BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

Department of Radiology
75 Francis Street
Boston, Massachusetts 02115
Tel: 617-732-7389; Fax: 617-582-6033
www.spl.harvard.edu/~kikinis
kikinis@bwh.harvard.edu

Ron Kikinis, M.D.
Professor of Radiology
Director, Surgical Planning Laboratory
Robert Greenes Distinguished Director of Biomedical Informatics

April 29, 2011

Division of Extramural Activities Support, OER
National Institutes of Health
6705 Rockledge Drive, Room 2207, MSC 7987
Bethesda, MD 20817

To Whom It May Concern:

On behalf of the Brigham and Women's Hospital Signing Official, Sheila M. Langlois (Grants Administrator II), please find enclosed the annual progress report for grant U54 EB005149, the "National Alliance for Medical Image Computing (NA-MIC)" on which I am the Principal Investigator.

If you have any questions, please do not hesitate to contact my office.

Thank you.

Sincerely,

Ron Kikinis, M.D.

NATIONAL ALLIANCE FOR MEDICAL IMAGE ANALYSIS

A National Center for Biomedical Computing
Funded under the NIH Roadmap Initiative

Annual Progress Report -- September 30, 2010 through June 1, 2011

1. INTRODUCTION

The National Alliance for Medical Image Computing (NA-MIC) is a multi-institutional, interdisciplinary community of computer scientists, software engineers, and medical investigators, who share the objective of improving healthcare through the development of computational tools for the analysis and visualization of medical image data. In the seven-year history of NA-MIC, the community has created a robust and flexible infrastructure for developing and applying advanced imaging technologies across a range of important biomedical research disciplines. Following application for competitive renewal, the Center was funded for an additional four years in October of 2011, making this the 7th annual report since inception in 2004, and the first annual progress report of the second funding cycle.

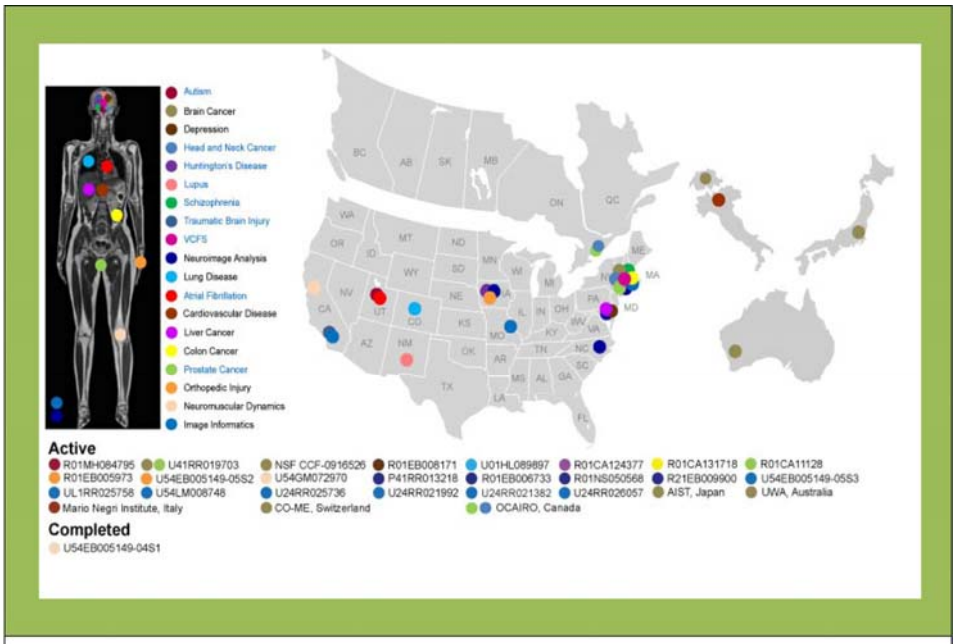

Figure 1-1. Geo-anatomical Map of NA-MIC Collaborations

With an overall theme of personalized medicine and patient-specific image analysis, NA-MIC is applying its technology to diseases of immense practical significance: heart disease, degenerative genetic disease, cancer, and trauma. In addition to activities that sustain the NA-MIC Kit and integrity of the Center's software infrastructure, much of the year has been spent analyzing, preparing and retooling for the new cycle of DBPs, namely, Atrial Fibrillation, Huntington's Disease, Adaptive Radiotherapy for Head and Neck Cancer, and Traumatic Brain

Injury in line with the specific aims presented in the Competitive Renewal. This report provides an overview of this work. A detailed presentation of all Cores was made at the All Hands Meeting in Salt Lake City, Utah, January 10-14, 2011, and is available on the NA-MIC Wiki [http://www.na-mic.org/Wiki/index.php/AHM_2011].

The following sections describe Center progress since September 30, 2010 and include Highlights and Impact statements, as well as reports from the new cycle of Driving Biological Projects (DBPs), the Computer Science Core (Algorithms and Engineering), the NA-MIC Kit, and recommendations of the External Advisory Board which also met in January at the annual All Hands Meeting.

2. HIGHLIGHTS

The scope of NA-MIC activities includes both highly speculative explorations of new mathematical formulations of core image analysis techniques and the ongoing effort of delivering and supporting binary distributions of software applications across a range of computing platforms. To address this continuum, NA-MIC Computer Science Core efforts are organized around two teams: Algorithms and Engineering. Their joint output is the NA-MIC Kit which embodies a comprehensive set of analysis techniques in a well architected, documented, and widely used platform as described in the following paragraphs.

Algorithms. The NA-MIC Computer Science Algorithm effort is responsible for pushing the boundaries of applied mathematical techniques in the context of the challenges of the DBPs. As such, the Algorithm activities are typically highly experimental, with a wide range of approaches that are rapidly prototyped, tested, and improved. These efforts, often undertaken by graduate students under the direction of more senior academics, generate novel approaches that can have wide applicability beyond the original motivating problems.

Engineering. The NA-MIC Computer Science Engineering effort is responsible for providing an integrated platform that supports the research requirements of the NA-MIC community. Consisting of both academic and commercial software developers, the Engineering team aims for a stable and reliable software platform with a sufficiently high level set of support to enable leading-edge clinical applications.

NA-MIC Kit. The NA-MIC Kit consists of a modular set of interoperable free open source software (FOSS) packages, managed under a collaborative, high quality software engineering methodology. These packages have been carefully architected to accommodate technology contributions from the NA-MIC Investigators, and to rapidly deploy these technologies to NA-MIC and the broader biomedical imaging community. A primary motivation for the creation and use of this common infrastructure is that new concepts, emerging perhaps after a productive discussion at a computer science seminar, can be directly and efficiently deployed into the hands of a clinical researcher seeking better insight on a difficult patient case. Thus, the process of closing the gap between idea and implementation, and supporting rapid iteration as new ideas are tested and improved, lies at the core of the NA-MIC software approach.

In the following subsections we highlight the accomplishments from this reporting period for algorithms, engineering, and NA-MIC kit.

2.1 Algorithms

The Algorithm component of Core 1 has defined four areas in which to build synergistic algorithms that address the challenges of the DBPs. Some major accomplishments for this reporting period in each of these areas are as follows:

Statistical Models of Anatomy and Pathology

- Best Paper Award, MedIA/MICCAI journal issue, [Gerber et al., 2010] for nonlinear statistical models of image databases.
- Demonstration of a non-parametric approach to segmentation to delineate anatomical structures in pre-treatment scans.
- Developed a method for joint segmentation of corresponding regions of interest in a collection of aligned images that does not require labeled training data.

Geometric Correspondence

- Shape model analysis of atria for normal controls and atrial fibrillation patients in collaboration with the Atrial Fibrillation (AF) DBP.
- Demonstration of effectiveness of tensor-based DTI registration for longitudinal analysis of Huntington's disease, for the Huntington's DBP.
- Development of an efficient computational framework for incorporating geodesic distances into correspondence selection and optimization.
- Development of a cross validation approach to parameter selection in high-dimensional registration methods.

User Interactive Tools for Segmentation

- Development of a user-interactive segmentation method using robust statistical estimators of image regions.
- Demonstration of effectiveness of coupled level sets in the segmentation of heart wall, in collaboration with the AF DBP.
- Development and demonstration of user-interactive tools and statistical tools for segmentation of MRI volumes of traumatic brain injury (TBI) patients.

Longitudinal and Time Series Analysis

- Development and deployment of a new longitudinal atlasing method for DTI.
- A new method for estimating changes in TBI lesion infiltration/recession from longitudinal data.
- Development of a formulation and method for estimating smooth trajectories for growth, recovery, and/or degeneration.

2.2 Engineering

The objective of the Engineering component of Core 1 is to provide software tools and software development processes to deploy innovative technology to clinical researchers, support the scientific algorithm innovation of the Algorithm scientists, and to foster a community to produce high quality software. The major accomplishments of the Engineering component for this reporting period are as follows:

Interactive Tools

- Developed 2D and 3D "widgets" that provide different modes of interaction between a user and Slicer. For example, widgets provide the ability to run algorithms as a user, to paint a segmentation on a slice (a "magic crayon") or to deform a surface in 3D.

Data Collections and Clinical Workflows

- Adding support for MIDAS databases. MIDAS is an open-source application that provides web and C++ interfaces for data it hosts. MIDAS is used to run BWH's PubDB and the Insight Journal. Additionally, MIDAS serves as a gateway to other systems including NCI/caBIG's NBIA database.
- Extending MIDAS to host Slicer MRML scenes so they can be searched, categorized, and viewed as thumbnails via the web interface to MIDAS.
- Providing DICOM Query and Retrieve functionality for interfacing Slicer with clinical PACS.

Dissemination and Cross-platform Support

- Devised a method for uploading compilation results from client machines to a central system for redistribution. This allows executables, extensions, and packages created by users and by dedicated machines to be made available for others to use. The process can be thought of as "crowd-sourcing" the creation of Slicer installation packages for an ever growing number of platforms (linux, mac, windows, etc).
- Providing 64-bit builds (in addition to 32-bit builds) of Slicer 4 for linux, Windows, and Macs. This allows Slicer to handle even the largest clinical scans.

Quality Software: Qt and GUI Testing

- Supporting the conversion of Slicer from KWWidgets to Qt for its user interface. This new "Slicer4" is available in Beta and contains many enhancements, including broad community support for Qt and increased stability afforded by refactoring much of the Slicer code base.
- Porting a GUI testing system from ParaView to Slicer. This will allow, for example, every tutorial to be made fully automated and to run as a nightly test on every Slicer-supported platform. The continued operation and relevance of every tutorial as well as the stability of the Slicer user interface will be assured.

2.3 NA-MIC KIT

The NA-MIC Kit is designed to accelerate innovation with a flexible execution engine on which community-developed analysis modules can be rapidly deployed to clinical researchers and the broader community via 3D Slicer.

One hallmark of this reporting period is the massive increase in Slicer downloads. During the current period, 3D Slicer version 3 was downloaded 13,913 times. Figure 2-1 illustrates the locations and number of downloads for the various versions of Slicer.

Figure 2-1. Slicer3 Downloads in the current reporting period.

Other accomplishments related to the NA-MIC Kit include the following:

- Developed new data structures for managing multivariate time-series data.
- Created new interfaces to statistical libraries.
- Implemented new components for interactive analysis methods.

2.4 Dissemination

The Dissemination Core has again been active in promoting NA-MIC methodologies and technologies among the research and clinical scientific communities. A complete list of events is available on the NA-MIC web site, but a few notable activities in the past year are described below.

Birds-of-a-Feather Meetings: The “Programming Week” event was started in 2005 to gauge the interest of participants in spending a week together working on NA-MIC projects. It was renamed "Project Week" to reflect its expanded scope and duration in the first cycle of NA-MIC and has continued to gain momentum this year. It continues to include projects that involve all Center cores as well as several funded and non-funded collaborators. The Center holds two week-long meetings of this type each year: the last week of June at MIT, as well as four days in conjunction with the All-Hands Meeting in January. The 11th PROJECT EVENT was held on

June 21-25, 2010 in Boston, at MIT and Brigham and Women's Hospital. It recorded 126 registered attendees, who worked on 71 projects. These attendees represent 30 academic sites and 15 companies. The 12th PROJECT EVENT was held on January 10-14, 2011 in Salt Lake City, Utah. It recorded 106 registered attendees, who worked on 59 projects. These attendees represent 20 academic sites and 9 companies. The projects, agenda, and affiliations of attendees are detailed below. Details of all programming/project weeks are available here: http://www.na-mic.org/Wiki/index.php/Engineering:Programming_Events.

In addition, the Dissemination Core has worked to foster connections with national and international communities of developers with similar goals and philosophies. For example, NA-MIC has remained an active participant in the Common Toolkit (CTK) effort, of which it was a founding member. The goal of this effort is to create a medical imaging software package that can be shared across many applications. Participants include The German Cancer Research Center (DKFZ), Inria, the Mallinckrodt Institute of Radiology at Washington University, and Siemens Corporate Research. Participation in CTK has expanded to include Georgetown University, UPF in Barcelona, and AZE, a Japanese radiology workstation vendor. The CTK group has adopted many of the core software technologies from the NA-MIC Kit (in particular ITK, VTK). Just as important, it has adopted the NA-MIC software engineering methodology of CMake/CTest/CDash, and has gained traction as a hub for medical image computing development. The Dissemination Core has also reached out to the Neuroimaging in Python (nipy) community to share code and information about fMRI and diffusion analysis. These groups share NA-MIC's commitment to open source for medical image analysis and bring important new ideas and software contributions to the NA-MIC effort. Connections with groups such as CTK and nipy, along with collaborations with NCIGT, BIRN, and the Harvard Catalyst CTSA, are an important source of new ideas to help NA-MIC software efforts grow and adapt to new opportunities.

Web Presence: The collaborative wiki (http://wiki.na-mic.org) has expanded to over 3300 pages and maintains over 730 users. (At the start of the first cycle (2004-2009), we had 350 pages and 150 users and at the end of the first cycle we had 2800 pages and 650 users). In addition to the use of these wiki pages by NA-MIC investigators, usage by external collaborators continues to expand and has led to independent wikis in several cases.

2.5 Training

Since September, 2010, the NA-MIC Training Core has delivered 15 workshops to 340 scientists, clinicians and clinical researchers at both national and international venues.

Over the past eight months, we delivered six workshops on NA-MIC technology at national universities. We organized two hands-on Slicer workshops on topics including 3D visualization, image registration, Diffusion Tensor Imaging, and Neurosurgical Planning. One was at UCSF in the Fall, and the other was at the Institute for Computational Medicine at Johns Hopkins University in the Spring [1][2]. Both workshops gathered a total of 75 scientists and clinical researchers. We organized two events aimed at introducing NA-MIC technology to the new DBPs: a workshop on NA-MIC tools for Traumatic Brain Injury case analysis at UCLA, and a workshop on Atrial Fibrillation at the University of Utah [3][4]. In addition, we pursued our integration effort with the CTSA Harvard Catalyst with two hands-on workshops “3D Slicer Quantitative Medical Image Data Visualization” delivered at the Harvard Countway Library of Medicine [5]. We also geared our training materials toward PhD students through a lecture on Diffusion Tensor Imaging, and two labs using NA-MIC technology, “The Life Cycle of Medical Imaging Data” and “Diffusion Tensor Imaging Analysis" in conjunction with the HST.583 course

"Functional Magnetic Resonance Imaging: Data Acquisition and Analysis" of the Harvard-MIT Health Science and Technology program [6][7].

In addition, we organized a series of outreach events at two international conferences: the Annual Meeting of the Radiological Society of North America (RSNA 2010, Chicago, IL), the largest medical conference in the world with more 60,000 participants, and the Medical Image Computing and Computer Assisted Intervention conference (MICCAI 2010, Beijing, China), one of the leading meetings in medical image analysis.

The NA-MIC presence at the RSNA 2010 consisted of daily series of hands-on demonstrations and "Meet-the-Experts" sessions, which were part of the "3D Slicer: An Open Source Application for Registration, Segmentation, Quantitative Analysis, and Visualization of Biomedical Image Data" exhibit in the Quantitative Imaging Reading Room [8]. In addition, we delivered two 1.5 hour hands-on educational courses: "3DVisualization of DICOM images with Slicer" in collaboration with Dr. Kitt Shaffer, Vice Chairman for Education at Boston University Medical Center and 2010 RSNA Outstanding Educator Award recipient, and "Quantitative Medical Imaging for Clinical Research and Practice" in collaboration with the Harvard Catalyst [9-11]. Each of our courses gathered between 70 and 100 international radiologists and clinical researchers.

