National Alliance for Medical Image Computing (NAMIC)

Core 1: Computational Foundations

A. Specific Aims:

As described in the original proposal, the aims of Core 1 are to create, develop, integrate and deploy computation tools for the analysis and visualization of medical image data. These computational tools are specifically focused on issues related to the driving biological problems posed by the study of schizophrenia. Consistent with these aims, work on computational methods during the first year has focused on:

- Definition of anatomical structures, at varying scales and levels of distinctiveness;
- Measurements of properties of extracted structures;
- Connectivity and systems analysis.

B. Studies and Results

Algorithm development for extracting model of anatomical structures has focused on two different classes of algorithms. Both use shape information to guide the segmentation of new scans: one is based on evolving boundaries of structures to fit image data, while incorporating prior knowledge about standard shapes of structures; the other is based on statistical assignment of tissue labels to voxels, while being influenced by prior knowledge about shapes of structures and their relative layout. Both classes of algorithms have been designed, implemented, tested and are being inserted into the NAMIC toolkit for use by other researchers.

Algorithm development for measurements of properties of anatomical structures has focused on shape measurements associated with segmented structures. We have developed mathematical modeling approaches to comparing populations based on the shape of anatomical structures. In contrast with shape-based segmentation that utilizes a statistical model of the shape variability in one population (typically based on the Principal Component Analysis) we are interested in identifying and characterizing differences between two sets of shape examples. We use a discriminative framework to characterize the differences in shape by training a classifier function and studying its sensitivity to small perturbations in the input data. Additional algorithmic methods have been incorporated for performing group-level statistical analysis of DTI data in a number of clinical applications.

In complementary work, we have developed novel methods in shape analysis for a) the computation of local thickness maps at the surface using Voronoi skeletons and b) the parcellation of 2D and 3D boundary shape descriptions in order to measure regional effects of volume, area, shape and diffusion tensor properties. The statistical local shape analysis methods were extended to incorporate multivariate Hotelling T^2 size and significance maps, both raw and corrected for multiple comparison, as well as effect size and regression coefficient r^2 maps. These additional maps are crucial in the correct validation and interpretation of local shape statistics.

We have also developed a novel algorithm that learns the shape variation at multiple scales and locations based on a training set. Our technique uses spherical wavelets to generate a multiresolution description of surfaces and spectral graph partitioning to adaptively discover independent shape variations at multiple scales. Our results show that our algorithm significantly improves the approximation of shapes in a testing set over PCA that tends to oversmooth the data.

In addition to creating algorithmic methods for measuring properties of structural elements, we have also been creating and deploying tools for measuring properties of white matter tracts. Whereas tractography on DTI is mostly used to study the white matter architecture, we extend this concept towards quantitative tractography. The development augments white matter bundle extraction by a set of methods that provide diffusion tensor analysis for individual tracts. The tool includes clustering of sets of streamlines into coherent bundles with outlier removal, interpolation of sets of curves by B-splines and arc-length parameterization, calculation of diffusion statistics in cross-sections and along bundles, and standardized output of statistics into files. User interaction is facilitated by a graphical user interface with fiber bundle editing and visualization options.

Algorithm development for connectivity analysis has focused on methods for analyzing and visualization DTI data. In particular, we are developing algorithms that measure connectivity of white matter using geodesic flow information, and that measure connectivity by directly tracking local orientation preferences at voxels. Secondly, we are developing algorithms for clustering tensor information into coherent bundles. Visualization methods have been incorporated into the NAMIC toolkit, which enable a user to view these bundles and their clusters, both within a patient and across sets of patients. These include tract based visualization tools, as well as tools for visualization of high angular resolution diffusion imaging data.

C. **Significance**

The primary goal of Core 1 is to develop algorithms that can be used by Core 3 (and other) collaborators to investigate questions about the development, and impact, of schizophrenia, as well as other diseases. The newly developed segmentation algorithms have been demonstrated to provide more accurate reconstructions of anatomical structures, leading to more detailed and refined analysis of differences in structure between normal and diseased subject populations. The standardization efforts in shape analysis will facilitate the development of tools incorporating methods from different NAMIC sites. Such tools designed for clinical study partners are currently non-existent in the shape analysis field. These new standardized tools will provide a significant impact on the measurement and comparison of shape populations.

The methods developed for parcellation and thickness analysis further strengthen shape analysis based studies and showed great potential in our initial analysis applied to the hippocampus and the corpus callosum. We expect these tools to further support the quantitative study of structures implicated by schizophrenia. The related tools developed for visualization of white matter tracts, and for clustering of tracts both within a subject and across subjects, are already being used by collaborators investigating questions in schizophrenia analysis.

D. **Plans**

Consistent with our original goals, the second year of NAMIC will focus on continued integration of algorithmic tools into a framework that is easily accessible to clinical researchers. The testing of the integrated framework on clinical data (already underway in a number of collaborations between Core 1 and Core 3 sites) will provide valuable feedback to the algorithm developers in creating the next generation of methods. Focus will again be divided between DTI processing and analysis, structure analysis, and shape population studies and comparisons.

Principal Investigator/Program Director (Last, First, Middle): Kikinis, Ron Core 2

PROGRESS REPORT SUMMARY

GRANT NUMBER
U54 EB005149

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PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR	FROM	THROUGH
Ron Kikinis, M.D.	09/17/04	07/31/05

APPLICANT ORGANIZATION
Brigham and Women's Hopital

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National Alliance for Medical Computing (NAMIC)

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Please see attached report.

National Alliance for Medical Image Computing (NAMIC)

Core 2: Engineering

A. Specific Aims

As described in the original proposal, the aims of Core 2 are to provide the software architecture, development, integration, and process for the NA-MIC.

B. Studies and Results

The first year of Core 2 has been expended in laying the software foundation as deciding how best and efficiently to do so. To that end, the core has now created a the concept of "NA-MIC Kit" which would be an ensemble of open source software and tools to run NA-MIC research on a stable, industry strength platform.

NA-MIC software resources include a number of toolkits, libraries, and applications. Here we provide a brief summary and links to additional information for each NA-MIC software component, as well as a set of processes that will be used for application development using the NA-MIC kit.

The NAMIC Kit

The current version of the NAMIC kit consists of the following end-user applications and software:

Software Applications for Core 3 (DPB) Users

The **3D Slicer** (***http://www.slicer.org***) (or simply **Slicer**) refers to a program historically developed primarily at the Surgical Planning Lab at Brigham and Women's Hospital (*http://spl.harvard.edu/*) and at the MIT AI Lab (*http://csail.mit.edu/*). This expansive research environment has resulted in a wide array of functionality to support a variety of medical imaging projects. Within NA-MIC, Slicer serves as a vehicle for delivering ITK and VTK based algorithms to the clinical investigators within the context of a complete end-user application reference framework. Slicer also serves as a research prototype from which to draw ideas for the implementation of next-generation medical image computing applications. The NA-MIC software engineering methodology, as applied to the problems Slicer has historically addressed, is expected to result in a cleaner architecture that is easier for developers to support and extend.

