable performance when compared with state-of-the-art works proposed in BRATS challenges (http://martinos.org/qtim/miccai2013/results.html).

Conclusions: We discuss a novel stochastic multiresolution texture feature model for robust brain tumor segmentation. In order to evaluate the effectiveness of our fractal features model, we test our method on a large-scale publicly available clinical dataset known as BRATS. We use both LGG and HGG patient data to show the efficacy of our method. The results show that our brain tumor segmentation performance is comparable with state-of-the-art works.

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A novel thermal accelerant with a high dipole moment to augment microwave energy within biologic tissues during image-guided thermal ablation: A porcine study

William Keun Chan Park; Aaron Wilhelm Palmer Maxwell; Michael Patrick Primmer; Scott Andrew Collins; Grayson Luderman Baird; Damian Edward Dupuy

Department of Diagnostic Imaging, The Warren Alpert Medical School of Brown University

**Objectives:** To investigate the effects of a novel cesium chloride-based thermal accelerant (TA) compound on ablation zone volumes following *in vivo* microwave ablation of porcine liver and skeletal muscle, and to examine the effects of TA administration on target organ perfusion.

**Materials & Methods:** Microwave ablation (915MHz, 60W, 10 minutes, TA injection 1.5 cm from antenna) was performed in liver and resting skeletal muscle in eight *Sus scrofa domesticus* swine with and without TA administration. Treated tissues were explanted and stained with triphenyltetrazolium chloride (TTC) for quantification of ablation zone volumes, which were compared between TA and non-TA conditions. Hematoxylin and eosin (H&E) staining was also performed for histologic analysis. Generalized mixed modeling with a negative binomial distribution was used for all quantitative comparisons. An overall *a priori* significance level of p=0.05 was used.

**Results:** The use of thermal accelerant significantly increased microwave ablation zone volumes in a dose-dependent manner in both porcine muscle and liver (p<0.01). Both the absolute mean ablation zone volume and percentage increase in ablation zone volume were greater in resting skeletal muscle than in liver, likely secondary to differences in organ vascularity. In one swine, a qualitative mitigation of heat sink effects was observed by TTC and H&E staining. Non-lethal polymorphic ventricular tachycardia was identified in one swine, necessitating treatment with intravenous amiodarone.

**Conclusion:** The use of a cesium-based thermal accelerant significantly increased mean ablation zone volumes following microwave ablation using a porcine model. The relationship between TA administration and ablation size was dose-dependent and inversely proportional to the degree of target organ perfusion, and a qualitative reduction in heat sink effects was observed.

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**Figures:** Mean ablation zone volumes in resting porcine skeletal muscle (left) and liver (right) at increasing thermal accelerant concentrations.