At MICCAI 2010, we delivered a full day tutorial "From MICCAI Algorithms to Clinical Translational Tools: The NA-MIC Platform" to computer scientists and biomedical engineers. The objective of the tutorial was to introduce the challenges inherent in delivering advanced medical imaging technologies to end users, and to present solutions available in the NA-MIC toolkit [12].

Finally, we disseminated NA-MIC technology at international venues in Europe and in Asia. In Europe, we delivered two hands-on workshops on Quantitative Imaging and Image-Guided Therapy at the University of Manchester and the University of Dundee in the UK [13][14]. In Asia, we were invited to teach at the General Hospital of the People's Liberation Army (PLA), China's largest military hospital with more than 4,000 beds and 2.5 million outpatients per year. We delivered a one-day hands-on workshop on NA-MIC technologies, which included 3D visualization, computer-assisted surgery and Diffusion Tensor Imaging to the clinicians of the Neurosurgery Department at the PLA General Hospital [15].

Since 2005, the NA-MIC Training Core has trained a total of 1,600 scientists and clinicians.

References

1. http://www.na-mic.org/Wiki/index.php/Events:UCSF-Slicer-Training-11-2010 (UCSF Workshop, Nov.9, 2010, San Francisco, CA)

2. http://www.na-mic.org/Wiki/index.php/Events:_Johns_Hopkins_University_Seminar_April_2011 (JHU Workshop, April 5, 2011, Baltimore, MD)

3. http://www.na-mic.org/Wiki/index.php/Events:UCLA-Slicer-Training-11-2010 (UCLA Workshop, Nov. 9, 2010, Los Angeles, CA)

4. http://www.na-mic.org/Wiki/index.php/Event:2011-04-UtahDBP-Training (University of Utah Workshop, April 22, 2010, Salt Lake City, Utah)

5. http://www.na-mic.org/Wiki/index.php/CTSC:Slicer_handson.021810 (Harvard Catalyst Workshops, Feb. 18 and March 11, 2011, Harvard Medical School, Boston, MA)

6. http://www.na-mic.org/Wiki/index.php/HST_583_2010 (Life Cycle of Medical Imaging Data HST.583 Lab, Sept. 13, 2010, Massachusetts Institute of Technology, Cambridge MA)

7. http://www.na-mic.org/Wiki/index.php/HST_583_2010_DTI_Course (DTI Analysis, HST.583 Lab, Oct. 18, 2010, Massachusetts Institute of Technology, Cambridge MA))

8. http://www.na-mic.org/Wiki/index.php/Events:RSNA_2010#Quantitative_Imaging_Reading_Room_Exhibit

   (Slicer exhibit, Quantitative Imaging Reading Room, RSNA 2010, Nov.28-Dec.3, 2010, Chicago IL)
9. http://www.na-mic.org/Wiki/index.php/Events:RSNA_2010 (RSNA 2010 Workshops, Nov.28-Dec.3, Chicago,IL)

10. http://rsna2010.rsna.org/search/search.cfm?action=add&filter=Author&value=107214 (3D Visualization of DICOM Images for Radiology Applications, RSNA 2010, Nov.29, 2011, Chicago, IL)

11. http://rsna2010.rsna.org/search/search.cfm?action=add&filter=Author&value=107236 (Quantitative Imaging for Clinical Research and Practice, RSNA 2010, Nov.30, 2011, Chicago, IL)

12. http://www.na-mic.org/Wiki/index.php/MICCAI_2010 (MICCAI 2010 Workshop, Sept.20, 2010 - Beijing, China)

13. http://www.na-mic.org/Wiki/index.php/Events:Dundee-Dec-2010 (University of Dundee Workshop, Dec.6, 2010, Dundee, UK)

14. http://www.na-mic.org/Wiki/index.php/Events:Manchester-Dec-2010 (University of Manchester Workshop, Dec.8, 2010, Manchester, UK)

15. http://www.na-mic.org/Wiki/index.php/Beijing_2010_NA-MIC_Workshop (PLA General Hospital Workshop, Sept.23, 2010, Beijing, China)

3. IMPACT AND VALUE TO BIOCOMPUTING

NA-MIC impacts the field of biocomputing through a variety of mechanisms. First, NA-MIC produces scientific results, methodologies, workflows, algorithms, imaging platforms, and software engineering tools and paradigms in an open environment that contributes directly to the body of knowledge available to the field. Second, NA-MIC science and technology enables the entire medical imaging community to build on NA-MIC results, methods, and techniques, permitting researchers to concentrate on the new science instead of developing supporting infrastructure, to leverage NA-MIC scientists and engineers to adapt NA-MIC technology to new problem domains, and to leverage NA-MIC infrastructure to distribute its own technology to a larger community.

3.1 Impact within the Center

Within the center, NA-MIC has formed a community around its software engineering tools, imaging platforms, algorithms, and clinical workflows. The NA-MIC calendar includes the All Hands Meeting and Winter Project Week, the Spring Algorithm Meeting, the Summer Project Week, 3D Slicer Mini-Retreats, Core Site Visits, and weekly telephone conferences. These events bring the NA-MIC community and the community at large together to address emerging needs through the joint development and application of methods and systems.

The NA-MIC software engineering tools (CMake, CDash, CTest, CPack) have enabled the development and distribution of a cross-platform, nightly tested, end-user application, the 3D Slicer, that is a complex union of novel application code, visualization tools (VTK), imaging libraries (ITK, TEEM), user interface libraries (Tk, KWWidgets), and scripting languages (TCL, Python). The NA-MIC software engineering tools have been essential to the development and distribution of the 3D Slicer imaging platform to the NA-MIC community.

NA-MIC's end-user application, the 3D Slicer, supports the research within NA-MIC by providing a base application for visualization, image analysis, and data management. The 3D Slicer supports multiplanar reformat, oblique reformat, surface and volume rendering, comparison viewers, tracked cursors, and multiple image layer blending. The 3D Slicer can communicate with an XNAT database to download data and upload results. The 3D Slicer provides a multi-layer plugin mechanism that permits researchers to quickly and easily integrate and distribute their technology with the 3D Slicer. Plugins can be authored as separate executables, shared libraries, Python scripts, or as full first class 3D Slicer modules. These plugins can be distributed with the 3D Slicer or distributed on a site maintained by the researcher (e.g., on the Neuroimaging Informatics Tools and Resources Clearinghouse, www.nitrc.org). The 3D Slicer is available to all Center participants and the external community through its source code repository, official binary releases, and unofficial nightly binary snapshots. There are 15 training modules on the 3D Slicer User Training 101 webpage, which educate 3D Slicer Users on basic image review, use of advanced modules, and integration of new technology into the 3D Slicer.

The next major release of the 3D Slicer, version 4, incorporates many advances in open source application development and will enable a host of new capabilities. Qt forms the interaction and display foundation for the new version of the 3D Slicer. Qt provides a rich set of user interface components as well as access to WebKit and Scalable Vector Graphics, SVG. These new capabilities will allow the developers to deliver a 3D Slicer that is rich in interaction models, annotations, and workflows.

NA-MIC drives the development of platforms and algorithms through the needs and research of its DBPs. Each DBP has selected specific workflows and roadmaps as focal points for development, with a goal of providing the community with complete end-to-end solutions using NA-MIC tools. Each DBP is connected to a member of the Engineering core and a member of the Algorithm core to orchestrate the NA-MIC activities to support their DBP. There are four new DBPs in NA-MIC that focus on the personal and longitudinal aspects of pathology and disease. These DBPs are Atrial Fibrillation, Traumatic Brain Injury, Adaptive Radiation Therapy, and Huntington's Disease. For each roadmap project, the software tools, exemplar data, and a tutorial are provided to the community to allow others to reproduce the results and apply the workflows in their own research programs.

NA-MIC algorithms are designed and used to address specific needs of the DBPs. Multiple solution paths are explored and compared within NA-MIC, resulting in recommendations to the

field. The NA-MIC algorithm groups have collaborated on a broad spectrum of methods for Structural Image Analysis, Diffusion Image Analysis, and Functional Image Analysis and have orchestrated the solutions to the DBP workflows and roadmaps. These efforts have led to fundamental advancements in shape representation, shape analysis, groupwise registration, diffusion estimation, segmentation and quantification, functional estimation, distortion correction, and clustering. To support the new DBPs, the algorithms team is focusing on Statistical Models of Anatomy and Pathology, Geometric Correspondence, User Interactive Tools for Segmentation, and Longitudinal and Time-Series Analysis.

3.2 Impact within NIH-Funded Research

Within NIH-funded research, NA-MIC is the National Center for Biomedical Computing (NCBC) collaborating center for eight other grants: PAR-05-063: R01EB005973 Automated FE Mesh Development, PAR-05-063: R01CA124377 An Integrated System for Image-Guided Radiofrequency Ablation of Liver Tumors, PAR-07-249: R01EB006733 Development and Dissemination of Robust Brain MRI Measurement Tools, PAR-07-249: R01MH084795 The Microstructural Basis of Abnormal Connectivity in Autism, PAR-07-249: R01CA131718 NA-MIC Virtual Colonoscopy, PAR-07-249: R01EB008171 3D Shape Analysis for Computational Anatomy, PAR-07-249: R01AA016748 Measuring Alcohol and Stress Interaction with Structural and Perfusion MRI, and PAR-08-183: R21EB009900 Johns Hopkins Skull Stripping.

NA-MIC also collaborates or has collaborated with other NIH-funded organizations, including: U24RR026057 Collaborative Tools Support Network for BIRN, U24RR025736 BIRN CC, U54GM072970 NCBC Stanford Simbios, U54EB005149-04S1 NA-MIC Collaboration with NITRC, COPDGene® quantitative analysis, R01NS050568 BRAINS Morphology and Image Analysis, NCBC Supplement for Microscopy and Slicer, R01CA111288 NA-MIC Collaboration with Prostate BRP, U24RR021992 fBIRN, U41RR019703 NA-MIC Collaboration with NCIGT, U54LM008748 NCBC I2B2, U24RR021382 mBIRN, P41RR013218 NA-MIC Collaboration with NAC, BrainColor, Real-Time Computing for Image Guided Neurosurgery, UL1RR025758 NA-MIC support for Harvard CTSC Translational Imaging Consortium, Children's Pediatric Cardiology Collaboration with SCI/SPL/Northeastern.

NA-MIC events and tools garner national and international interest. Over 100 researchers participated in the NA-MIC All Hands Meeting and Winter Project Week in January, 2011. Many of these participants were outside of NA-MIC and were attending the meetings to gain access to the NA-MIC tools and researchers. The Winter Project Week was expanded to include NA-MIC, NAC, NCIGT, the Harvard Catalyst, and CIMIT.

3.3 National and International Impact

NA-MIC collaborations include a number of international communities and organizations, including: Ontario Consortium of Adaptive Interventions for Radiation Oncology (OCAIRO), Computer Aided and Image Guidance Medical Interventions (CO-ME), Common Toolkit (CTK), Real Time Computer Simulation of Human Soft Organ Deformation for Computer Assisted Surgery, NA-MIC Collaboration with Research and Development Project on Intelligent Surgical Instruments, and the Vascular Modeling Toolkit Collaboration. NA-MIC collaborates with the organizations at all levels: tools, algorithms, clinical domain, and training.

Components of the NA-MIC Kit are used globally. The software engineering tools of CMake, CDash, and CTest are used by many open-source projects and commercial applications. For example, the K Desktop Environment (KDE) for Linux and Unix workstations uses CMake and

CTest. KDE is one of the largest open source projects in the world. Many open source projects and commercial products are benefiting from the NA-MIC related contributions to ITK and VTK. The 3D Slicer version 3 was downloaded 13,913 times during the current reporting period. The 3D Slicer also is being used as an image analysis platform in several fields outside of medical image analysis, in particular, biological image analysis, astronomy, and industrial inspection.

NA-MIC science is recognized by the medical imaging community. There are 278 NA-MIC related publications listed on PubMed. Many of these publications are represented in the most prestigious journals and conferences in the field. Overall, there are 447 publications that acknowledge NA-MIC support. Portions of the DBP workflows and roadmaps already are being used by researchers in the broader community and in the development of commercial products.

NA-MIC sponsored several events to promote NA-MIC tools and methodologies. In 2010 alone, NA-MIC hosted 16 workshops and training sessions at 9 domestic universities. NA-MIC also extended its reach in the international arena with 9 international workshops and training sessions, including a workshop in Japan, a workshop in Switzerland, two workshops in the United Kingdom, and two workshops in China. Several of these workshops were held at international conferences including CARS, RSNA, and MICCAI. The workshops and training sessions are individually targeted to meet the specific needs and interests of clinicians, biomedical engineers, or algorithm developers. Six hundred and thirty-five clinical, biomedical, and algorithm researchers attended these events. Since 2005, one thousand five hundred and fifty-five clinical, biomedical, and algorithm researchers have been trained by NA-MIC.

4. DRIVING BIOLOGICAL PROJECTS

The current DBPs--Atrial Fibrillation, Huntington's Disease, Adaptive Radiotherapy for Head and Neck Cancer, and Traumatic Brain Injury--bring challenging problems in patient-specific analysis of images that represent opportunities for technical innovation in medical image analysis. A summary of progress since September 30, 2010, is provided for each DBP.

4.1 Atrial Fibrillation

Key Investigators
Rob MacLeod, PI, SCI University of Utah, Bioengineering
Josh Cates, Research Associate, SCI University of Utah, Computer Science
Allen Tannenbaum, Georgia Tech, NA-MIC Algorithms Core
Ross Whitaker, SCI University of Utah, NA-MIC Algorithms Core
Jim Miller, GE, NA-MIC Engineering Core
Host Institution: CARMA, University of Utah Health Sciences (www.carmacenter.org)

BACKGROUND

The aim of this DBP is to develop MRI-based techniques to treat and manage atrial fibrillation (AF), a growing clinical problem with enormous impact on quality of life, survival and healthcare costs. AF is the most common clinically significant cardiac arrhythmia and a significant risk factor for ischemic stroke. Approximately 15% of all strokes in the US are attributable to AF. Moreover, the prevalence of AF is rising. The number of persons who experience AF is projected to increase 2.5-fold through the year 2050. This increase is largely the consequence of an aging population, as prevalence of AF has been associated with both male gender and advanced age. Approximately 0.5% of patients develop AF in the 50 to 59 age group, whereas up to 9% have AF in the 80 to 89 age group.

Pathogenesis
The factors responsible for onset of AF include a trigger, an electrical impulse that causes the arrhythmia, and a substrate or permanent condition that sustains it. Triggers include sympathetic or parasympathetic stimulations, bradycardia, atrial premature beats or tachycardia, accessory AV pathways, and acute atrial stretch. In normal individuals, electrical impulses generated by the heart's pacemaker cells travel through the upper chambers of the heart (left and right atria). AF occurs when an extra electrical signal emerges, usually from the pulmonary veins (PV). The extra signal causes the electrical impulses inside the left atrium (LA) to rotate in a "wavelet." As a consequence, the LA fails to contract and this causes the left ventricle to beat rapidly and irregularly. Repeated episodes of AF lead to permanent tissue remodeling. The longer AF persists, the more tissue remodeling occurs, and the more difficult it is to restore sinus rhythm and prevent recurrence.

Treatment Options
Strategies for treatment also may involve (1) anticoagulant medication to prevent the formation of clots, (2) antiarrhythmic medication to control the rate of ventricular contraction, permitting sufficient time for the ventricles to fill with blood, (3) cardioversion to restore normal heart rhythm, permitting the atria and ventricles to work together, and (4) treating the underlying disorder (e.g., hyperthyroidism). Many of these strategies produce uncomfortable side effects and a lifelong burden of chronic medication. Some patients undergo an operation called the Maze procedure. This surgery is performed in conjunction with open heart surgery in patients who are being treated for other underlying heart problems, for example, valve surgery. It

involves a series of small cuts or burns in the atria that prevent the spread of disorganized electrical signals. It is applicable in a small subset of patients. The final option is catheter ablation which is the method under investigation by this DBP.

Catheter Ablation

Catheter ablation is an emerging noninvasive strategy that offers a permanent cure in 40-80% of patients and freedom from the necessity of lifelong medication. The inability to rapidly identify extent of lesion ablation immediately post-procedure, as well as subsequent to scarification, is an impediment to achieving approved success with this treatment modality. In this regard, MRI offers the most promising technology to overcome this obstacle. Rapid, automated image processing and analysis have been identified as the rate-limiting steps to the development of practical MRI-based therapies. At least two major obstacles to this treatment approach have been identified: (1) inability to distinguish which patients will (or will not) benefit from the procedure, and (2) inability to rapidly identify extent of lesion ablation immediately post-procedure and subsequent to scarification. Rapid, automated image processing and analysis have been identified as the rate-limiting steps to the development of practical MRI-based therapies.