Software Toolkits for Core 1&2 Developers

The following software toolkits are being used to develop software within the NA-MIC community. These should be primarily of interest to the Core 1& 2 participants of NA-MIC.

The Insight Segmentation and Registration Toolkit (ITK (*http://www.itk.org*)) is an open-source software toolkit for performing registration and segmentation. Segmentation is the process of identifying and classifying data found in digitally sampled representations. Typically the sampled representation is an image acquired from such medical instrumentation as CT or MRI scanners. Registration is the task of aligning or developing correspondences between data. For example, in the medical environment, a CT scan may be registered with a MRI scan in order to combine the information contained in both.

The Visualization ToolKit (VTK (*http://www.vtk.org*)) is an open source, freely available software system for 3D computer graphics, image processing, and visualization used by thousands of researchers and developers around the world. The major objective of VTK is to support the visualization process: mapping data into perceptual forms (typically visual). VTK supports a wide variety of visualization algorithms including scalar, vector, tensor, texture, and volumetric methods; and advanced modeling techniques such as implicit modelling, polygon reduction, mesh smoothing, cutting, contouring, and Delaunay triangulation. In addition, dozens of imaging algorithms have been directly integrated to allow the user to intermix 2D imaging / 3D graphics algorithms and data.

The LONI Pipeline Processing Environment has been used quite successfully since its release in the neuroimaging field. The Pipeline has sped up research in this area, allowing researchers to focus upon the research and not the mundane and repetitive administrative tasks of data management and processing. It also has provided an easy mechanism for researchers to disseminate their research processes. A modular architecture, with task specific components that provide quick and easy customization, is currently under development.

Software Tools

In addition the many other software tools are being used to develop software within the NA-MIC community such as dashboards that provide ready feedback on software builds, bugtrackers to report on defect, as well as other software engineering tools such as version control software (e.g. CVS), scripting tools, etc.

All components of the NA-MIC toolkit have an associated dashboard and bugtracker so that the current state of the toolkit is publicly accessible at all times. NA-MIC uses a variety of software packages to meet its goals. Many of these software packages have nightly dashboards created using Dart (*http://www.itk.org/Dart*). Dart is an open-source, distributed, software quality system. Dart allows software projects to be tested at multiple sites in multiple configurations (hardware, operating systems, compilers, etc.). Results from a build/test sequence are transmitted to a central server using standard internet protocols. The server produces concise dashboards, summarizing the current state of a software system. The dashboards link to detailed reports on inter- and intra- configuration results. Testing results are tracked over time, allowing developers to trace the history of development.

C. **Significance**

The need for very strong software engineering standards was identified in early meetings of NA-MIC PIs. There are set processes, tools and documentation, which has allowed a very robust, extensible software contribution of NA-MIC, which is now collectively called the NA-MIC toolkit. All these processes lead to robustness and reliability of the software, which is critical for continued use and credibility of the tools methods created in other cores of the project.

D. **Plans**

Consistent with our original goals, the second year of NAMIC will focus on continued contribution of tools and software components into the NA-MIC toolkit. Continued feedback from collaborators after using the NA-MIC kit will help direct further work.

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Please see attached report.

Progress Report for Core 3.1 (Harvard, PI: Shenton)

A. Specific Aims

The overall aims of Core 3.1 have remained the same, to investigate abnormalities of connectivity at the anatomical and functional level in schizophrenia. We will also work closely with Core 3.2 where the focus is on discovering endophenotypes as revealed through combining cognitive, clinical, and genetic assessments with anatomic and functional circuitry abnormalities in schizophrenia. These complementary approaches will require highly sophisticated and advanced computational strategies and robust software implementation provided by Core 1 (Computer Science) and Core 2 (Engineering). Investigators in Core 1 and 2 will thus work closely with investigators in Core 3.1 and Core 3.2 to develop novel tools that can be applied to our brain imaging studies of schizophrenia. Specific needs for development tools include, but are not limited to, improved cortical and subcortical segmentation, improved co-registration of multimodal imaging data, as well as new analysis techniques for quantifying and visualizing diffusion tensor images. Additionally, our group will work with investigators in the other cores in disseminating information, and in training others in the use of tools in the 3D slicer.

B. Studies and Results

The work accomplished in Core 3.1 over the last funding period includes:

(1) Medical image data sets from published Brigham/Harvard studies have been collected and organized and made available to our computer and engineering Cores (**Core 1 and 2**) for tool development. These data sets include well-delineated neuroanatomical regions of interest, as well as diffusion tensor imaging data with brain regions of interest delineated. Specifically, raw structural images and regions of interest have been uploaded to the NA-MIC website and include the following structures: a) amygdala-hippocampus, b) super temporal gyrus, c) middle temporal gyrus & inferior temporal gyrus, d) caudate nucleus, and e) insular cortex & temporal pole. There are a total of 188 morphology cases and 80 diffusion tensor cases. Information about diagnosis, data parameters and labels associated with the Region of Interests (ROI) can be found on the NA-MIC website at: http://www.na-mic.org/Wiki/index.php/DataRepository#Brockton_VA.2Fharvard_Structural_and_DTI_Images

(2) We have worked with **Core 5** to provide them with resources we have developed such as an informal manual with instructions for using 3D slicer software that was developed by our research assistants. This has been given to **Core 5** for further development and refinement.

(3) We have worked with **Core 5** on their tutorial for the 3D slicer at Dartmouth on May 26-27, 2005. As our research group is one of the heaviest users of the 3D slicer, Sylvain Bouix, Ph.D., a computer scientist from our group as well as three Research Assistants, were involved in the tutorial with **Core 5**.

(4) We have worked with **Core 2** to add functionalities to the Slicer. The DTMRI analysis module has been improved by NA-MIC collaborators

and tested by us. We also have initiated the addition of a resampling module in the Slicer and extensively tested the linear and non-linear registration as well as the automatic segmentation modules.

(5) In addition to raw images, and regions of interest, we have also provided data for software testing on the NA-MIC Wiki website (http://www.na-mic.org/Wiki/index.php/DBP:Harvard:Software:Testing). Structural volumes for three cases are now available for the following brain areas and structures: 1) intracranial contents, 2) gray matter, 3) white matter, 4) CSF, 5) superior temporal gyrus, 6) amygdala, 7) hippocampus, and, 8) parahippocampus. The purpose of providing these data is so that computer scientists who are developing new tools can check the validity of volume measures using these data.

(6) In an effort to keep track of the development of analysis modules in the 3D Slicer, we have created an interactive website interface on the NA-MIC Wiki page, where researchers can report "bugs" they notice while using the software (http://www/na-mic.org/Wiki/index.php/DBP:Harvard#Software_Testing). These problems are then discussed at weekly DTI/Slicer development meetings, and the website is then updated, weekly. In addition, the website also contains a wish list, so that researchers can suggest tools or functions they feel would be useful in Slicer. This use of the NA-MIC Wiki website has proven extremely helpful for communication between researchers and developers, and it provides an excellent interface whereby software developments can be organized, tested, and disseminated.

(7) We also met with investigators from Utah, Drs. Ross Whitaker and Tom Fletcher, in March to discuss comparison of old and new anisotropy measures in schizophrenia. Dr. Fletcher also presented a non-linear statistical approach to tensors for the schizophrenia and neuroscience investigators.

C. Significance

We have made great strides in making data available to Cores 1 and 2. Making data available to computer scientists and engineers for the development of new tools to be applied for the purpose of investigating brain disease is important to the larger community as the tools developed can be applied to multiple brain disorders. Moreover, working with computer scientists and engineers is an important model for the larger scientific community as it provides a template for future work with investigators who are in different disciplines but share a common vision of improving tools for their clinical applications. The work performed by NA-MIC is thus critical to driving software development as well as being important in the training and dissemination of information, which Core 3.1 has been closely involved in over the previous grant period.

D. Plans

In the next year, fMRI data will be collected to prospectively test hypotheses of interest to Core 3.1. This was not done in the first year of the grant as much more effort was needed to get the retrospective data up and available for Core 1 and 2 personnel.

NAMIC Core 3.2. Scientific Progress Report

A. Specific Aims

Specific Aim #1—Determine the contribution of dysfunction in DPFC and connected forebrain structures to schizophrenic subtypes.
Specific Aim #2—Determine the level of organization at which the circuitry produces different schizophrenic syndromes.
Specific Aim #3—Determine the influence of normal genetic allelic variation on DPFC and related structures function in Aim #1, and in corresponding neural circuits described in Aim #2.

B. Studies and Results

Significant progress has been made in testing the hypotheses related to our specific aims during this early stage of the project. Due to the intensive interactions with other cores, some materials may overlap with other reports.

1. Creating custom brain segmentations using semi-automated techniques

The UCI Core 3.2 and Georgia Tech Core 1 have successfully developed a method for taking lengthy and complex neuroanatomical rules for defining a cortical area (Fallon) and creating a new semiautomated segmentor program that is anatomically accurate, but takes only a fraction of the time to carry out. This collaboration was completed through two face-to-face conversations and presentations at two NAMIC meetings, and through individual and conference calls, and email.

First, we chose a highly variable and complex-shaped cortical area involved in executive brain functions and short term memory, the dorsolateral prefrontal cortex (DLPFC). We then created both quantitative and qualitative distance and shape 'rules' (based on neuroanatomical expertise and the literature) for defining its boundaries in different subjects.

This information was then tested in a series of subjects using manual segmentation techniques to create the most realistic 2-D and 3-D models of DLPFC. The rules were then sent to the Tannenbaum lab for adapting the neuroanatomical rules into a semiautomated algorithm program. Using this new algorithm, the time to segment the DLPFC was reduced from over an hour or more to approximately 5 minutes. Future work is to implement the algorithm into 3D Slicer of Brigham and Women's Hospital.

2. Functional connectivity of the DLPFC investigated using partial least squares correlation

Drs. Lisa Kilpatrick and James Fallon investigated the functional connectivity of the DLPFC using partial least squares (PLS). PLS is a multivariate analytical technique used to summarize large neuroimaging datasets in such a way as to correlate patterns of activation with a variable(s) of interest (i.e. DLPFC activity). PLS works on the assumption that the focus of analysis is on aspects of the signal in one dataset (neuroimaging data) which are related directly to signals in another dataset (DLPFC activity). PLS computes a matrix that defines the relation between the two datasets then analyzes that "cross-block" matrix through singular value decomposition. PLS, as applied here, enables us to derive commonalties and differences among experimental conditions in DLPFC functional interactions with other brain regions.

The functional connectivity of the DLPFC during performance of the Sternberg working memory task under a low memory load and a high memory load condition was examined. Areas displaying positive correlation with activity in the DLPFC during both low and high load conditions included other prefrontal areas such as the orbitofrontal cortex. Areas displaying a more positive correlation with activity in the DLPFC during the high load condition than during the low load condition included inferior parietal cortex.

An additional partial least squares analysis to investigate relationships between DLPFC functional connectivity and accuracy performance during the working memory task was performed. In this analysis, both DLPFC activity and accuracy were simultaneously entered as variables of interest. The results support the view that prefrontal dysfunction underlies working memory deficits in schizophrenic patients and suggest that there may be more dysfunctional and functional aspects of DLPFC networks in terms of supporting working memory performance. This analysis complies with Specific Aims #1 and #2 by investigating the role of the DLPFC through interactions with other regions in prefrontal and extended networks.

3. Preliminary analysis on genetic allelic variation of schizophrenia at UCI

We have genotyped 27 polymorphisms and tested for Hardy Weinberg Equilibrium across all the SNPs that had 2 alleles. We have also calculated the relative distance from consecutive polymorphisms (e.g., all the SNPs in the DRD2)

and built their maps with the LD matrix. Results have shown that several SNPs have deviation from HWE, which may be informative when other imaging and clinical data have become available. It is difficult to interpret at the present time in the absence of other information.

Due to the lengthy output, we are unable to show all allelic frequency tables in this report. Detail information such as Haploview of LD structure and map of those genes with multiple SNPs will be uploaded on the NAMIC Wiki website.

4. Imaging genetic article submitted for publication

A manuscript entitled "Imaging phenotypes and genotypes in schizophrenia" has been submitted for publication. In this paper we reviewed some of the key findings in imaging phenotyping and genotyping of schizophrenia, and the initial endeavors at their combination into more meaningful and predictive patterns, or endophenotypes identifying the relationships among clinical symptoms, course, genes and the underlying pathophysiology.

5. Brains / Slicer workshop, March 23, 2005

A collaborative effort between FBIRN and NAMIC led to UCI hosting a workshop on March 23 highlighting how to use two different analysis and visualization packages: BRAINS (University of Iowa/FBIRN) and Slicer (BWH/NAMIC). This Education and Dissemination event was publicized to the local UCI imaging community and was well-attended by BIRN, NAMIC, and UCI imaging researchers.