Role of Imaging Modalities in Catheter Ablation of AF

The role of imaging in AF is to identify and mark structures (segmentation), measure structures, and quantify change in structures and function over time. Incomplete ablations around the roots of the pulmonary veins result in recurrence of AF after ablative treatment at great expense to the healthcare system and the patient. Our goal is to enable early post-ablation assessment of the extent of tissue destruction while the patient is still on the procedure table. This will allow the treating clinician to detect an incomplete ablation and do a second procedure during the same session, thereby ensuring a significantly higher success rate for the initial intervention. While improvements in image acquisition and quality have led to breakthroughs in the use of MRI for patients with AF, the bottleneck to widespread implementation now lies in the need for improvements in image processing.

Quantifying enhancement in patients

Processing each MR image set from a new patient requires extensive segmentation of organs and regions within organs. This process currently takes 2-3 hours of manual labor per case by an experienced technician. The results display large variance because of the subjective nature of crucial thresholds. To effectively deliver catheter ablation, the post-ablation analysis (i.e., rapid registration of pre- and post-ablation images, segmentation of the atria, identification of tissue changes from ablation, and interactive visualization of the heart and ablated regions) must be accomplished within 30 minutes, while the patient is still on the procedure table and available for adjustments. An integrated customized set of automated software tools for image processing and analysis, based on state-of-art 3D image processing, would dramatically improve all stages of patient management. The NA-MIC Kit, Slicer, and supporting algorithms form the basis for such development.

Delayed enhancement MRI sequence

Previously we described a noninvasive method of detecting and quantifying left atrial (LA) wall injury after pulmonary vein antrum isolation (PVAI).This method involves a 3D delayed-enhancement magnetic resonance imaging (MRI) sequence and novel processing methods. Controlled lesion delivery and scar formation within the LA are indicators of procedural success, but the assessment of these factors is limited to invasive methods. Noninvasive evaluation of LA wall injury to assess permanent tissue injury may be an important step in improving procedural success.

RESEARCH PROGRESS REPORT

Much of our initial progress has involved gaining exposure to and experience with the Slicer environment, evaluating its current segmentation and registration capabilities, and developing a close collaboration with the Georgia Tech group under Allen Tannenbaum to create advanced automated segmentation schemes. Progress on the first goal has included sharing of anonymized datasets to evaluate registration schemes within Slicer and exploration by developers on the CARMA team of the existing framework and algorithms.

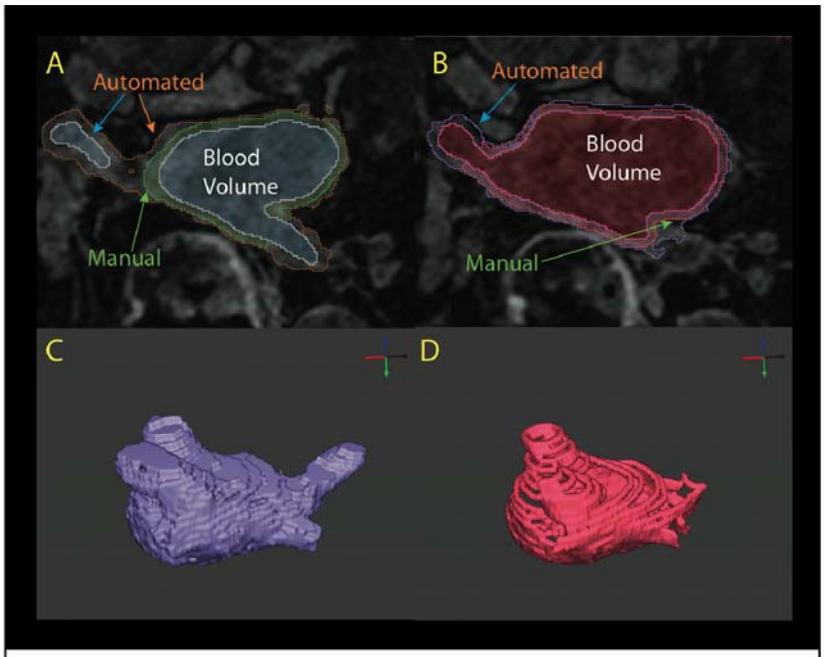

Figure 4-1. Comparisons of manual and automated segmentation of the endocardium (inner surface) and epicardium (outer surface) of the left atrium given an existing segmentation of the blood pool contained in the left atrium. Panels A and B show single slices with overlays of automated and manual epicardial and endocardial surfaces. Panels C and D show the complete segmentations for automated and manual approaches, respectively.

We have shared sample datasets with the Georgia Tech team for training and developing new level-set-based approaches that benefit from training using expert generated segmentations. The result has been new modules within Slicer, which have been tested on additional datasets outside those used for training. Figure 4-1, below, summarizes our early results. In general, automated segmentations included more volume, in part because they extended into the pulmonary veins and in part because of errors in the automated identification of atrial wall boundaries. The statistical results in Figure 4-2 support this overall rather poor agreement or overlap between the modalities. Results from the automated method did, however, show improved consistency between multiple segmentations of the same image set based on different blood pool segmentations than those from the manual method.

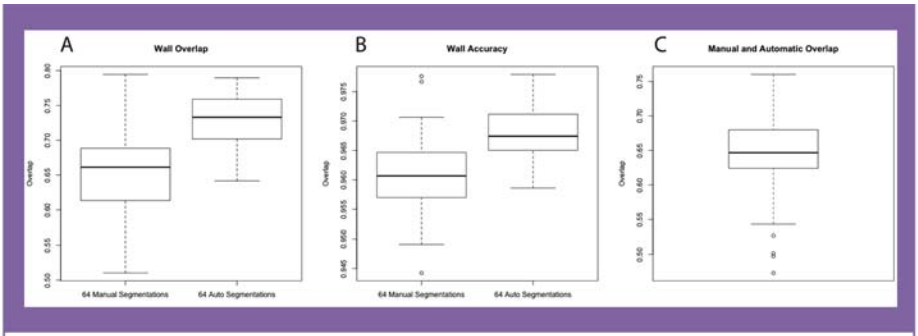

Figure 4-2. Statistical comparison of agreement within the manual and automated segmentations (Panels A and B) and overall agreement between the two approaches (Panel C).

Plans for the Coming Year

In year 2 we plan to continue with the development of automated approaches for segmentation, by: (1) constraining the segmentations to ignore pulmonary vein extension; (2) increasing the number of datasets available for training; and (3) exploring more specific constraints dictated by known features of atrial anatomy. We also plan to explore the development of Slicer based workflows for the segmentation processing of clinical images within the CARMA Center. We will identify overlap and differences with existing workflow and attempt to extend Slicer as needed to replicate the process, and evaluate the relative accuracy and efficiency of both approaches. In the area of registration, we will attempt to use Slicer for several projects aimed at merging sequentially obtained MRI image sets from the same patients, who typically undergo 3-6 separate scans over the time course of their diagnosis, treatment, and follow up. We will also explore the registration of previously acquired MRI images into the imaging space of the ablation procedures, comparing to industry standards (Biosense Webster CARTO system and St. Jude Medical NavX) for this process. The second year will also see the project fully staffed with developer (DIllon Lee) and graduate student (Gregory Gardner) so that a more consistent application and evaluation of Slicer capabilities will be possible.

Papers that Acknowledge NA-MIC

Because the DBP has been funded for less than a year, it has not generated any published papers that acknowledge NA-MIC.

Additional information is available on the NA-MIC wiki.
http://www.na-mic.org/pages/DBP:Atrial_Fibrillation

4.2 Roadmap Project: Huntington's Disease

Key Investigators
Hans Johnson, PI
Mark Sculley, Computer Science, University of Iowa
Jane S. Paulsen, Predict HD PI
Dan Marcus, NA-MIC Neuro-informatics Contact, Washington University
Martyn Stiner, NA-MIC Algorithms and Engineering Contact, UNC
Host Institution: The University of Iowa

BACKGROUND

The Huntington's Disease DBP brings an impressive dataset from the NIH-funded project "Neurobiological Predictors of Huntington's Disease" (PREDICT-HD) based at the University of Iowa. This NIH-funded study is investigating Huntington's disease (HD), a neurodegenerative genetic disorder that affects muscle coordination, behavior, and cognitive function, causing severe debilitating symptoms by middle age. The aim is to capitalize on two unique aspects of HD among neurodegenerative disorders—the ability to know in advance exactly who will develop the disease and the knowledge that all affected individuals have the same root cause (i.e., a CAG repeat expansion in the huntingtin gene). The Iowa investigators are collaborating with the Computer Science Core to develop new and refine existing tools to achieve the specific aims of the HD-DBP. The NA-MIC efforts will facilitate the DBP's needs to: (1) integrate data from multiple protocols for generating a set of measures that can be studied to explore the longitudinal inter-relationships between known areas of degeneration; (2) disseminate a well documented set of best practices and training events for the HD imaging community to empower collaboration; (3) deploy a common centralized data-sharing infrastructure (i.e., XNAT) that is well integrated with the training software and development practices necessary to gain access to new imaging methodologies.

Pathogenesis

Huntington's disease displays autosomal-dominant genetic transmission. The mutation that leads to Huntington's disease involves an excessive number of CAG repeats in exon 1 of the gene (*IT15*) that encodes the huntingtin protein (htt). Although generally regarded as a late-onset neurodegenerative disorder, in Huntington's disease the length of the repeat is inversely proportional to the age of onset of symptoms. Normal individuals have 6 to 35 repeats; whereas individuals with the dominant HD mutation have 36 to 121 repeats. Adult onset is usually observed with repeat lengths of 36-50. Juvenile onset, though more rare, is often seen with greater than 60 repeats. Death usually occurs 15-20 years after onset of symptoms.

Genetic testing can reveal which individuals have inherited the mutated gene. The ability to study early disease in individuals with a 99% certainty of manifesting symptoms later in life creates a valuable opportunity to study the natural history of the disease, as well as to support ongoing clinical trials that are investigating means to alleviate or reduce symptoms and slow the progression of disease in patients with clinically diagnosed HD.

Role of Imaging in Huntington's Disease

Diffusion-weighted MRI (dMRI) is often used to investigate progressive white matter changes during disease progression. This imaging modality is capable of detecting varying levels/changes of anisotropic diffusion *in vivo*. These diffusion changes reflect tissue integrity, which in turn, provides information about the disease state. The published knowledge on DWI in HD is based on smaller studies. To draw meaningful conclusions, a larger data pool is required.

Although it is possible to gather data at multiple sites simultaneously, technical problems arise when using different scanners that produce data which is incompatible with our computer processing software. To account for new types of subjects requires different assumptions in the analysis. The ultimate aim of studying brain atrophy in HD is to use this information for surgical planning. In this regard it will be necessary to acquire preoperative or even intraoperative DWI data. The rate limiting step is speed: We must have the ability to process DWI data faster.

In addition to morphometric gray matter measurements, diffusion tensor imaging (DTI) based fractional anisotropy measurements indicate that white matter changes occur very early in HD. The development of tools for DTI data hold great promise for identifying early disease markers suitable for measuring longitudinal trajectory changes over short time intervals. Tools for segmenting white matter based on the high-resolution 3T multimodal scans plus DTI data consistently identify white matter anatomical regions. Methods for white matter fiber tracking from DTI data can identify anatomically connected regions within a single subject. Longitudinal analysis of white matter changes will help identify cause/effect relationships of disease progression between cortex, white matter, and sub-cortical connected regions.

RESEARCH PROGRESS REPORT

To investigate longitudinal shape changes, extensive preprocessing must be carried out. BRAINS is a suite of morphometric processing tools created at the University of Iowa and represents the first step in the data processing required to examine shape changes over time. Over the past several months, substantial effort has gone into developing and improving cross-platform compatibility of the BRAINS tools and integrating those tools with 3DSlicer. In maintaining integration with 3DSlicer, the BRAINS Tools' test suite has been expanded to improve the discovery and correction of errors in the processing steps. As part of that error correction, fixes for underlying software such as ITK have been submitted back to the community.

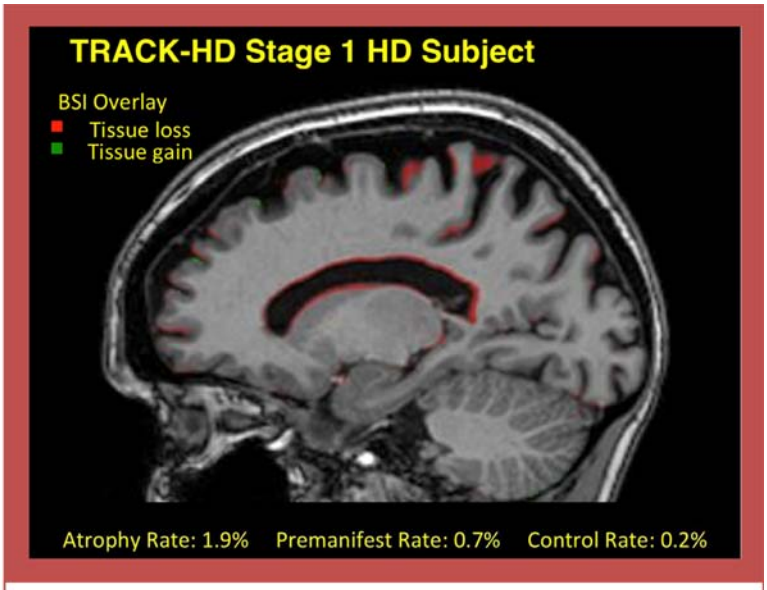

Figure 4-3. Image preprocessing demonstrated on an axial slice of brain demonstrates the areas where tissue has been gained or lost over a one-year period, as well as the atrophy rates for the different subject types.

An example of the shape change quantification possible after morphometric preprocessing can be seen in Figure 4-3. This image displays an axial slice of a patient's brain and demonstrates the areas where tissue has been gained or lost over a one-year period, as well as the atrophy rates for the different subject types.

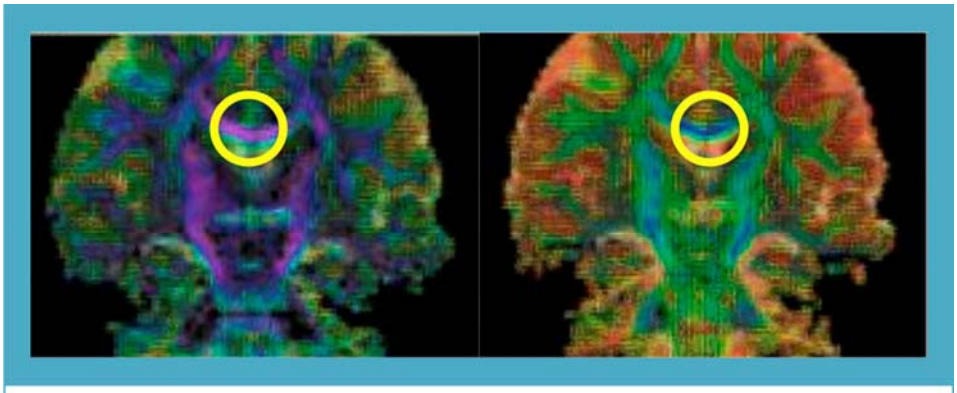

Figure 4-4. Improvements gained by using DicomToNrrdConverter.

The PredictHD project spans multiple sites, scanners, and scanner software versions. This introduces many data consistency issues. Two tools, DicomToNrrdConverter and DTIPrep, were created to compensate for those inconsistencies. DicomToNrrdConverter converts all the varieties of dMRI from the multiple sites in Predict into a standard format. DTIPrep identifies errors in the dMRI scans and corrects them if possible or removes them if not. An expanded testing suite was created for DicomToNrrdConverter and made available to the community to facilitate the rapid inclusion of support for previously unknown image types. Extensive quality assurance was performed on DTIPrep to ensure that it could operate correctly on all data in the PredictHD project.The improvements gained by using DicomToNrrdConverter are evident in Figure 4-4. This image demonstrates the difference in diffusion directions based on generating the gradients from the b-matrix instead of the standard tags. The image to the left is anatomically implausible, while the image to the right is correct.

To encourage further research into Huntington's disease, approval was granted to share the data collected by PredictHD. An XNAT instance has been deployed (https://predict.hd.net/xnat) to make a substantial subset of this data available to the research community, and an initial data set consisting of 81 subjects with sMRI, dMRI, and fMRI sequences is shared on this site. The groundwork accomplished over the past several months sets the stage for accomplishing the year 2 aims.

Plans for the Coming Year

Our major plans for year two include: (1) Use the results obtained from applying longitudinal shape change tools to existing data in order to improve those tools before applying to a larger cohort; (2) Incorporate the refined tool for longitudinal analysis of fiber tracts into workflow and apply to subjects with apparent pathologic changes; (3) Continue improving the XNAT instance's ability to deal with diverse data types while incorporating the PREDICT-HD specific workflows into XNAT.

Papers that Acknowledge NA-MIC

Because the DBP has been funded for less than a year, it has not generated any published papers that acknowledge NA-MIC.

Additional information is available on the NA-MIC wiki.
http://www.na-mic.org/pages/DBP:HD

4.3 Roadmap Project: Adaptive Radiotherapy for Head and Neck Cancer

Key Investigators
Gregory C. Sharp, PI, Massachusetts General Hospital
Allen Tannenbaum, NA-MIC Algorithms, Georgia Tech
Polina Golland, NA-MIC Algorithms, MIT
Steve Pieper: NA-MIC, Engineering, Isomics
Host Institution: University of North Carolina

BACKGROUND

Head and neck cancers account for about 60,000 new cancer cases per year and represent 4-6% of all cancers in the United States. Sixty percent of patients present with advanced disease. The five-year survival is approximately 50%. These cancers are treated by a combination of chemotherapy, radiotherapy, and surgery. During a six-week regimen of radiotherapy, head and neck cancer patients often exhibit anatomic changes that affect their treatment. These changes include tumor regression or growth, changes in lymph node size, and changes in air cavities. Left uncorrected, these changes can increase the risk of treatment complications or reduce treatment efficacy.

Adaptive radiotherapy addresses the problem of anatomic change by incrementally adjusting the radiotherapy plan. It is a prime example of personalized medicine. A mid-treatment adjustment is complex, requiring a new CT image, image segmentation, deformable registration, and mapping of the previously delivered dose onto the new image. This project proposes to use the NA-MIC Kit to develop a simple, practical workflow for achieving adaptive radiotherapy which can be applied on a case-by-case basis.

Role of Imaging in Adaptive Radiotherapy

Biology of radiation therapy
Ionizing radiation, such as photons or charged particles, creates ionized atoms and molecules as it travels through matter. Energy is transferred from the incident radiation beam to the aqueous solution within a cell, which creates free radicals. The most important of these radicals, the hydroxyl radical (OH*), indiscriminately attacks neighboring molecules and binds with them in a chemical reaction. A radiation beam of high intensity will create a large number of these radicals, which bind with nuclear DNA in a cell, thereby breaking the deoxyribose backbone of the DNA molecule. When both DNA strands are broken, the cell can no longer reproduce itself, and therefore can no longer proliferate as cancer.

Proton Therapy
Proton-beam radiotherapy operates on the same biological principles as traditional photon-beam treatments, but the physical properties are quite different. When a photon interacts with

matter, it delivers most of its energy locally, and the beam is attenuated exponentially as the number of photons is reduced with depth. In contrast, each proton has many interactions as it travels through matter, and it loses a little energy with each interaction. When it has lost almost all of its energy, the proton stops and delivers its entire remaining dose. This means that protons are an effective technique for sparing healthy tissues distal to the tumor, which reduces radiation-related side effects.

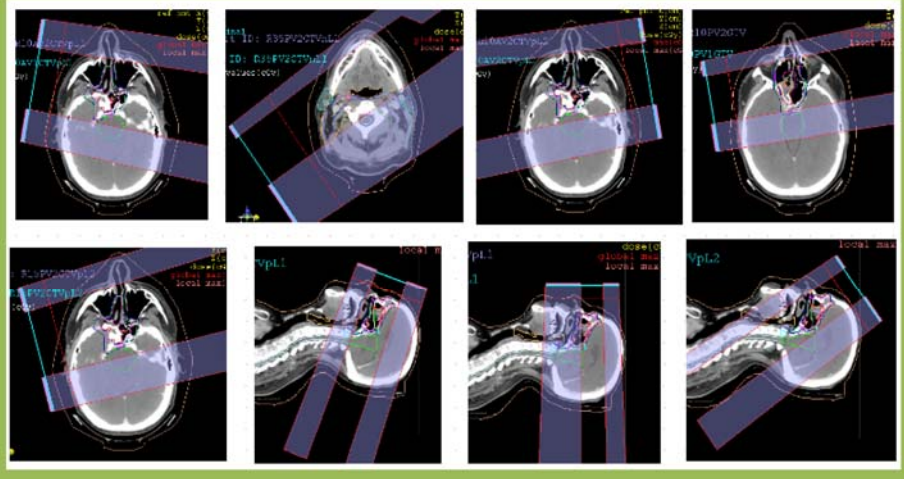

Figure 4-5. Beam arrangement for proton radiotherapy in the base of skull. A typical plan consists of about 15 beams.

Figure 4-5 shows a selection of beams for a proton-beam treatment to the base of skull. In a typical plan, approximately 15 beams are used to cover both the primary target and the tumor spread into the lymphatic system. The highest dose is at the site of the primary tumor where the beams intersect.

RESEARCH PROGRESS REPORT

Clinical

Over the past several months, retrospective clinical data have been collected, de-identified, and shared with NA-MIC collaborators. Two datasets have been collected: a smaller set of six patients for the study of intra-subject registration and segmentation, and an additional dataset consisting of thirteen patients for the inter-subject study. The intra-subject dataset contains for each patient a pre-treatment CT, a mid-treatment CT, physician-labeled structures on the pre-treatment CT, and a radiotherapy plan with radiation dose. The additional inter-subject dataset contains a pre-treatment CT and physician-labeled structures. There remains some additional work to perform quality assurance on the physician-labeled data and to label structures that are missing in some scans.

The data management methodology for the adaptive radiotherapy study has been designed and implemented. First, the pre-treatment CT is aligned with the mid-treatment CT using rigid registration to remove setup error. Second, deformable registration with B-splines is performed between the two CT scans. This allows us to transfer the physician's manually labeled structures from the pre-treatment CT onto the mid-treatment scan, which is not normally

labeled. Third, the beam data from the original treatment plan are copied onto the rigidly transformed mid-term CT and a new dose distribution is computed. Fourth, the original dose distributions are transferred from the pre-treatment CT to the mid-treatment CT using the deformable registration results. Finally, the new dose distribution is compared with the original planned dose, and the dose difference is evaluated.

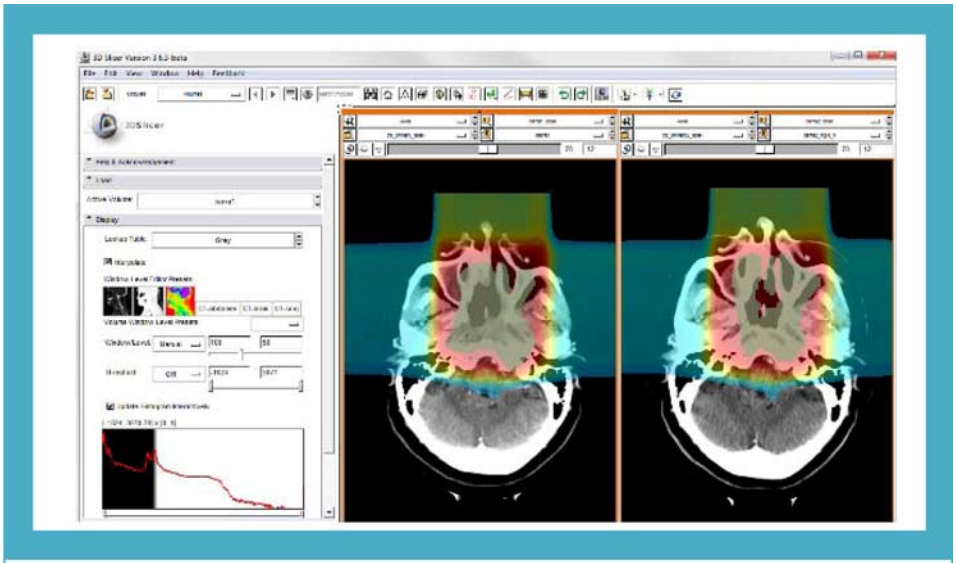

Figure 4-6. Visualization of radiotherapy structures and dose in 3D Slicer

An example of the method application for one patient is shown in Figure 4-6. On the left is an axial view of a slice of the planning CT with the primary CTV shown in brown and the dose distribution shown in rainbow colors. On the right is the mid-term CT with CTV transferred from the planning CT and recomputed dose distribution. At this time, rigid registration, deformable registration quality assurance, and visualization of results are performed within the NA-MIC environment.

Algorithms

During this year, we investigated the use of a non-parametric approach to segmentation to delineate anatomical structures in pre-treatment scans. The inference algorithm used to decide on the segmentation labels relies on pairwise registrations between the test image and individual training images. The training labels are then transferred to the test image and fused to compute the final segmentation of the test subject. Such label fusion methods have been shown to yield accurate segmentation, since the use of multiple registrations captures greater inter-subject anatomical variability and improves robustness against occasional registration failures. We use affine alignment followed by a non-rigid log-domain diffeomorphic variant of the Demons algorithm. In application to the pre-treatment CT images, we observed reasonable quality of alignment of anatomical structures across subjects and a promising accuracy of the resulting segmentations. We are currently refining the algorithms and preparing a manuscript for submission.

We have worked on problems concerning segmentation and registration for the adaptive radiotherapy project with our MGH partners. We have proposed a sequential method to estimate a shape prior using previously segmented structures as landmarks. It is founded on

probabilistic principal component analysis and probabilistic canonical correlation analysis. We derive equations in order to utilize these techniques for prediction. At a given stage in a sequence of segmentations, this approach predicts the most likely shape of the structure being segmented based solely on the segmentations of completed structures. Hence, the shape prior is independent of the image information around the target. This is applied to the problem of adaptive radiotherapy in oncology. Structures of interest in the head and neck region have insufficient image information and strictly image based approaches fail. Such cases also present major problems for methods that simultaneously perform segmentation and fitting of a shape model to image data. The strength of our method is the flexibility that it provides to the user in determining what image information to trust. We have demonstrated our technique on datasets that are illustrative of real-world data for our applications in volume and in variance. Finally, we have been applying optimal mass transport ideas to the elastic registration problem for CT and MRI data for radiation planning as part of this project.

Plans for the Coming Year

Our major plans for year two include: (1) Validation experiments with image registration algorithms to validate their accuracy and reliability; (2) Design and implement plan review tools within 3D Slicer, especially isodose lines and dose volume histogram analysis; (3) Implementation of dose warping within 3D Slicer; (4) Experimentation and prototyping of automatic image segmentation methods.

Papers that Acknowledge NA-MIC

Because the DBP has been funded for less than a year, it has not generated any published papers that acknowledge NA-MIC.

Additional information is available on the NA-MIC wiki
http://www.na-mic.org/pages/DBP:Head_and_Neck_Cancer

4.4. Roadmap Project: Traumatic Brain Injury

Key Investigators
Jack Van Horn, PI, UCLA
Guido Gerig, NA-MIC Algorithms, Utah and SCI Institute
Stephen Aylward, NA-MIC Engineering, Kitware
Host Institution: UCLA

BACKGROUND

Traumatic brain injury (TBI) is a major health care and research challenge. Each year there are 1.7 million new cases of TBI, fully half are considered mild. Severe, or long-term brain injury, results in 650,000 hospitalizations each year. Known as the ‘silent epidemic,’ these cases are associated with unresponsiveness, coma, brain death, and eventually death. The cost to society is enormous. The estimated cost is $48 billion in case management and loss to the US workforce. Many of these injuries occur during motor vehicle accidents and incidents at the workplace. Returning war veterans are also particularly affected.

The neurobiology of TBI is poorly understood. It is common for these patients to acquire other conditions, including TBI-related epilepsy, paralysis, memory loss, and so forth. Attempts to

define strategies for treatment in over 85 trials have been uniformly unsuccessful. There remain few treatment options and no proven methods for rehabilitation, only management. The CDC estimates the lifetime cost of managing a patient with TBI to be approximately $1 million per case. (http://www.cdc.gov/TraumaticBrainInjury/tbi_concussion.html)

Role of Imaging in TBI

Patients with traumatic brain injury at specialized trauma centers like UCLA undergo a long series of brain imaging studies in the course of their treatment. The first CT is taken in the emergency room. CT provides important information about the initial extent of injury. Neurological parameters are measured including mass lesion (subdural, epidural), midline shift, asymmetry, swelling, compression of subarachnoid space, change of ventricle size. A follow-up CT is typically performed 24 hours to 3 days after the injury.

After a period of time, patients at our institution participate in a study involving MRI scanning as well as other techniques to show whether the patient is continuing to bleed and if there is active swelling. Multiple MRI parameters including T1, TSE, FLAIR, etc., provide information about brain sacrifice and blood signature (i.e., toxic, midline shift). DT-MRI and DW-MRI studies that are sensitive to white matter changes provide information about the extent of axonal injury. These scans show axons that have become disconnected or stretched and indicate the magnitude of shearing forces associated with the injury. At approximately six months, patients undergo follow-up scanning and longitudinal assessment of their injury to assess the level of residual damage as well as the number of changes over time.

Problems under investigation

Few non-commercial software tools are available to help clinicians analyze and solve problems of quantitative analysis and visualization. Problems on which there has been significant progress up to this point include data processing challenges, problems recognizing acute versus chronic phases of traumatic brain injury, establishing the means of performing more sensitive quantification of change, and determining extent of cortical and ventricular injury, amount of white matter injury and axonal damage, and the means of associating change TBI morphometry over time with clinical outcome.

To date, the UCLA team has successfully performed co-registration of several baseline and follow-up TBI volumes, classification of healthy and injured tissues, as well as longitudinal analysis of TBI cases. Specifically, we have introduced the combined use of multimodal TBI segmentation and longitudinal analysis using 3D Slicer. For three representative TBI cases, semi-automatic tissue classification and 3D model generation have been performed to assess longitudinal TBI evolution using multimodal volumetrics and clinical atrophy measures. Identification and quantitative assessment of extra- and intra-cortical bleeding, lesions, edema and diffuse axonal injury was also performed. 3D Slicer tools have been used to perform cross-correlation of multimodal metrics from structural imaging (structural volume, atrophy measurements, etc.) and with clinical outcome variables (time since injury, age, gender, etc.) and other potential factors predictive of recovery.

3D Slicer workflows have been found to be suitable for TBI clinical practice and patient monitoring, particularly for assessing damage extent as well as for the measurement of neuroanatomical change over time. With knowledge of general location, extent, and degree of change, such metrics computed in 3D Slicer can be associated with clinical measures and subsequently used to suggest viable treatment options for individual subjects against patterns

that are typical of TBI populations. Thus, the methodology that has been demonstrated up to this point using the 3D Slicer platform has the potential for significant impact on the state of the art in TBI neuroimaging as well as on the added benefit of TBI neuroimaging techniques from the standpoint of clinical monitoring, diagnosis, and treatment.

Although the UCLA team is only 8 months into the first year of participating in the NA-MIC project, we have not only already fulfilled all of our specific aims for Year 1, but also have made a significant amount of progress beyond these aims.

3D Slicer as a software platform

To address the urgent need for clinician-friendly TBI analysis tools, we have combined the use of multimodal, semi-automatic TBI analysis methods within 3D Slicer. To showcase the ability of the UCLA team to perform quantitative longitudinal analysis of TBI in 3D Slicer, we have analyzed three cases of semi-automatic TBI volume segmentation and 3D brain model generation while also highlighting the added clinical insight which 3D Slicer can offer.

Slicer 3 has the capability of providing visual assessment of multimodality imaging of 3D fiber tracts and morphometry. It provides the possibility for potential identification of specific targets for neurological testing enabling the clinician or researcher to deploy tests based on hypotheses derived from image analysis. Ultimately, through a more principled approach, quantitative assessments can be made.