6. IRB permission for NAMIC community use of legacy data

UCI IRB approval was requested and obtained to share deidentified, defaced legacy data sets with NAMIC investigators. The resulting structural MRI, functional MRI, genetic and PET data for a particular legacy data set have been defaced when necessary, deidentified, and uploaded to a sharing area hosted by BIRN but made available to NAMIC investigators. The data collection and analysis methods were documented and made available on the NAMIC Wiki. These data have been uploaded for use by other NAMIC Cores.

C. Significance

All these activities and works comply with the project's specific aims of Core 3.2. We have demonstrated that the multilateral collaboration proposed in the NAMIC is feasible and fruitful in achieving our research goals. We have established the value of Core 3.2 as a driving biological project in shaping the tools of the other NAMIC cores. By increasing the sample size and continuing tool development, we are confident that we will be able to test all our hypotheses associated with the specific aims.

D. Plans

In the next project year, we will continue with our proposed timeline to (1) implement the DLPFC segmentation algorithm into 3D Slicer of Brigham and Women's Hospital, (2) apply the semi-automated techniques to other forebrain structures to determine the level of organization at which the circuitry produces different schizophrenic syndromes, and (3) use PLC analysis to explore the functional connectivity between DPFC structures and other variables, such as behavioral performance and genetic profile.

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Core 4: Service

A. Specific Aims

The Service Core has four aims: (1) establish the computational infrastructure; (2) deploy collaboration resources; (3) support the software development process, and (4) foster the NAMIC community.

B. Studies and Results

Initial Core 4 activities have focused on establishing the initial collaboration infrastructure for NAMIC. This includes putting in place resources such as web pages, Wiki, mailing lists, and other supporting software services. We have also established the computing infrastructure (both hardware and software resources) necessary to research, develop, test and deploy the NAMIC software tools and data. Finally, we have participated with Cores 5 & 6 to disseminate the necessary information to enable the NAMIC community to use these resources.

The following list highlights Core 4 contributions to the NAMIC community in Core 4. These highlights are categorized as *hardware, software,* and *collaboration*.

- *Hardware*. We have purchased six systems dedicated to NAMIC. The NAMIC server is located at Brigham to leverage their high-bandwidth internet connectivity (Internet 2). Five other systems are located at Kitware. These systems are rack mounted with high-speed gigabit Ethernet connectivity. They are dedicated to testing ITK and Slicer on Linux and gcc compilers, Windows XP with MS Visual Studio Versions 6.0, 7.0, and 7.1 compilers, and Windows with the mingw tools.

- *Software*. We have installed and configured many supporting software packages. This includes the compilers and operating systems mentioned previously; the testing framework with DART, DART2 and CMake; dashboards for Slicer; Slicer bug tracker; CVS (for source code control), and various web servers. We have also installed many collaboration tools as described below.

- *Collaboration*. One of our most significant impacts has been the installation, configuration and maintenance of the NAMIC Wiki. We have also setup and maintain dozens of mailing lists. We also host many of the NAMIC web pages and other web resources. Finally, we are working with the dissemination and training cores (Cores 5 & 6) to organize and teach dissemination workshops.

C. Significance

From the very first task of creating the NA-MIC.org website Core 4 has been instrumental in providing the infrastructure to allow other Cores to do their work. The next tools deployed were email lists for the Pis, for the cores and for all, which were important to disseminate information at a formative stage of NAMIC; very quickly the Wiki was deployed, which has now been an important collaborative and record-keeping tool for all the activities within NAMIC.

In addition, deployment of resources including hardware, operating systems, compilers, and communications equipment are to support of Core 2 software development process, to insure the seamless integration of software and data; and to provide platforms for the delivery of technology to NAMIC and its customers.

D. **Plans**

Consistent with the original plan, Core 4 will continue to support primarily Core 2, but also the entire NAMIC community in its needs for hardware, software and other tools to allow collaboration and software development process.

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Core 5: Training

A. Specific Aims

The function of the training core is to provide an integrated educational program for all aspects of the NAMIC project and to enhance the multi-disciplinary training experience for the next generation of biomedical scientists.

B. Studies and Results

The first year of Core 5 has been expended in developing the educational materials in basic and clinical neurosciences, functional neuroimaging, computational infrastructure, and image acquisition and analysis.

At the NAMIC Kick-Off meeting in October 2004, the members of the NAMIC Training Core established means of coordinating our efforts, identified and prioritized our initial work. Working within Core 5 and jointly with Core 6, we have used email, teleconference calls, our own lab web sites and our NAMIC Wiki pages (http://www.na-mic.org/Wiki/index.php/Training:Main) to communicate and to disseminate our Training materials. Face-to-face meetings at NAMIC and other events (e.g. MICCAI) supplement this long distance communication. Notably at the February NAMIC AHM the Core 5 team agreed upon plans to focus training efforts in the domain of DTI acquisition and calibration with a goal of improving the quality of image data acquired by all our co-investigators, collaborators and the wider scientific community.

Development of training materials

The Training Core Wiki pages will be used to curate both NAMIC and non-NAMIC web based medical imaging educational materials.

The UNC group has developed a set of training and teaching tools to explore and understand diffusion tensor image data. The main purpose is to give users a hands-on experience with tensor data and some basic analysis and visualization options. These tools can be used in combination with other teaching material like overview presentations, book chapters, and papers describing fundamental issues. The tools are as follows:

A) **Glyph**: Representation of multi-planar orthogonal slice display of DTI fractional anisotropy and overlay of tensors displayed as ellipsoids. The size of the tensors reflects the magnitude of the apparent diffusion and the color coding reflects the directionality of the anisotropy. Users can define bounding boxes, minimum FA to display tensors, location and number of orthogonal planes, and a 3D rendering of the white matter surface.

B) **Fiber**: The "Fiber" tool offers the same visualization features as the "Glyph" tool, but demonstrates the basic idea of fiber tracking. A user interactively specifies a source location and can visually inspect the resulting streamline obtained by tracking the principal direction vector field.

C) **Conn**: The "Connectivity" tool is a re-implementation of the concept of Riemannian flow as developed by Lauren O'Donnell et. al., at MIT (NAMIC Core 1). Based on the selection of a seed point, e.g. placed in a strongly structured bundle, the program calculates the tensor warped distance as a 3D volume. The color-coded distance maps from the original DTI volume

are displayed side by side with multi-planar slice visualization. Users can interactively change slice locations and explore the 3D nature of the result.

D) **MriWatcher**: This is a display tool designed for simultaneous visualization of sets of volumetric image data. An arbitrary number of volumetric datasets, e.g. baseline DTI and gradient directions, or co-registered structural images and segmentation results, can be displayed simultaneously. This tool supports visual inspection for quality assurance checks for expert users as well as exploration to aid more novice users in understanding these complex image data. Users can zoom and pan images, change their intensity range, switch between axial, coronal and sagittal views, and even overlay existing multi-label segmentations with user-selected transparency.