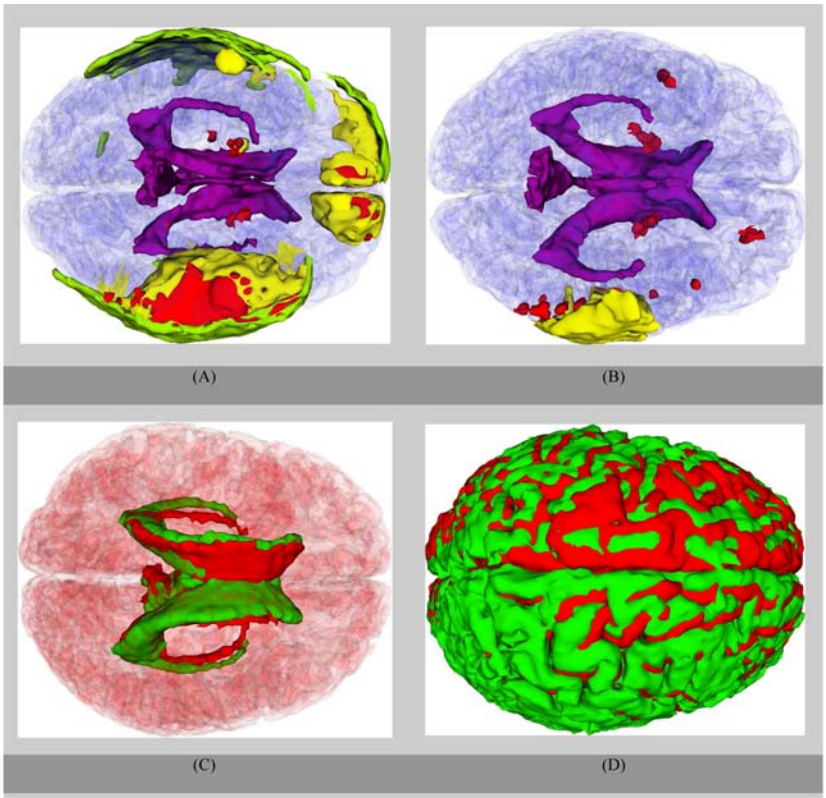

Figure 4-7. Gray matter - blue (transparent); ventricular system - purple; extracerebral lesions - green; nonhemorrhagic cerebral lesions - yellow; hemorrhagic cerebral lesions - red.

Figure 4-7 shows a segmentation of acute baseline (A) and chronic follow-up (B) volumes for a TBI patient admitted to the Ronald Reagan Medical Center. Subfigures (C) and (D) illustrate a longitudinal comparison of the ventricular system (C) and gray matter (D) volumes in the same patient. Shown are volumes corresponding to the acute baseline (red) and chronic follow-up (red) volumes. In (C), the difference in ventricle locations is caused by a compression and shift of the ventricles as a result of left temporal lobe swelling. In (D), swelling of the left hemisphere is apparent in the acute baseline compared to follow-up because the red surface (baseline) lies above the green surface (follow-up).

Examples of lesion and ventricle segmentation are shown in Figure 4-8. In (A), the MR images are also shown. This figure showcases Slicer's ability to visualize both intra- and extra-cortical lesions. (B) shows subdural swelling and hemorrhage, as well as intracerebral lesions with a transparent version of the gray matter volume included as well. The primary lesion is located in the left temporal lobe, although some injury is also apparent in the frontopolar area. (C) shows gray matter (transparent), ventricles, and a large WM-GM lesion in the left temporal lobe. Swelling of the meninges is also evident. (D) Use of 3D Slicer allows one to compare lesion shape and size both in the acute and follow-up scans. Swelling and bleeding present at acute baseline (green, red, respectively) is not apparent at follow-up, where a lesion of much smaller size (purple) is visible instead. 3D Slicer allows volumetric and surface-based characterization of these lesions, as well as longitudinal comparison.

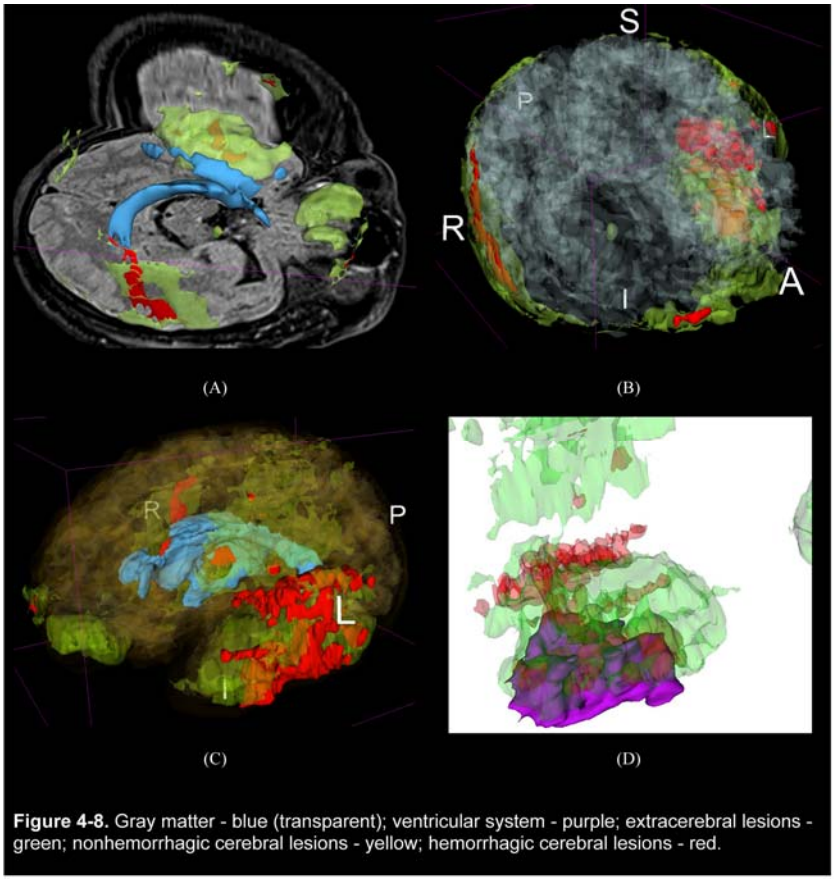

Figure 4-8. Gray matter - blue (transparent); ventricular system - purple; extracerebral lesions - green; nonhemorrhagic cerebral lesions - yellow; hemorrhagic cerebral lesions - red.

Over the past 8 months, the UCLA team has developed a sophisticated protocol for image segmentation and model generation, which has been applied to three representative TBI patients with spectacular results. This standard protocol has been confirmed to be optimal for TBI case analysis in 3D Slicer. Specifically, brain lesions adjacent to CSF were segmented from volumes acquired using FLAIR, GRE imaging, TSE T2-weighted volumes as well as DWI. Because SWI is generally superior to GRE and T2-weighted imaging to detect hemorrhagic lesions, volumes acquired using the former modality were used to identify micro-hemorrhages. Images that were additionally available in the context of our protocol were used to confirm segmentation accuracy as well as to illustrate the additional capabilities of 3D Slicer to segment images from a variety of MR datasets and combination of sequences.

Throughout the past several months, the UCLA team has demonstrated the usefulness of semi-automatic segmentation tools available in 3D Slicer software, including the Atlas Based Classification (ABC) segmenter. As opposed to other specialized segmenters where access is often restricted from outside users, the ABC segmenter is freely available as a segmentation module in 3D Slicer. The method is automatic, its execution requires minimal user supervision, and its appropriateness for TBI case analysis is excellent. In addition, the ABC segmenter possesses the ability to perform co-registration of an arbitrary number of MR volumes acquired using various sequences. This makes ABC highly suitable to the UCLA multimodal TBI imaging paradigm, where as many as 12 distinct sequence types are employed in the context of a sophisticated TBI analysis protocol.

At UCLA, tissue-type segmentation has already been used to calculate the total volumes of selected structure types (ventricular system, non-hemorrhagic lesions, and hemorrhagic lesions, white matter and gray matter). Volume changes have been computed as the ratio of the difference in volume between the follow-up and acute baseline time points, to the volume at the latter time point. In addition to these measures, the UCLA team has also computed five measures of atrophy, namely the bifrontal index, the bicaudate index, Evan's index, the ventricular index, and Huckman's index. These measures as computed in Slicer have been found to be in excellent agreement with previous results available in the TBI literature.

Algorithms

TBI lesion infiltration/recession estimation: Standard image registration methods do not account for changes in image appearance. Hence, metamorphosis approaches have been developed which jointly estimate a space deformation and a change in image appearance to construct a spatio-temporal trajectory smoothly transforming a source to a target image. For standard metamorphosis, geometric changes are not explicitly modeled. We have developed a geometric metamorphosis formulation, which explains changes in image appearance by a global deformation, a deformation of a geometric model, and an image composition model. This work is motivated by the clinical challenge of predicting the long-term effects of traumatic brain injuries based on time-series images. This work is also applicable to the quantification of tumor progression (e.g., estimating its infiltrating and displacing components) and predicting chronic blood perfusion changes after stroke. Figures 4-9 and 4-10 illustrate the utility of the method using time-series clinical scans from a traumatic brain injury patient.

Sliding geometries in deformable image registration: In deformable image registration, regularization is commonly used to encourage plausible displacement fields and has a significant impact on the derived correspondences. Sliding motions complicate the registration of multi-structure images because many regularization methods enforce a global smoothness constraint and produce errors at the boundaries between sliding objects. We present a spatially-

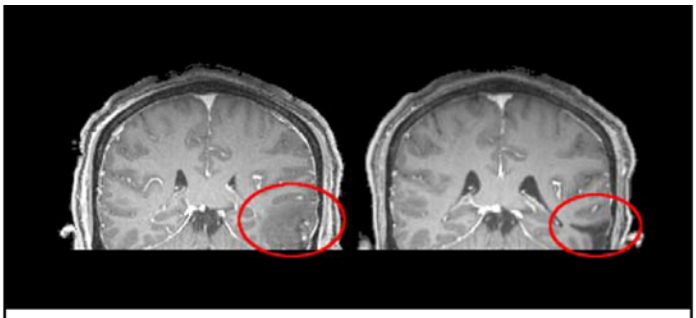

Figure 4-9. MP-RAGE, post-contrast MRI scans from TBI. *Left:* Initial Scan. *Right:* Eight months after initial scan. Rigidly registered. 1x1x1mm voxels.

varying regularization that handles sliding objects having locally-planar and tubular geometries. The regularization allows discontinuities to develop in the displacement field at sliding interfaces and increases the independence with which regions surrounding different geometric structures can behave. We anticipate that supporting sliding boundaries will be critical for longitudinal registration of TBI data for registration healthy anatomic atlases to TBI cases. We are presenting a paper at the ISBI in April, [Pace, 2011] which shows that, for data from an abdominal phantom, our geometry conditional deformable registration performs as well as the diffusive regularization with respect to image match, while producing more realistic correspondences that may better reflect the underlying physical motion. Work is under way to apply this directly to TBI data.

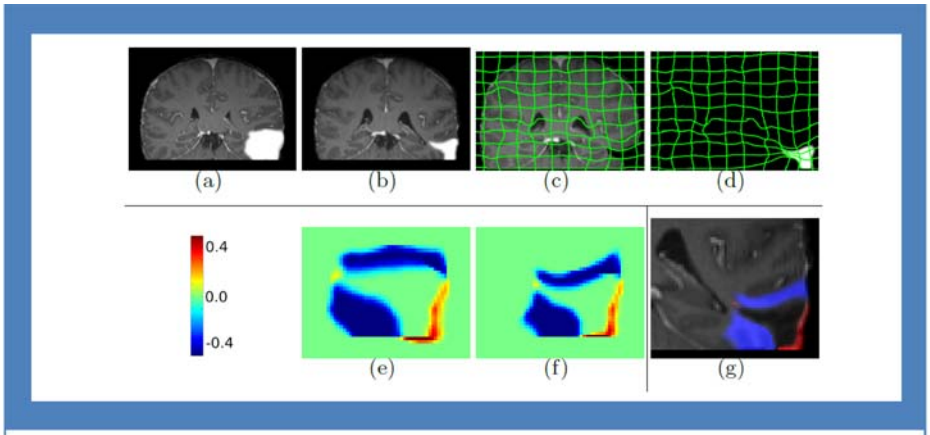

Figure 4-10. TBI Results. *Top:* (a) Initial scan with lesion segmentation overlaid. (b) Second scan with lesion segmentation overlaid. (c) Global deformation estimation. (d) Global deformation plus estimated lesion-specific shape change. Difference in lesion shape between global deformation and lesion-specific deformation is an indication of lesion infiltration/ recession. *Bottom:* (e) Difference shown in the source image coordinate frame. (f) Difference shown in the target image coordinate frame. (g) Estimated infiltration (red) and recession (blue) of the lesion.

In conclusion, over the past 8 months, the TBI DBP has used Slicer 3 to perform multimodal data fusion (linear co-registration, segmentation using ABC, etc.) and tissue classification with normal atlas prior and deformable (fluid) atlas to subject registration. Segmentation involving lesions, bleedings, and shunts has also been performed.

Plans for the Coming Year

Currently, we are interacting with the team at the University of Utah to address the following goals:

- User-guided seeding to perform high-throughput segmentation and characterization of lesions, edema, and other pathological features,
- Advanced tools for longitudinal structural comparison, including white matter fiber comparison,
- Automatization of the process to create quantitative clinical reports.

Papers that Acknowledge NA-MIC

Because the DBP has been funded for less than a year, it has not generated any published papers that acknowledge NA-MIC.

Additional information is available on the NA-MIC wiki
http://www.na-mic.org/pages/DBP:TBI

5. COMPUTER SCIENCE CORE

Overview
The scope of NA-MIC activities includes both highly speculative explorations of new mathematical formulations of core image analysis techniques *and* the ongoing effort of delivering and supporting binary distributions of software applications across a range of computing platforms. To address this continuum, NA-MIC Computer Science Core efforts are organized around two teams: Algorithms and Engineering.

Algorithms The Algorithms team provides computational methods that support patient-specific analysis of medical images. The clinical data presented by the DBPs involve sequences of images of individuals with distinct anatomy, pathology, and function. This requires analysis of images that vary significantly from one patient to another, or from one time point to another, in ways that present distinct challenges to existing state-of-art image analysis algorithms. These technical challenges will be addressed using four computational approaches: (1) Statistical models of anatomy and pathology; (2) Geometric correspondence; (3) User interactive tools for segmentation; and (4) Longitudinal and time-series analysis.

Engineering
The objective of Engineering is to provide software tools and software development processes to deploy innovative technology to clinical researchers, support the scientific algorithms innovation of the Algorithm scientists, and to foster a community to produce high quality software. The specific aims of this Core reflect the maturation of the NA-MIC community, the capabilities of the current 3D Slicer platform and NA-MIC Kit, and the changing needs of the

Algorithm team and DBPs as NA-MIC pursues *personalized medicine* through the patient-specific analysis of images. Specifically, these aims are: (1) Architecture; (2) End-user platform; (3) Computational platform; (4) Data management platform; (5) and Software engineering and software quality.

5.1 Algorithms

Key Investigators
Martin Styner, UNC
Polina Golland, MIT
Guido Gerig, Utah
Allen Tannenbaum, Georgia Tech
Ross Whitaker, Utah

Over the past 8 months, the algorithms scientists have been evaluating the challenges and needs of the individual DBPS. In addition to evaluating existing algorithms, our team has been investigating the application of four approaches: (1) Statistical models of anatomy and pathology; (2) Geometric correspondence; (3) User interactive tools for segmentation; (4) Longitudinal and time series analysis. The challenges of subject-specific image analysis include the need for rapid, efficient algorithms and flexible workflows for managing large sequences of images from the same patient, pronounced individual pathologies, and conditions that produce subject-specific anatomies with high geometric variability.

A. Statistical Models of Anatomy and Pathology

Statistical models play an important role in virtually all types of advanced algorithms in medical image analysis. Recently, a great deal of progress has been made by using modeling approaches that systematically capture the statistics of a problem domain from a collection of examples and then use these statistics to interpret novel images. Examples include the use of probabilistic atlases in the Bayesian segmentation strategy of the EM-Segmenter and knowledge-based priors in a Bayesian context. Another class of methods uses statistical shape priors in the form of active shape and appearance models and shape-based descriptors such as spherical harmonics or spherical wavelets. Recently, in the computer vision literature, scenes or configurations of objects have been modeled with stochastic grammars. Many of the state-of-art methods in medical image analysis rely on relatively simple parametric distributions, such as multivariate Gaussians. Learning is therefore reduced to estimating a small number of parameters, e.g., the mean and the modes of variation of the Gaussian distribution.

Unfortunately, large, inherently nonlinear anatomical variations in heterogeneous populations cannot be captured accurately by traditional parametric models. For instance, the changes in the surrounding anatomy induced by a tumor cannot be represented as small, continuous deviations from a mean. Likewise, the positions of organs in a highly deformable anatomy, such as abdomen, do not form small variations around a mean value. Thus, there is a need for more sophisticated models to adequately address problems in personalized medicine. The challenge of developing and using statistical models is the necessary balance between the expressiveness of the model and the ability to robustly learn the appropriate parameters from limited sets of examples and to apply these models.

The use of statistical models will address the needs of the DBPs in several ways. Our research in statistical modeling from images will lead to practical algorithms directly relevant to the clinical problems of the DBPs. Specifically, we will develop models that can handle the severe effects of

traumatic brain injury (TBI) on intensity and shape of brain structures, the differences in anatomical images induced by changes in the tumor and surrounding structures in the course of radiation treatment, the changes in heart images that result from fibrosis and remodeling (before and after ablation), the effects of lesions on white matter connectivity, and the longitudinal change due to brain tissue degeneration in brain disorders such as Alzheimer's and Huntington's disease.

Progress for Aim 1 has addressed several challenges.

Nonparametric Priors for Segmentation: We have proposed and demonstrated a nonparametric, probabilistic model for the automatic segmentation of medical images, given a training set of images and corresponding label maps. Such label fusion methods have been shown to yield accurate segmentation, since the use of multiple registrations captures greater inter-subject anatomic variability and improves robustness against occasional registration failures. We developed the first comprehensive probabilistic framework that rigorously motivates label fusion as a segmentation approach. The proposed framework allows us to compare different label fusion algorithms theoretically and practically. We demonstrated the method on a large collection of brain images, achieving state-of-the-art segmentation accuracy and identifying atrophy trends correlated with age [Sabuncu, 2010]. We also applied this algorithm to segment the left atrium of the heart. Automatic segmentation of the heart's left atrium offers great benefits for planning and outcome evaluation of atrial ablation procedures. This algorithm demonstrated accurate automatic segmentation that was robust to the high anatomical variations in the shape of the left atrium in a clinical dataset of MRA images (Figure 5-1) [Depa, 2010]. More recently, we have developed a fast computational scheme, which relies on efficient, approximate bipartite feature-matching from the computer vision literature. This scheme allows us to perform very fast, shape-based lookups of nearest neighbors in large sets of images.

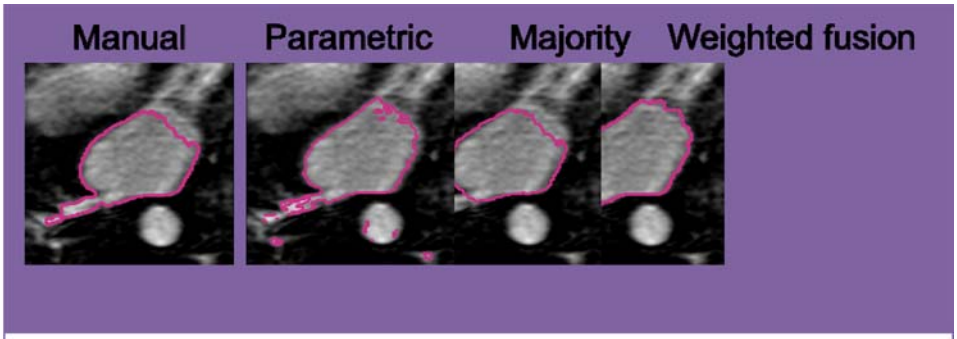

Figure 5-1. Left atrium segmentation

Latent Priors for Segmentation: Spatial priors, such as probabilistic atlases, play an important role in MRI segmentation. However, the availability of comprehensive, reliable and suitable manual segmentations for atlas construction is limited. We developed a method for joint segmentation of corresponding regions of interest in a collection of aligned images that does not require labeled training data [Riklin-Raviv, 2010]. On the basis of this same idea, we developed a generative probabilistic model for segmentation of tumors in multi-dimensional images (Figure 5-2). The model allows for different tumor boundaries in each channel, reflecting difference in tumor appearance across modalities. We augmented a probabilistic atlas of healthy tissue priors

with a latent atlas of the lesion and derived the estimation algorithm to extract tumor boundaries and the latent atlas from the image data.

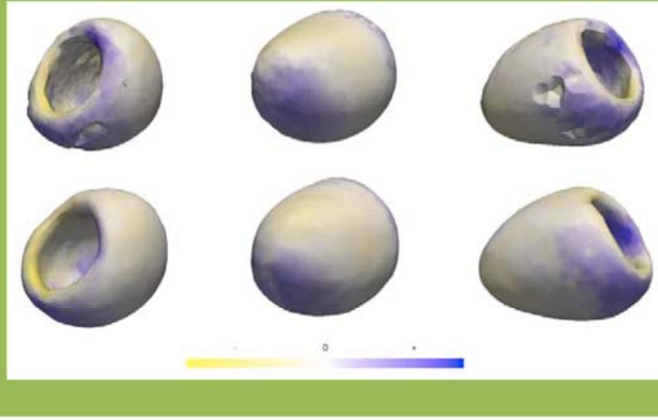

Figure 5-2. Group comparisons, mapped as colors on mean shapes, show significant differences in shapes of the left ventricle between normal controls and patients with ischemia.

B. Geometric correspondence

Establishing anatomical correspondences between pairs of patients, groups of patients, patients and templates, and individual patients over time is important for automatic and user-assisted image analysis. Typically, we consider geometric correspondence problems to be one of two types: image registration, which estimates dense correspondences and coordinate transformations between images; and set-correspondence, which determines geometric mappings between sparse or lower dimensional sets of data such as points, curves, surfaces, etc. As with statistical models, state-of-art approaches typically rely on assumptions about geometric mappings or transformations, such as smoothness or inevitability, which make the analysis and computation more tractable. However, in applications that entail pathologies and thus more deformable anatomies, collections of anatomical objects can have very different shapes, topologies, and intensity boundary profiles. The ability to establish geometric correspondences, with and without expert guidance, in challenging clinical circumstances is essential for the DBPs. For example, to evaluate a patient with traumatic brain injury relative to a model (statistical or otherwise), we will need to identify anatomy in the presence of large displacements and missing parts of organs and tissues, as well as dramatic discrepancies in intensity or signal. In the case of radiation treatment planning for head and neck cancer, the patient's pose can dramatically affect the relative positions of tissues and organs. Likewise, the physicians who manage cardiac fibrillation have requested comparisons of heart images taken before and after treatment and remodeling. Developments in geometric correspondence have focused on several challenges.

For surface correspondence, we have made developments on the software packages SPHARM and ShapeWorks. The SPHARM-based shape analysis toolbox developed in the previous NA-MIC years was extended into a full 3D Slicer module incorporating QC visualizations of both the geometric correspondence as well as the derived statistics. Shape studies are ongoing at

several labs that are performing shape studies for the first time, thanks to the availability of this tool. Some studies in brain pathology [Looi, 2010, Walterfang, 2011] and in cranio-maxillofacial surgery [Paniagua, 2010a; Paniagua, 2010b] have already been published.

ShapeWorks, which finds discrete point-based correspondences on surfaces by minimizing entropy, is being moved to NITRC, where it will undergo development from both UNC and Utah groups. This technology is currently being incorporated into the Slicer shape toolkit, and it has been used for cortical correspondence in our Slicer cortical thickness module GAMBIT. Technological developments for ShapeWorks include a method of particles interacting (distributing) on surfaces that relies on geodesic distances. Conventionally, geodesic distances are computationally expensive and therefore prohibitive in an optimization context. However, a recently developed fast, GPU-based eikonal solver for unstructured meshes allows us to precompute distances on a dense set of mesh vertices and interpolate these distances on the fly as particles move and interact. Figure 5-2 shows an application of this technology to the left ventricle.

We have also made progress on extending image-registration methods to address specific needs of the DBPs. For instance, in the context of the Huntington's disease DBP, we performed a study of the performance of DTI registration algorithms in the presence of low signal-to-noise settings as well as white matter pathology [Wang, 2011]. Our results showed that full tensor registration outperforms scalar DTI property registration methods both in regional as well as DTI fiber tract based evaluation criteria. We are also developing fundamentally new technologies for registration. For instance, image registration is typically formulated as an optimization problem with multiple tunable, manually set parameters. We have proposed a principled framework for learning thousands of parameters of registration cost functions, such as the spatially varying tradeoff between the image dissimilarity and regularization terms. Our approach belongs to the classic machine learning framework of model selection by optimization of cross-validation error. This framework allows for a systematic adaptation of generic registration cost functions to specific applications by learning the "free" parameters in the cost functions. We have evaluated the method in the context of localizing underlying cytoarchitecture and functional regions in the cerebral cortex by alignment of cortical folding and demonstrate state-of-art localization results in both histological and functional magnetic resonance imaging datasets (Yeo, 2010).

C. User Interactive Segmentation

Despite many important advances in medical image processing, most projects on the cutting edge of clinical research still rely on the time-consuming process of segmenting objects of interest in a three-dimensional dataset one slice at a time. Thus, advanced image analysis technologies that better leverage expert user interaction are imperative in patient-specific image analysis. Our goal is to develop methodologies for image segmentation that can be used in settings where the heterogeneity and variability of anatomy and pathology impedes the immediate construction of conventional high level statistical models, but where users can see the structures of interest by observing contrast, lines, shapes, textures, etc.

The field of computer vision has addressed the issue of user-assisted segmentation, mostly in terms of image partitioning or contours. Examples of such general purpose techniques include parameter-based active contours or snakes, curvature flows implemented via level-sets, variational formulations, the live-wire method, label spaces, and diffusion and graph-cut methods. Virtually all of these methods are formulated as either geometric or statistical optimizations. Despite all of these developments, the typical segmentation problem in medical

imaging is still largely solved by hand contouring, although new tools with intuitive user-guidance for 3D level-set segmentation are increasingly used as an alternative.

Several algorithmic challenges are important to these methods. First is the necessity to pose the formulation to capture the relevant image properties, particularly the more subtle features that do not always coincide with sharp intensity contrast. The second challenge is finding the optimal configuration for the nonconvex energies that result from these formulations. Third is the incorporation of user input into the definition of the objective function and the optimization procedure. Our work will address these important aspects of user-interactive segmentation.

We expect that the patient-specific analysis suggested by the DBPs will present images of patients with pathologies and/or injuries that sometimes defy automated approaches. Beyond the DBPs, our experience is that the range of medical and biological applications is so diverse that a set of reliable, light-weight, easy-to-use tools is a critical need. Furthermore, even when more automated analyses are feasible, they usually require some level of training or bootstrapping, which requires examples from segmentations that are driven by user interaction and low-level image features.

Robust Statistics Segmentation: We have been developing an interactive segmentation scheme based on a statistical model of deformable contours to capture multiple anatomical features simultaneously. It is called the Robust Statistical Segmenter (RSS) and is now a module in 3D Slicer [GAO_RSS]. RSS uses interactively placed seeds to estimate local robust statistics features of interest, which are adaptively learned. Geometric active surfaces evolve in order to optimize these statistical descriptions, while respecting constraints among the various evolving surfaces. The balance of forces in conjunction with energy minimization and robust statistics guarantees that the active surfaces interact and converge to equilibrium at the desired positions of the given objects. Accordingly, this novel procedure naturally treats problems such as leakage and overlapping. The user has the ability to make hand corrections after equilibrium is reached and so the method is fully interactive. An example is provided in Figure 5-3.

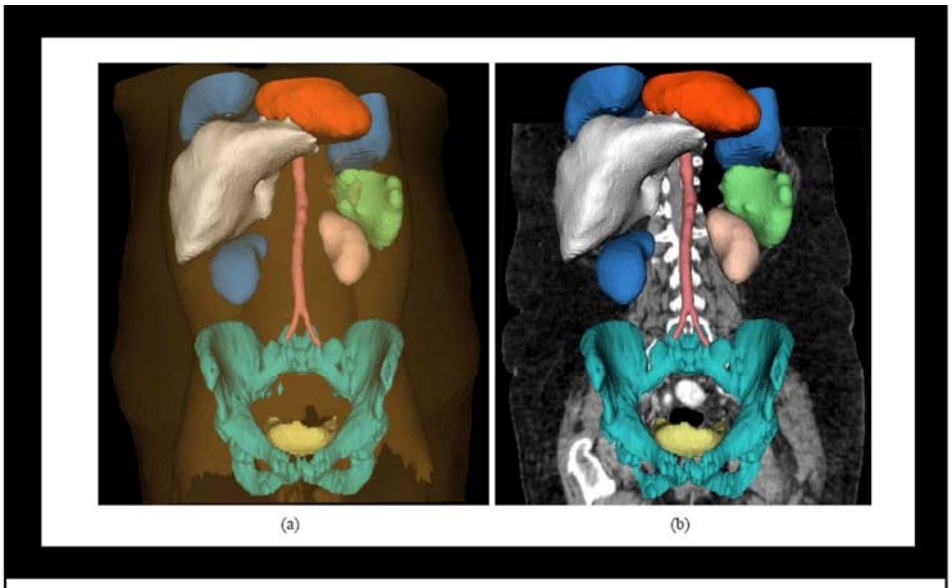

Figure 5-3. Segmentation of heart, two lungs, liver, two kidneys, spleen, abdominal aorta, pelvis, bladder, skin/muscle/fat. The subplot (b) removes skin/muscle/fat but overlays the original image.

Local/Global Active Contours for the Segmentation of Left Atrium: We have been working on various methods to robustly segment the endocardial wall of the left atrium in delayed-enhancement magnetic resonance images (DE-MRI). We have found that the use of local-global active contours combined with coupled level sets as well as shape learning can lead to a very effective method for this challenging problem [Gao_atrium]. We give an example of the procedure below in Figure 5-4. Future work in this area will include the computer-aided statistical assessment of the enhanced regions in the DE-MRI which can greatly benefit the study of ablation therapy for atrial fibrillation patients.

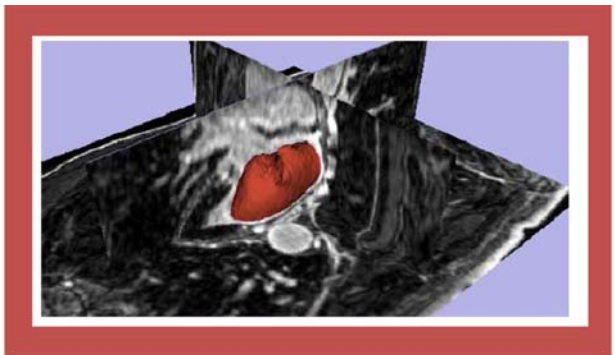

Figure 5-4. 3D view of segmentation of the endocardial wall of the left atrium.

User-Assisted Segmentation for MRI analysis of TBI: Motivated by challenging image analysis problems of the UCLA DBP partner on traumatic brain injury (TBI), we will develop image segmentation methodology that helps clinical researchers characterize and quantify a variety of different cerebral lesion types. Standard automated image analysis methods are not

robust with respect to the TBI-related changes in image contrast, changes in brain shape, cranial fractures, lesions, white matter fiber alterations, and other signatures of head injury. We are currently extending the existing ABC tool (atlas-based brain classification) with user-assisted definition of various lesion patterns for efficient segmentation and quantification of pathological regions in the 5 to 12 MRI modality image sets. In close collaboration with the UCLA partners, we have applied these tools to 3 clinical TBI cases with single time points, and to 1 case with baseline and follow-up. Lesions and ventricles were segmented with user-supervised level-set segmentation.

D. Longitudinal and Time Series Analysis

An important component of patient-specific data analysis is the ability to analyze multiple images from the same patient over time, as a disease or injury progresses or responds to treatment, or to assess neurodevelopment or neurodegeneration. Standard cross-sectional analysis of longitudinal data does not provide a model of growth or change that considers the inherent correlation of repeated images of individuals. Nor does it tell us how individual patients change relative to normal trajectories of a population. Two aspects are of particular importance for this project. First, when the progression or time behavior of a condition is an important component of the differences between groups, the statistical power of comparisons benefit from subject-specific analysis, and allow one to apply time-series analysis. Second, the availability of longitudinal data presents an opportunity to leverage images at multiple time points for segmentation and evaluations of shape and function, and thus adds a dynamic aspect to the process that can be useful in recognition. Longitudinal image analysis is important for all four DBPs in this project. The TBI DBP, for instance, will monitor the progress of patients during recovery, and tools for systematically analyzing these changes will be essential. Likewise, the Head and Neck Cancer DBP, the Atrial Fibrillation DBP, and the Huntington's disease DBP all will require comparisons of patients across multiple time points, and the ability to consolidate these longitudinal models across collections of patients in comparison to healthy controls.

We have several new developments relating to this aim.

Longitudinal analysis of DTI: Subject-specific analysis of image data often includes comparison of follow-up to baseline, or serial staging of progress of disease or for monitoring therapeutic intervention. Key methodological components are intra-subject registration of the set of scans, and analysis of geometric deformations and appearance changes. In DWI data, such analysis includes deformation of the set of DWI with associated correction of tensor orientation or local ODF adjustment. In addition, scalar invariants such as FA, MD, axial and radial diffusivities have to be compared in regions or along tracts at corresponding anatomical locations. Our methodology developments focus on tract-oriented analysis of white matter diffusivity over time, using previously developed tensor-field registration for preprocessing [Goodlett et al., Neuroimage 2009]. Diffusion along tracts is considered a function of arc-length, and regression is applied to mapping these functions over time. This includes extending our previous work, which was limited to regression of average diffusion along tracts, to include the full distribution of diffusion measures within cross-sections.