The BWH/Brockton/MGH sites have worked separately and together to gather existing training materials for 3D Slicer, and develop updated materials to support the new release of Slicer version 2.4 (January 2005). Some of the development has been specifically tailored to fulfill the needs of Core 3 investigators, such as management of file formats from all Core 3 sites, visualization of 3D shapes/volumes- specifically hpc, tractography, co-registration of multi-modal datasets. This is being done in conjunction with the Core 2 Engineers who are developing the new modules and capabilities for 3D Slicer. Personnel from the Harvard sites (Randy Gollub, MGH and Sylvain Bouix, Ph.D., a computer scientist as well as three Research Assistants, Brockton) are all providing the expertise required for the 1:1 training effort at the Workshop.

Personnel from the Utah site have also participated in several training Workshops locally Feb17-18 2005: ITK Segmentation, and Summer 2005 Workshop: Object population description and general feature analysis framework (Martin Styner - UNC, Tom Fletcher - Utah, Jim Miller - GE Research) http://www.namic.org/Wiki/index.php/Engineering:Project:Feature_Analysis_Framework).

C. **Significance**

. As outlined in our grant proposal, we have focused our initial training efforts within the NAMIC community as they provide excellent beta testers for the materials to be shared with the scientific community when completed. Importantly, these materials are available to the scientific community. These materials are already in use for the support of the on-going Training and Dissemination Workshops, such as the May Dartmouth Workshop (see http://www.na-mic.org/Wiki/index.php/Dissemination:Workshop_May_26-27_2005).

D. **Plans**

Consistent with our original goals, the second year of NAMIC will focus on other training needs by the NAMIC community (Structural MRI, Image Registration, etc.), and the subsequent design of new tutorials. Some goals for the coming year include:

1. Develop metrics to determine the impact of our Training efforts and mechanisms to obtain user feedback for improvements.
2. Further customization and elaboration of Slicer training including additional Workshops to be offered summer 2005 at MGH, October 2005 at the BIRN AHM in San Diego.
3. Development of DTI image acquisition, distortion correction methods, and post-acquisition processing tutorial materials in collaboration with Allen Song (Duke) and Susumu Mori (Johns Hopkins) both members of the Morphometry BIRN testbed.

Principal Investigator/Program Director (Last, First, Middle): Kikinis, Ron Core 6

PROGRESS REPORT SUMMARY	GRANT NUMBER U54 EB005149	
	PERIOD COVERED BY THIS REPORT	
PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR Ron Kikinis, M.D.	FROM 09/17/04	THROUGH 07/31/05

APPLICANT ORGANIZATION
Brigham and Women's Hopital

TITLE OF PROJECT (Repeat title shown in Item 1 on first page)
National Alliance for Medical Computing (NAMIC)

A. Human Subjects (Complete Item 6 on the Face Page)

Involvement of Human Subjects ☒ No Change Since Previous Submission ☐ Change

B. Vertebrate Animals (Complete Item 7 on the Face Page)

Use of Vertebrate Animals ☒ No Change Since Previous Submission ☐ Change

SEE PHS 2590 INSTRUCTIONS.

WOMEN AND MINORITY INCLUSION: See PHS 398 Instructions. Use Inclusion Enrollment Report Format Page and, if necessary, Targeted/Planned Enrollment Format Page.

Please see attached report.

National Alliance for Medical Image Computing (NAMIC)

Core 6: Dissemination

A. Specific Aims

The Aims of the Dissemination Core did not change from the original submission. With release of the NIH program announcement for collaboration grants with the NCBCs, the Dissemination Core took on the role of organizing and coordinating the application process.

B. Studies and Results

The Dissemination Core was extremely active in outreach activities as described in more detail in the attached progress report. Our strategy during the first year of the Center's existence was to work with all the Alliance sites to develop a curriculum of basic material with which to bring new researchers into the NA-MIC software engineering methodology and familiarize them with the existing toolset. This effort was implemented through a series of workshops held at various institutions on both coasts and documented on the NA-MIC Wiki. These Wiki pages contain the agendas and the presentation material including software and sample data sets. By opening these workshops beyond the NA-MIC investigator group, we have begun to recruit additional research partners and are establishing the collaboration framework as described in Specific Aim 1. Each of these workshops has included significant question and answer time to solicit input from the community and an electronic feedback system has been incorporated into the Wiki so that attendees can provide suggestions about areas for NA-MIC research. This feedback has been transferred through participation Drs. Pieper and Kapur in the NA-MIC Algorithm and Engineering teleconferences and other communication (addressing Specific Aim 2). The NA-MIC mailing lists, Wiki (http://wiki.na-mic.org) and NA-MIC web site (http://www.na-mic.org) are managed by the Dissemination Core in collaboration with the Service Core in support of Specific Aim 3. These resources, in particular the Wiki, have proven to be of tremendous value in organizing the work and materials of the geographically dispersed Alliance.

C. Significance

While it is too early to measure the specific impact of the Dissemination Core activities on clinical research, each of our workshops has led to the initiation of new joint projects among previously independent researchers. Often, this takes the form of application of existing techniques (typically drawn from ITK, Slicer, or the LONI Pipeline) to data already collected. We expect to see publications arising from these new initiatives to begin appearing in the next year. Examples include the application of ITK K-Means statistical classifiers to DTI Tractography by MIT researcher Lauren O'Donnell after a Developer Dissemination Workshop at MIT, and the application of Slicer's DTMRI Module to DWI data collected at Dartmouth as a result of the User Dissemination Workshop held at Dartmouth.

D.Plans

In the second year of the Center we plan to widen the circle of activities for the Dissemination Core beyond the first year's focus on Alliance investigator sites. Where the first year events were

held at MIT, BWH, University of Utah, UCSD, and Dartmouth, we plan to hold sessions at outside locations. Plans in preparation include a workshop in conjunction with the MICCAI, ISMRM, RSNA conferences, a training workshop in Switzerland, and a session at the NIH. Specific venues will be formalized during the coming months. We plan to hold further retreats as well – an initial programmer's retreat is planned for the last week of June 2005 where over 30 programmers from NA-MIC sites will get together to work on specific programming projects. We have also received requests from end users to hold a similar type of event where users will bring their data to a retreat where they will be trained in depth on processing and analyzing these data using the NA-MIC tools. Both these types of retreats will by organized using the Wiki and will serve as opportunities to collect information that needs to be channeled between the algorithm/engineering efforts and the broader biomedical research community.

PROGRESS REPORT SUMMARY

GRANT NUMBER
U54 EB005149

PERIOD COVERED BY THIS REPORT

PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR	FROM	THROUGH
Ron Kikinis, M.D.	09/17/04	07/31/05

APPLICANT ORGANIZATION
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Please see attached report.