We have also developed explicit growth modeling of diffusion measures extracted from co-registered DTI data with the nonlinear Gompertz functions. Parameters of this function will inform clinicians about growth rate and time delay, information which will help to understand type, nature and growth trajectories of significant differences. The procedure is applied to early brain development data in a study of autism of our former NA-MIC partner UNC Chapel Hill.

Currently, we perform tests on three time point serial DTI data of Huntington Disease provided by the NA-MIC DBP partner IOWA.

We have also developed and deployed a deformable, longitudinal DTI atlas method [Hart, 2010] using intensity calibrated DTI property images. This longitudinal framework explicitly accounts for temporal dependencies via iterative subject-specific statistical growth modeling, and cross-sectional atlas-building. To effectively account for measurements sparse in time, a continuous-discrete statistical growth model is proposed incorporating also patient co-variates [Zhu, 2010]. See also Figure 5-5.

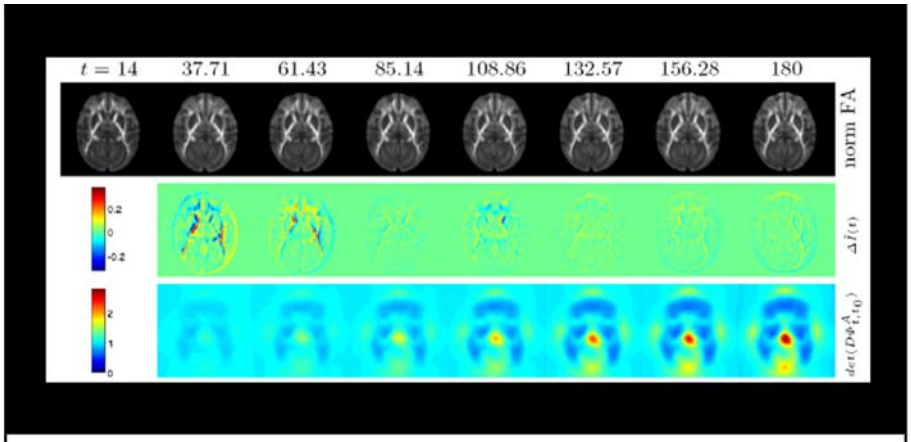

Figure 5-5. Preliminary longitudinal DTI atlas from postnatal day 14 to 180 as visualized on a center axial slice. *Top row:* Reconstructed atlas image at each age pulled back to day 14. The high quality of the longitudinal modeling is visible through the close similarity of the pulled-back atlas images. *Middle row:* Estimated change in FA between time points displaying major change occurring in the first 60 days (overshadowing the magnitude of later changes). *Bottom row:* Jacobian determinant of the pull-back deformation field. Key: Cyan = no change, dark blue = growth (most of white matter), yellow-red = shrinkage (here seen on the 3rd ventricle in the center of the image) .

Smooth Growth Trajectories from Time Series Shape Data: Longitudinal shape analysis often relies on the estimation of a realistic continuous growth scenario from data sparsely distributed in time. In this project, we develop a new type of growth model parameterized by acceleration, whereas standard methods usually control the velocity. This mimics the behavior of biological tissue as a mechanical system driven by external forces. We have proposed a new formulation, where growth trajectories are estimated as continuous flows of deformations, which are twice differentiable. The shape regression is based on a correspondence-free technique using *currents*, which calculates diffeomorphic flows between set shapes represented as surface data. In pilot tests on an infant growth study, we demonstrate that volume measurements taken out of our 3D shape regression are compatible with a 1D regression of these measurements. This implies that other morphometric measurements of interest to clinicians might also be smooth and thus model biological change in a realistic way. We plan to apply this method to anatomical shapes of image data on Huntington's disease (HD) provided

by the IOWA DBP partner. Preliminary studies showed that an inflection of change, rapid decrease of striatal volume trajectory, and application of this methodology to three time point data might reveal morphological characteristics of such volume loss.

4-D Segmentation: In view of the strong focus of NA-MIC on spatio-temporal analysis of subject-specific image data, we are developing a new concept for joint segmentation of serial 3D image data. The main aim is to improve the consistency of the set of segmentations assuming temporal smoothness of anatomical entities. The procedure includes temporal smoothness of tissue priors via kernel regression w.r.t. age and of the diffeomorphic registration maps cascaded across time points. A prototype implementation is applied to multi-time point data in infant studies, with the goal of improving the reliability and consistency of brain tissue segmentations over the whole time series. Results on synthetic and real data from several studies demonstrate significantly improved consistency. Within NA-MIC, we plan to test the new segmentation procedure on the longitudinal structural MRI in Huntington disease (HD) in collaboration with the IOWA DBP partner.

Plans for the Coming Year

Aim 1

During the next year, we will refine our methodology for non-parametric segmentation and work closely with the MGH and the Utah DBPs to develop segmentation methods for their specific applications.

We will also continue developing segmentation and registration methods that use prior information effectively in the presence of pathologies.

This will include methods for efficient queries of nearest-neighbor examples from large sets of data and effective mechanisms for registration in the presence of large discrepancies.

Aim 2

We will investigate an unbalanced version of optimal mass transport (the total integrals of the initial and target densities need not be equal) for elastic image registration. We will also pursue a novel formulation of the attacharyya coefficient for 3D elastic registration. To address the issue of smooth transformations and nonhomologous anatomy/pathology, we are investigating the use of alternative norms for regularizing displacement fields and of explicit identification of sparse sets of feature outliers.

Aim 3

We plan to refine the current interactive segmentation code (ABC-Slicer plugin) after tests with new NA-MIC multimodal brain data (HD, TBI). We also plan to develop methodology and prototype software (Matlab) for user-initialized segmentation of various cerebral white matter lesions in TBI, using UCLA descriptions of specific multimodal patterns. Likewise, we will continue to develop, as needed, user-guided tools that address the specific needs of the DBPs.

For instance, in the AF project, we plan to add computer-aided statistical assessment of the enhanced regions in the DE-MRI which can greatly benefit the study of ablation therapy for atrial fibrillation patients.

For adaptive radiotherapy, we plan to use local/global contours in conjunction with the Robust Statistical Segmenter for head and neck tumors.

Aim 4
We will continue to develop and extend our shape-based tools for longitudinal data. This includes the integration of hierarchical models into the correspondence-based shape regression framework in ShapeWorks, which is being moved to NITRC for better distributed development support and dissemination.

We are also conducting feasibility tests of the diffeomorphic/currents-based shape regression on segmentations of striatum structures in HD longitudinal MRI.

Similar tools for longitudinal analysis are being developed for diffusion weighted images. This includes tools for diffusion statistics of parametrized fiber tracts-delivered to NITRC and a methodology and prototype software (Matlab) for tract-based longitudinal analysis of DTI changes, tested on Huntington 3 time point DTI data.

Papers that Acknowledge NA-MIC

Depa M., Sabuncu M., Holmvang G., Nezafat R., Schmidt E., Golland P. *Robust Atlas-Based Segmentation of Highly Variable Anatomy: Left Atrium Segmentation*. Int Conf Med Image Comput Comput Assist Interv. 2010;13(WS):85-94. Proceedings of the Workshop on Statistical Atlases and Computational Models of the Heart: Mapping Structure and Function

Hart G., Shi Y., Zhu H., Sanchez M., Styner M., Niethammer M. *DTI Longitudinal Atlas Construction as an Average of Growth Models*. Int Conf Med Image Comput Comput Assist Interv. 2010;13(WS):1-12. Workshop on Spatio-Temporal Image Analysis for Longitudinal and Time-Series Image Data.

Looi J.C.L., Walterfang M., Styner M., Svensson L., Lindberg O., Ostberg P., Botes L., Orndahl E., Chua P., Kumar R., Velakoulis D., Wahlund L-O. *Shape Analysis of the Neostriatum in Frontotemporal Lobar Degeneration, Alzheimer's Disease, and Controls*. Neuroimage. 2010 Jul 1;51(3):970-86. PMID: 20156566.

Menze B.H., Van Leemput K., Lashkari D., Weber M-A., Ayache N., Golland P. *A Generative Model for Brain Tumor Segmentation in Multi-modal Images*. Int Conf Med Image Comput Comput Assist Interv. 2010;13(Pt 2):151-9. PMID: 20879310. PMCID: PMC3050038.

Paniagua B., Cevidanes L., Walker D., Zhu H., Guo R., Styner M. *Clinical Application of SPHARM-PDM to Quantify Temporomandibular Joint Osteoarthritis*. Comput Med Imaging Graph. 2010a Dec 23. PMID: 21185694.

Paniagua B., Cevidanes L., Zhu H., Styner M. *Outcome Quantification using SPHARM-PDM Toolbox in Orthognathic Surgery*. Int J Comput Assist Radiol Surg. 2010b Dec 16. PMID: 21161693.

Riklin-Raviv T., Van Leemput K., Menze B.H., Wells III W.M., Golland P. *Segmentation of Image Ensembles via Latent Atlases*. Med Image Anal. 2010 Oct;14(5):654-65. PMID: 20580305. PMCID: PMC2932709.

Sabuncu M.R., Yeo B.T.T., Van Leemput K., Fischl B., Golland P. *A Generative Model for Image Segmentation Based on Label Fusion*. IEEE Trans Med Imaging. 2010 Oct;29(10):1714-29. PMID: 20562040.

Walterfang M., Looi J.C.L., Styner M., Walker R.H., Danek A., Niethammer M., Evans A., Kotschet K., Rodrigues G.R., Hughes A., Velakoulis D. *Shape Alterations in the Striatum in Chorea-acanthocytosis*. Psychiatry Res. 2011 Apr 30;192(1):29-36. PMID: 21377843.

Wang Y., Gupta A., Liu Z., Zhang H., Escolar M.L., Gilmore J.H., Gouttard S., Fillard P., Maltbie E., Gerig G., Styner M. *DTI Registration in Atlas Based Fiber Analysis of Infantile Krabbe Disease*. Neuroimage. 2011 Apr 15;55(4):1577-86. PMID: 21256236. PMCID: PMC3062693.

Yeo B.T.T., Sabuncu M.R., Vercauteren T., Holt D.J., Amunts K., Zilles K., Golland P., Fischl B. *Learning Task-optimal Registration Cost Functions for Localizing Cytoarchitecture and Function in the Cerebral Cortex*. IEEE Trans Med Imaging. 2010 Jul;29(7):1424-41. PMID: 20529736.

5.2 Engineering

Key Investigators
Will Schroeder, Kitware
Steven Aylward, Kitware
Steve Pieper, Isomics
Jim Miller, GE Research

The Engineering component of the Computer Science Core has been focusing on the infrastructure needed for the Algorithms component to implement their methods, and has been working closely with them so that the functionality Engineering provides can serve to inspire new methods as well. Herein we provide more details regarding our accomplishments in those directions.

Interactive tools: Three new software infrastructure components are under development to host and inspire the work of the algorithms team.

(1) vtkWidgets are interactive actors in 2D and 3D renderings of a MRML Scene. Common examples are the familiar bi-dimensional widgets used to measure the length and width of lesions on a slice. Recent work has extended this concept to host interactions with more complex structures and processes such as, for example, the user-controlled deformation of a surface in 3D.

(2) vtkButtons are actors that indicate the presence of companion data for that spatial location in a scene. For example, a button may indicate the presence of biopsy information from that point, the presence of a recorded EKG signal, or the availability of an article in PDF format that discusses the indicated tumor. vtkButtons may appear in any form – as subsampled versions of the data or as icon representations of the data type.

(3) The labelmap editor has been made fully scriptable – in this manner, an algorithm can guide a user to circle an object of interest, then identify landmarks, and then edit the results of the segmentation it produces, without requiring the user to switch between edit modes. This is well demonstrated by the graph-cut segmentation algorithm now included with Slicer.

Data collections and Clinical Workflows: Slicer is being extended to interface with more data servers, including clinical PACS systems.

Regarding databases, we are in the process of adding the ability to gather data from any MIDAS installation. MIDAS is an open-source application developed by Kitware that provides web and C++ interfaces to the images and multimedia data it hosts. MIDAS is used, for example, to host data for the Optical Society of America and to host NA-MIC's PubDB which holds NA-MICs publications and public data. Additionally, MIDAS is able to harvest data from and contribute data back to the NCI/caBIG's NBIA image archive.

Regarding Clinical workflows, our focus is DICOM. We have prototyped a Qt module that brings DCMTK's extensive DICOM query and retrieve capabilities into Slicer. These capabilities also include DICOM push capabilities, and we are exploring ways to embed Slicer's output into DICOM objects so that Slicer's output can then be pushed back to clinical PACS and thereby complete Slicer's tie into clinical workflows.

Dissemination and cross-platform support: Herein we have focused on making Slicer and the NA-MIC Kit available on the largest number of platforms possible. This effort is in contrast, for example, to Osirix which is only available on Macs.

To achieve the maximal cross-platform distribution we have devised a method for uploading compilation results from any client machine to a central system for redistribution. This allows executables, extensions, and packages created by users and by dedicated machines to be made available for others to use. The process can be thought of as "crowd-sourcing" the creation of Slicer installation packages for an ever growing number of platforms (linux, mac, windows, etc). It is being used, for example, to provide 64-bit builds (in addition to 32-bit builds) of Slicer 4 for linux, Windows, and Macs. These 64-bit builds allow Slicer to handle even the largest clinical scans on nearly any compute environment.

Quality software: Qt and GUI Testing:

- Supporting the conversion of Slicer from KWWidgets to Qt for its user interface. This new "Slicer4" is available in Beta and contains many enhancements, including broad community support for Qt and increased stability from refactoring much of the Slicer code base.
- Porting a GUI testing system from ParaView to Slicer. This will allow, for example, every tutorial to be made fully automated and to run as a nightly test on every Slicer-supported platform. The continued operation and relevance of every tutorial as well as the stability of the Slicer user interface will be assured.

5.3 NA-MIC Kit

In the NA-MIC Kit (Figure 5-6), Algorithm developers contribute to the computational platform (image analysis: ITK and Teem; visualization: VTK and OpenCL) and application developers create tools within an architectural framework (scene graph: MRML, GUI: Qt, scientific computing: Python) in conjunction with data management facilities (XNAT) and under the control of the quality software process (CMake and CDash). The 3D Slicer platform is designed to accommodate accelerated innovation with a flexible execution engine on which community-

developed analysis modules can be rapidly deployed to clinical researchers and the broader community via the 3D Slicer.

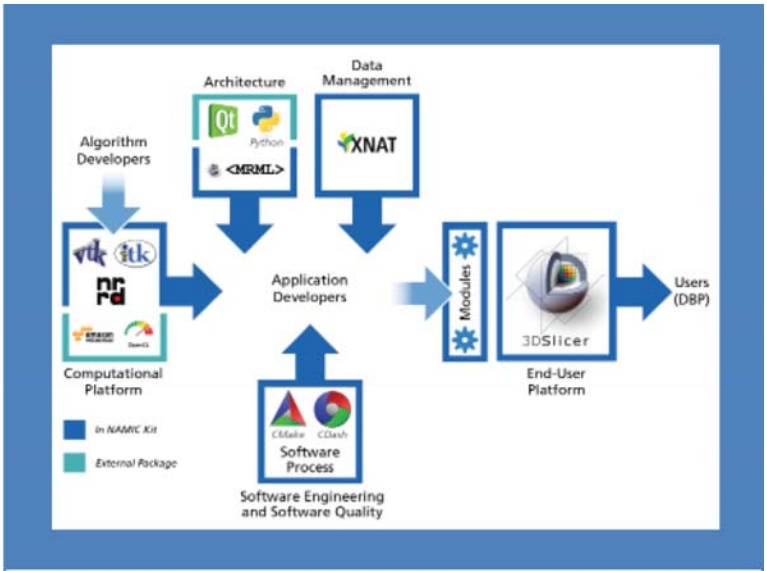

Figure 5-6. The NA-MIC Kit provides avenues for access for algorithms researchers, data managers, software engineers, and end users.

Expansion:

The NA-MIC Kit has been strategically expanded in three regards during this funding period:

(1) The University of Iowa's BRAINS package has been more tightly integrated with Slicer. BRAINS is a suite of morphometric processing tools that represents the first step in data processing required to examine shape changes over time. Over the past several months, substantial effort has gone into developing and improving cross-platform compatibility of the BRAINS tools and integrating those tools with 3DSlicer. In maintaining integration with 3DSlicer, the BRAINS Tools' test suite has been expanded to improve the discovery and correction of errors in the processing steps. As part of that error correction, fixes for underlying software such as ITK have been submitted back to the Community. BRAINS is now supported on every platform on which Slicer is supported. It is now distributed directly with Slicer

(2) DicomToNrrdConverter and DTIPrep tools have for normalizing data across multiple scanners and multiple scanner software versions

(3) The Common Toolkit (CTK) is an international effort to provide the basic yet critical functionality needed to create a clinical application. It is based on Qt, VTK, and DCMTK. The NA-MIC Kit is contributing components to it (e.g., many of its Qt-based widgets as well as it's cmake-based build process). This budget period also saw the expanded integration of CTK methods (contributed by others) into the NA-MIC Kit. For example, Slicer is now launched using a cross-platform launcher distributed with CTK.

Furthermore, there have been numerous plug-ins contributed to Slicer. We differentiate them as either built-in, Loadable, Scripted, or Command-line based. There are now 5 built-in, 33 loadable, 28 scripted, and 133 command-line plug-ins for Slicer. They are distributed directly with Slicer or available via the Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC) website.

Additional statistics on the NA-MIC Kit for 2010 are as follows:

- Subversion Commits: 4188 (15,729 total)
- Lines of Code*: 925,398
- Bugs & Features:
    - 521 Closed
    - 1046 Total
- Active Developers: 81

Release:
Beyond the NA-MIC Kit expansions, a key component of our work with the NA-MIC kit during this period has focused on creating stable releases. Figure 5-7 shows the release cycle being followed for Slicer 3 and Slicer 4.

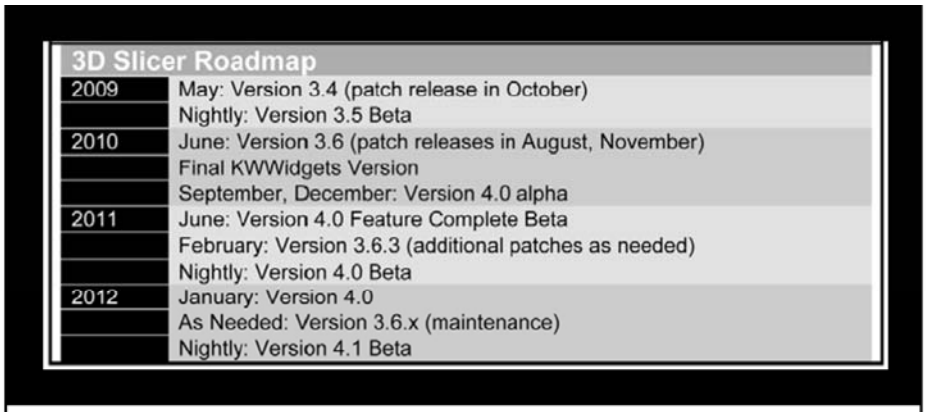

Figure 5-7. Schedule for the release of Slicer 3 as well as the transition to and release of Slicer 4.

Publications that Acknowledge NA-MIC

[Pace, 2011] Danielle F. Pace, Andinet Enquobahrie, Hua Yang, Stephen R. Aylward, Marc Niethammer, “Deformable image registration of sliding organs using anisotropic diffusive regularization” International Symposium on Biomedical Imaging: From Nano to Macro, April, 2011.

6. ARRA SUPPLEMENT

ARRA Supplement Funded Activity. With the funds provided by the ARRA, NA-MIC has been able to retain experienced medical imaging analysis engineers with advanced training in statistics to assist the Service, Training, and Dissemination Core teams with quality assurance activities for the NA-MIC Kit. The ARRA funded engineer provides critical support to both the NA-MIC Kit user community and algorithm developers. They monitor the activity on the mailing lists and bug report tracking responding to all requests that do not require the deeper expertise of the actual development team. With each new stable release of the Slicer software, the engineers port the large compendium of Basic, Advanced and Specialized Tutorials, ensuring that all instructions are correct. This actually provides feedback to the Engineering team and assists in correction of minor bugs in the code. The ARRA funded engineer has also become an integral member of the Slicer Training team, assisting in hands-on workshops as described in section 2.5, Training.

7. NA-MIC Publications

1. Destrieux C., Fischl B., Dale A., Halgren E. Automatic Parcellation of Human Cortical Gyri and Sulci using Standard Anatomical Nomenclature. Neuroimage. 2010 Oct 15;53(1):1-15. PMID: 20547229. PMCID: PMC2937159.

2. Elhawary H., Oguro S., Tuncali K., Morrison P.R., Tatli S., Shyn P.B., Silverman S.G., Hata N. Multimodality Non-rigid Image Registration for Planning, Targeting and Monitoring during CT-guided Percutaneous Liver Tumor Cryoablation. Acad Radiol. 2010 Nov;17(11):1334-44. PMID: 20817574. PMCID: PMC2952665.

3. Gao Y., Sandhu R., Fichtinger G., Tannenbaum A.R. A Coupled Global Registration and Segmentation Framework with Application to Magnetic Resonance Prostate Imagery. IEEE Trans Med Imaging. 2010 Oct;29(10):1781-94. PMID: 20529727. PMCID: PMC2988404.

4. Gerber S., Bremer P-T., Pascucci V., Whitaker R. Visual Exploration of High Dimensional Scalar Functions. IEEE Trans Vis Comput Graph. 2010 Nov-Dec;16(6):1271-80. PMID: 20975167.

5. Gerber S., Tasdizen T., Thomas Fletcher P., Joshi S., Whitaker R. Manifold Modeling for Brain Population Analysis. Med Image Anal. 2010 Oct;14(5):643-53. PMID: 20579930. PMCID: PMC3020141.

6. Ghosh S.S., Kakunoori S., Augustinack J., Nieto-Castanon A., Kovelman I., Gaab N., Christodoulou J.A., Triantafyllou C., Gabrieli J.D.E., Fischl B. Evaluating the Validity of Volume-based and Surface-based Brain Image Registration for Developmental Cognitive Neuroscience Studies in Children 4 to 11 Years of Age. Neuroimage. 2010 Oct 15;53(1):85-93. PMID: 20621657. PMCID: PMC2914629.

7. Kikinis Z., Fallon J.H., Niznikiewicz M., Nestor P., Davidson C., Bobrow L., Pelavin P.E., Fischl B., Yendiki A., McCarley R.W., Kikinis R., Kubicki M., Shenton M.E. Gray Matter Volume Reduction in Rostral Middle Frontal Gyrus in Patients with Chronic Schizophrenia. Schizophr Res. 2010 Nov;123(2-3):153-9. PMID: 20822884. PMCID: PMC2975427.

8. Kremen W.S., O'Brien R.C., Panizzon M.S., Prom-Wormley E., Eaves L.J., Eisen S.A., Eyler L.T., Hauger R.L., Fennema-Notestine C., Fischl B., Grant M.D., Hellhammer D.H., Jak A.J., Jacobson K.C., Jernigan T.L., Lupien S.J., Lyons M.J., Mendoza S.P., Neale M.C., Seidman L.J., Thermenos H.W., Tsuang M.T., Dale A.M., Franz C.E. Salivary Cortisol and Prefrontal Cortical Thickness in Middle-aged Men: A Twin Study. Neuroimage. 2010 Nov 15;53(3):1093-102. PMID: 20156572.

9. Langs G., Golland P., Tie Y., Rigolo L., Golby A.J. Functional Geometry Alignment and Localization of Brain Areas. Proceedings of the 24th Annual Conference on Neural Information Processing Systems 2010; 1:1225-1233.

10. Leritz E.C., Salat D.H., Williams V.J., Schnyer D.M., Rudolph J.L., Lipsitz L., Fischl B., McGlinchey R.E., Milberg W.P. Thickness of the Human Cerebral Cortex is Associated with Metrics of Cerebrovascular Health in a Normative Sample of Community Dwelling Older Adults. Neuroimage. 2011 Feb 14;54(4):2659-71. PMID: 21035552. PMCID: PMC3026290.

11. Mohan V., Sundaramoorthi G., Tannenbaum A. Tubular Surface Segmentation for Extracting Anatomical Structures from Medical Imagery. IEEE Trans Med Imaging. 2010 Dec;29(12):1945-58. PMID: 21118754.

12. Nho K., Shen L., Kim S., Risacher S.L., West J.D., Foroud T., Jack C.R., Weiner M.W., Saykin A.J. Automatic Prediction of Conversion from Mild Cognitive Impairment to Probable Alzheimer's Disease using Structural Magnetic Resonance Imaging. AMIA Annu Symp Proc. 2010 Nov 13;2010:542-6. PMID: 21347037. PMCID: PMC3041374.

13. Oguro S., Tuncali K., Elhawary H., Morrison P.R., Hata N., Silverman S.G. Image Registration of Pre-procedural MRI and Intra-procedural CT Images to Aid CT-guided Percutaneous Cryoablation of Renal Tumors. Int J Comput Assist Radiol Surg. 2011 Jan;6(1):111-7. PMID: 20499194. PMCID: PMC3050046.

14. Pohl K.M., Konukoglu E., Novellas S., Ayache N., Fedorov A., Talos I-F., Golby A., Wells III W.M., Kikinis R., Black P.M. A New Metric for Detecting Change in Slowly Evolving Brain Tumors: Validation in Meningioma Patients. Neurosurgery. 2011 Mar;68(1 Suppl Operative):225-33. PMID: 21206318.

15. Riklin-Raviv T., Van Leemput K., Menze B.H., Wells III W.M., Golland P. Segmentation of Image Ensembles via Latent Atlases. Med Image Anal. 2010 Oct;14(5):654-65. PMID: 20580305. PMCID: PMC2932709.

16. Sabuncu M.R., Yeo B.T.T., Van Leemput K., Fischl B., Golland P. A Generative Model for Image Segmentation Based on Label Fusion. IEEE Trans Med Imaging. 2010 Oct;29(10):1714-29. PMID: 20562040.

17. Salat D.H., Chen J.J., Van der Kouwe A.J.W., Greve D.N., Fischl B., Rosas H.D. Hippocampal Degeneration is Associated with Temporal and Limbic Gray Matter/White Matter Tissue Contrast in Alzheimer's Disease. Neuroimage. 2011 Feb 1;54(3):1795-802. PMID: 20965261. PMCID: PMC3021138.

18. Shenton M.E., Whitford T.J., Kubicki M. Structural Neuroimaging in Schizophrenia: From Methods to Insights to Treatments. Dialogues Clin Neurosci. 2010;12(3):317-32. PMID: 20954428.

19. Wang X., Grimson W.E.L., Westin C-F. Tractography Segmentation using a Hierarchical Dirichlet Processes Mixture Model. Neuroimage. 2011 Jan 1;54(1):290-302. PMID: 20678578. PMCID: PMC2962770.

20. Wang Y., Gupta A., Liu Z., Zhang H., Escolar M.L., Gilmore J.H., Gouttard S., Fillard P., Maltbie E., Gerig G., Styner M. DTI Registration in Atlas Based Fiber Analysis of Infantile Krabbe Disease. Neuroimage. 2011 Apr 15;55(4):1577-86. PMID: 21256236. PMCID: PMC3062693.

8. EAB

To: Dr. Ron Kikinis, National Alliance for Medical Image Computing

From: NA-MIC External Advisory Board

Date: 4/28/2011

Re: 2011 EAB Meeting: NA-MIC Progress

The External Advisory Board (EAB) for the National Alliance for Medical Image Computing (NA-MIC), one of seven National Centers for Biomedical Computing funded by NIH, convened in Salt Lake City, Utah on January 13, 2011. Dr. Ron Kikinis hosted the meeting. Bill Lorensen (GE Retired, Chair), Chris Johnson (Utah), Morry Blumenfeld (Meditech Advisors), Sandy Napel (Stanford) and Terry Yoo for Michael Ackerman (NIH NLM) represented the EAB. Zohara Cohen, the NIH Program Officer also participated. The EAB Meeting was part of the NA-MIC All Hands Meeting (AHM).

The EAB members attended the morning and afternoon sessions of the AHM along with the rest of the NA-MIC community. This combination format was started after the first year and the EAB favors this format over one that has separate presentations for the EAB. After the AHM, the EAB met with NA-MIC leadership and PI's. Each EAB member provided comments to the NA-MIC team. This report highlights the ensuing discussions.

EAB Impressions

- *The EAB was impressed with the diversity of the new DBP's*. The new DBP portfolio includes cardiac analysis, Huntington's disease, head/neck cancer and traumatic brain injury. These DBP's have important clinical potential and provide new challenges to the Algorithms and Engineering cores. The new DBP's are off to a quick start and the Algorithms core has already made contact with the DBP's to assess their needs. DBP workshops were held to introduce the DBP's to the NA-MIC kit.

- *The EAB endorses the Center software focus on interoperability and usability.* Slicer3 has become stable and there has been more effort on data exchange, plug-ins and user interface. These are important engineering efforts and the EAB appreciates the extent of the work required to accomplish these improvements. Fortunately, the initial Slicer design goals of separating interface from algorithms facilitate these changes.

- *The EAB is impressed with the progress and potential of Slicer4.* The Slicer4 effort is moving along faster than the EAB had expected. A

sizable percentage (70%) of the original Slicer code base is being reused. The high reuse rate was possible because of architecture and design decisions made for Slicer3. The major changes are in the user interface components and scripting. Slicer4 is using the Qt toolkit while Slicer3 uses the KWWidgets toolkit. Qt has a much larger customer base. KWWidgets served NA-MIC well for Slicer3 but Qt provides a broader community and a wider range of user interface elements. Also, Slicer4 is moving from tcl/tk (used in Slicer3) to Python. Python has become the de-facto interpreter standard in the biomedical community. The EAB endorsed these changes at last year's meeting.

- *The EAB recognizes the impact on the international community*. Due to the reputation of NA-MIC, the NA-MIC Kit is being used by many groups outside of the U.S. Several of these groups, along with members of NA-MIC's Engineering core have formed a group called the Common Toolkit, CTK. CTK is developing reusable user interface elements. These are based on Qt, vtk and itk. For example, CTK is working on a DICOM user interface component that will present Qt applications with an interface to DICOM databases. This component and several others are already part of the nightly Slicer4 build. Several Slicer3 capabilities have been adapted into CTK components.

- *The EAB reiterates that the Center's training and education program is a critical component to the Center's success.* The number and diversity of tutorials and workshops at a variety of National and International meetings is impressive. Many of these sessions are presented to audiences outside of NA-MIC and have increased the acceptance of NA-MIC as a national and international resource. The tutorial content introduces the attendees to advanced medical imaging techniques that are not typically available in existing applications. The quantity and quality of the online tutorials has increased each year. The tutorial contests at Project Week are vehicles to introduce NA-MIC customers to new features as soon as they are added. The EAB appreciates how much effort it takes to provide robust and informative demonstrations to attendees with a mix of computing sophistication.

- *The EAB considers the biannual Project Week to be unique and recognizes it as a jewel of the Center.* Project Week brings together software engineers with a diverse group of NA-MIC customers. In this active, open, no-holds-barred environment, both developers and users benefit from the intense productivity sessions. Project Week also provides a venue to introduce new technology to NA-MIC members and customers, e.g. updates and user feedback sessions for Slicer4.

Recommendations

- *NA-MIC should continue to follow the DICOM WG23 efforts.* The Engineering core is actively following the WG23 efforts. WG23 is working towards a standard interface between post-processing software and medical imaging workstations. There may be opportunities to adapt Slicer's Execution Model to this evolving interface. A Slicer compatible DICOM plug-in mechanism would offer Slicer technology to the mainstream radiological community via commercial workstations.

- *Spotlight the impact of the training*. Something needs to be done to underscore the impact of the NA-MIC training. The EAB has always been impressed with the training effort as presented at the AHM. Still, as noted in the renewal comments, outsiders do not have the same appreciation.

- *Impact of international interactions*. NA-MIC was formed by the NIH to be a national resource. However, the NA-MIC Kit is having impact on an international scale. This impact is fostered by word-of-mouth and seminars given outside the U.S. These seminars are most often by invitation and are funded by non-NIH means. The EAB feels that NIH should take note of this effort.

Summary

In summary, NA-MIC continues to make excellent progress in all areas. NA-MIC provides unique techniques and tools to a large national and international community. Under Dr. Kikinis' leadership, NA-MIC leverages multiple funding sources focused on consistent delivery of NA-MIC technology to a broad biomedical imaging audience. The EAB looks forward to the new algorithms, software and biomedical application progress that NA-MIC will provide in the coming year.

Sincerely,

Bill Lorensen, EAB Chair, GE Research (retired)