National Alliance for Medical Image Computing (NAMIC)

Core 7: Management

A. Specific Aims

The function of the management core is to provide a flexible yet effective administrative structure for managing the many collaborative activities of 3 technology and 4 service cores of NAMIC.

B. Studies and Results

To achieve the aim above, Core 7 has executed on a management plan that called for a balanced management strategy that accommodates shared decision-making and mutual responsibility among the core PIs, while providing the oversight and leadership in central functions, inter-Core or extra-NAMIC activities and functions.

Some of the results and activities of the past year are delineated below:

1. Finance and administration

NOGA for NAMIC was received on September 17, 2004. From this date onwards 17 subcontracts for 14 sites were prepared and sent out. In addition, at BWH, the accounts for all 7 Cores were created so that all invoices that arrived would be charged against the correct accounts. Core 7 members review all invoices coming through and recommend for approval by the PI, Ron Kikinis.

Invariably, some cores need to make changes to their subcontracts, which Core 7, coordinate with BWH Finance as well as the Finance departments of the corresponding institution.

In April 2005, Core 7 sent out reminder for the Progress Report and has coordinated the financial as well as science progress report collection for arrival at NIH by June 1, 2005.

2. IRB coordination

Early on, Core 7 coordinated efforts with Core 3 (the DBPs) to allow access to their retrospective data by NAMIC members so that Core 1 and Core 2 could start their work. All 4 DBPs (Harvard/VA, Dartmouth, UCI and U of Toronto/CAMH) we able to amend their IRB protocols at their respective sites to allow sharing of their retrospective data to the NAMIC community. After this was achieved, BWH approached the IRB committee at Partners Healthcare (IRB body for BWH) to allow secondary-use IRB protocol for all of NAMIC—although the data was not collected at BWH, it was important to get the approval as BWH was a "transit" point and the NAMIC contract with NIH was signed with BWH.

In March 2005, coordination for prospective data from the same 4 DBP sites was started. At the time of this writing all but Harvard/VA IRB for prospective data collection for NAMIC was approved. After Harvard/VA prospective data IRB is approved, Core 7 will again approach Partners Healthcare for secondary-use IRB approval for sharing the prospective data.

3. All-Hands-Meetings

Within 4 weeks of the NOGA, Core 7 brought all the Cores and participants together for introductions to each other and also to NAMIC at a Kickoff Meeting on October 15, 2004. At the

conclusion of the Kickoff Meeting the goal was to have an AHM within 6 months to start substantive coordination of science. The few months of the year was expended in setting up the finance/administrative infrastructures and securing IRB approvals and setting up processes—in the interim, all Cores and their PIs were also coordinating among themselves. Hence, in November 2004, Core 7 members picked late February 2005 in Salt Lake City to be date and venue of the AHM.

By all accounts, the AHM was a resounding success. We had 85 participants from all Cores as well as NIH. All the Core PIs presented their activities as well as goals for the year. Inter-Core workshops, primarily between Core 1 and Core 3, Core 1 and Core 2 as well as different sites within the same Core, e.g. sites from Core 1, sites from Core 2 and sites from Core 3 were able to discuss and coordinate their efforts. It was helpful to have NIH members as participants as much helpful feedback was gleaned from.

Logistically, the venue, the hotel and the date worked very well. Using the Wiki as the primary coordinating tool was invaluable. Our colleagues from University of Utah were very helpful in making local arrangements.

C. **Significance**

Coordinating and securing secondary-use IRB approval from the 4 DBP sites as well as BWH for sharing retrospective data early on in NAMIC's Year01 was critical. Until some data was available, Core 1 could test their algorithms and Core 2 would not be able to make full use of the engineering/software processes and platform that they were building and as a result Core 3 (DBPs) would not be served and Dissemination and Training Cores would also be affected. Hence, the decision was made at the outset to get IRB approvals in two-steps: a) Retrospective data from other projects to be shared with NAMIC and b) Prospective data specifically for NAMIC.

In a complex, multi-site national project like NAMIC, face-to-face interactions with colleagues is critical. After months of email or teleconference, an All-Hands-Meeting was very important for all. Many decision among a single core or between cores were made; some NAMIC-related issues such as data sharing, publishing and authorship conventions, IRB filings and cooperation among researchers outside NAMIC were discussed. The AHM achieve its intended goal and we hope to have an annual AHM at a different collaborator's hometown.

D. **Plans**

Core 7 will continue with the plan of balanced management strategy—we do not want to have too strong a central control (we believe different Cores and leadership from their PIs is very good), yet we do take a proactive role in inter-core or extra-NAMIC activities as well as central functions such as finance and IRB approval for data that is generated. We will continue to plan one or two AHMs per year and will also run and participate in frequent teleconferences to understand the needs and difficulties of the researchers to make NAMIC a successful, multi-site national project.

Progress Report 2005, Year 1

National Alliance for Medical Image Computing

Core 1 at MIT

We describe progress by the MIT site for Year 1 of the NA-MIC project. While our primary activities within NA-MIC have focused on the integration of algorithms into the NA-MIC toolkit (either by incorporation into ITK or into Slicer) we have also focused efforts on refinement and extension of algorithmic methods to meet requirements from Core 3 collaborators.

Shape-Based Segmentation

The goal of this project is to augment the segmentation process with prior information on the shape of the anatomical structures (shape atlas) learned from previously segmented scans (using, for example, Principal Component Analysis). We are working on methods that integrate shape atlases with two types of segmentation algorithms as described below.

Boundary Localization: This class of algorithms explicitly manipulates the representation of the object boundary to fit the strong gradients in the image, indicative of the object outline. Bias in the boundary evolution towards the likely shapes improves the robustness of the segmentation results when the intensity information alone is insufficient for boundary detection.

This approach builds on earlier algorithmic developments by the MIT group, which pioneered the use of shape priors in deformable surface based segmentation methods. These methods use a distance map to represent the shape of a segmented structure, and learn a statistical description of shape variation from a set of training examples. During segmentation, a level-set based implementation evolves a distance map to segment a new scan. The evolution couples information about strong gradients in the image (likely boundaries) with continuity properties of the shape. In addition, by adding prior shape information from the learned model, the algorithm both guides the final solution to the correct location, and uses knowledge of likely shapes to interpolate across subtle boundaries.

This approach has been used both to segment individual structures and to use learned properties of relative shape and layout to segment sets of nearby structures. In the latter case, landmarks of readily visible structures can be used as anchor points to guide the segmentation of more subtle structures.

Software

A version of this approach already exists in ITK.

Publications

Michael Leventon, Eric Grimson, Olivier Faugeras. "Statistical Shape Influence in Geodesic Active Contours" Comp. Vision and Patt. Recon. (CVPR), 2000.

Michael Leventon, Olivier Faugeras, Eric Grimson, William Wells. "Level Set Based Segmentation with Intensity and Curvature Priors" Mathematical Methods in Biomedical Image Analysis. (MMBIA), 2000.

A. Tsai, W. Wells, C. Tempany, E. Grimson, A. Willsky, "Mutual Information in Coupled Multi-Shape Model for Medical Image Segmentation", Medical Image Analysis 8:429-445, 2004.

Voxel Classification: This type of algorithm assigns a tissue type to each voxel in the volume. The object boundaries are represented implicitly as boundaries of regions with uniform labels. Incorporating prior shape information biases the label assignment towards contiguous regions that are consistent with the shape model.

Algorithms developed under this approach build on a long sequence of approaches, starting with the original Expectation/Maximization segmenter. Recent work, partially funded under other sources, has extended the EM segmentation approach to include several key factors: incorporation of shape information that biases the label assignment towards regions more consistent with general anatomical structures; hierarchical methods that use coarse tissue classes for initial segmentation, then provide refined regions of interest in which to focus more detailed models. We have used this approach to segment up to 30 different neuroanatomical structures.

Software

A prototype implementation has already been developed and tested on some of the data available through NA-MIC. More importantly, integration into Slicer is in progress. Once this integration is complete, the algorithms will be available to collaborators for testing on a broader range of datasets.

Publications

W.M. Wells, III, W.E.L. Grimson, R. Kikinis, and F.A. Jolesz, Adaptive Segmentation of MRI data, IEEE Trans. Medical Imaging, **15**(4):429—442, 1996.

Kilian M. Pohl, Simon K. Warfield, Ron Kikinis, W. Eric L. Grimson, William M. Wells. Coupling Statistical Segmentation and PCA Shape Modeling, Seventh International Conference on Medical Image Computing and Computer Assisted Intervention, LNCS 3216, Springer, 2004, p. 151 - 159, 2004.

Kilian M. Pohl, John Fisher, W. Eric L. Grimson, William M. Wells. An Expectation Maximization Approach for Integrated Registration, Segmentation, and Intensity Correction. CSAIL Publications - Artificial Intelligence Series Publications, AIM-2005-010, 2005.

Shape Analysis Across Populations

Our goal in this project is to develop mathematical modeling approaches to comparing populations based on the shape of anatomical structures. In contrast with shape-based segmentation that utilizes a statistical model of the shape variability in one population (typically based on the Principal Component Analysis) we are interested in identifying and characterizing differences between two sets of shape examples. We use the discriminative framework to characterize the differences in shape by training a classifier function and studying its sensitivity to small perturbations in the input data.

Software

Stand alone code exists for training a classifier, as well as for jackknifing and permutation testing. Current plans include integration within the shape analysis pipeline, in collaboration with UNC (Martin Styner). This integration process is underway, with detailed discussions between MIT and UNC ongoing.

Publications

P. Golland, W.E.L. Grimson, M.E. Shenton, R. Kikinis. Detection and Analysis of Statistical Differences in Anatomical Shape. Medical Image Analysis, 9(1):69-86, 2005.

P. Golland and B. Fischl. Permutation Tests for Classification: Towards Statistical Significance in Image-Based Studies. In Proc. IPMI'2003: The 18th International Conference on Information Processing and Medical Imaging, LNCS 2732:330-341, 2003.

DTI Analysis and Visualization

Our work in DTI analysis focuses on identifying new ways to provide an interpretation of the white matter connectivity. In the past, we have demonstrated ways to characterize the strength of connectivity between selected regions in the brain based on several alternative ways to integrate local diffusion tensor measurements into a global field that provided connection strength estimates for

distant points. Our current work aims to provide structural description of the white matter as partitioned into coherent fiber bundles and clusters.

In particular, we are developing algorithms that measure connectivity of white matter using geodesic flow information, and that measure connectivity by directly tracking local orientation preferences at voxels. Secondly, we are development algorithms for clustering tensor information into coherent bundles. Borrowing techniques from the computer vision field, we have designed prototype methods for clustering connected tracts based on commonality of orientation, proximity and strength of local anisotropy. These methods can further partition the large numbers of tracts into coherent regions. Of particular interest is the consistency of such clusters across subjects, an issue that we are in the process of evaluating. If consistent clusters can be extracted from different subjects, this would then support the comparison of white matter properties across subjects, as well as building shape atlases of white matter tracts, which could then be factored into the segmentation methods described above. Work on this front is ongoing.

Software

Implementations of our visualization algorithms are already integrated into Slicer.

Publications

Lauren O'Donnell, W. Eric L. Grimson, Carl-Fredrik Westin. Interface Detection in Diffusion Tensor MRI. MICCAI, 360-367, 2004.

Lauren O'Donnell, Steven Haker, and Carl-Fredrik Westin. New Approaches to Estimation of White Matter Connectivity in Diffusion Tensor MRI: Elliptic PDEs and Geodesics in a Tensor-Warped Space. MICCAI, 459-466, 2002.

Collaborations with other groups in NA-MIC

We have established working collaborations both within the Algorithms Core and with the Driving Biological Problems Core.

- Algorithms:
  - Shape Analysis: joint pipeline I/O formulation and development with UNC (Martin Styner).
- Clinical:
  - Continuing collaboration with Harvard on shape-based segmentation and DTI analysis.
  - New collaboration, enabled and facilitated by NA-MIC, with Dartmouth on DTI and fMRI analysis.

Progress Report 2005, Year 1
National Alliance for Medical Image Computing
Core 1 at MGH

Scientific Accomplishments

The Algorithms Core (Core 1) at MGH is charged with developing advanced algorithms for group-level analysis of diffusion MRI data. This involves capitalizing on our existing experience on novel, high angular resolution diffusion acquisition as well as the tools for visualization and analysis that have been developed (Figures a & b). In this cycle, the two most significant contributions from our group included:

- ***Porting q-ball imaging into the 3DSlicer environment***, This will allow for visualization of high angular resolution diffusion imaging data by research/clinical sites which use 3DSlicer. Additionally, we have defined a process for migrating algorithms developed at MGH into the 3DSlicer environment (Figure c).

- ***Development of algorithms for statistical group comparison of DTI***. This has enabled group-level analysis of DTI data in a number of clinical applications as evidenced by our publication record for this cycle (see Applications, below).

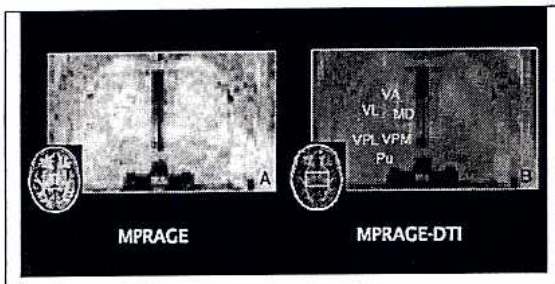

Fig. a) DTI of thalamic nuclei.

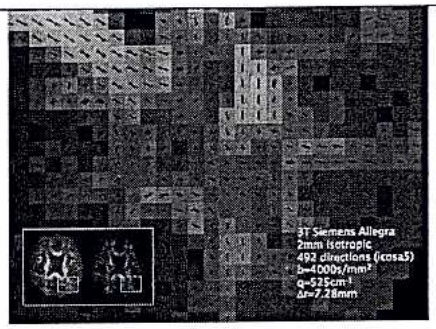

Fig. b) High angular resolution diffusion MRI

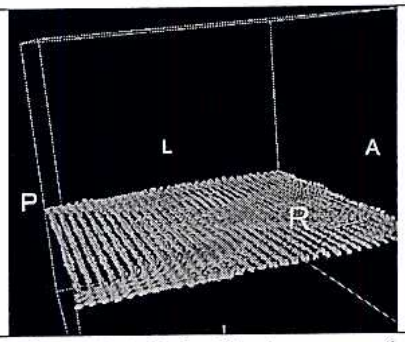

Fig c) Q-ball image (axial orientation) rendered in 3DSlicer.

Example Applications

As these techniques are being developed and ported into the NA-MIC environment, it is critical that actual biological applications are engaged, in order to validate and text the quality and usability of the resultant analytic techniques. To this end, we report example applications that utilize these new algorithms.

q-Ball imaging of macaque white matter architecture

Diffusion-weighted magnetic resonance imaging holds substantial promise as a technique for noninvasive imaging of white matter (WM) axonal projections. For diffusion imaging to be capable of providing new insight into the connectional neuroanatomy of the human brain, it will be necessary to histologically validate the technique against established tracer methods such as horseradish peroxidase and biocytin histochemistry. The macaque monkey provides an ideal model for histological validation of the diffusion imaging method due to the phylogenetic proximity between humans and macaques, the gyrencephalic structure of the macaque cortex, the large body of knowledge on the neuroanatomic connectivity of the macaque brain and the ability to use comparable magnetic resonance acquisition protocols in both species. Recently, it has been shown that high angular resolution diffusion imaging (HARDI) can resolve multiple axon orientations within an individual imaging voxel in human WM. This capability promises to boost the accuracy of tract reconstructions from diffusion imaging. If the macaque is to serve as a model for histological validation of the diffusion tractography method, it will be necessary to show that HARDI can also resolve intravoxel architecture in macaque WM. We have sought to test whether the technique can resolve intravoxel structure

inmacaque WM. Using a HARDI method called q-ball imaging (QBI) it was possible to resolve composite intravoxel architecture in a number of anatomic regions. QBI resolved intravoxel structure in, for example, the dorsolateral convexity, the pontine decussation, the pulvinar and temporal subcortical WM. In Figure d, we see that the multi-modal diffusion (MMD) can be seen at the intersection (arrow 1) between the projections of the scc (red) and the superior–inferior directed fibres (blue–green) connecting to the motor cortex, and where the projections segregate into the superior parietal lobule (SPL) and postcentral gyrus (PoG, arrow 2). MMD is also seen in the WM beneath the supramarginal gyrus (SMG; arrow 3), including a lateral (red) component along the gyral axis and a transverse anterior–posterior component (bright green). The parietal lobule has dense reciprocal connections with visual association, cingulate, premotor and prefrontal cortical areas (Petrides & Pandya 1984). The intersection of intrinsic and extrinsic parietal lobule fibres is demonstrated in the ODF map (arrow 2). Extrinsic fibres from this area of the parietal lobule, specifically the SPL and dorsal bank of the intraparietal sulcus (itps), contribute to the superior longitudinal fasciculus (slf), frontooccipital fasciculus and bcc.

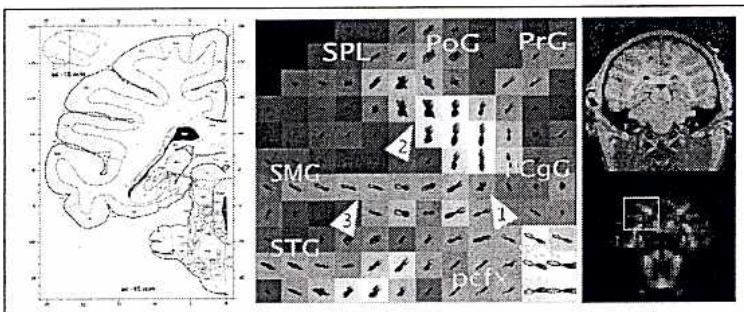

Fig. d) Diffusion orientation distribution function (ODF) map of precentral gyrus (PrG) and the dorsolateral convexity which includes, respectively, projections to the motor, parietal and temporal cortices. See text.

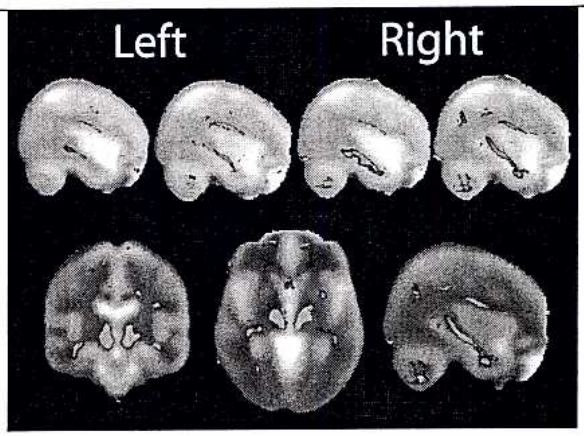

Fig. e.) Voxel-based statistical maps demonstrating regions of altered FA in CAA compared to CON in four sagittal slices in the top panel, and in the coronal (left) axial (center) and sagittal (right) planes in the bottom panel. FA was significantly reduced in temporal and frontal white matter and in the splenium of the corpus callosum

Cerebral Amyloid Angiopathy

Cerebral amyloid angiopathy (CAA) is a neurological condition in which ß-amyloid is deposited in the small and medium-sized vessels of the brain and meninges. This deposition contributes to reduced vessel integrity resulting in white matter damage, cognitive impairment, and most noticeably, hemorrhagic stroke. We used diffusion tensor imaging (DTI), a neuroimaging technique providing sensitive measures of white matter tissue structure, to evaluate the anatomic distribution of white matter degeneration in participants diagnosed with advanced CAA. DTI was obtained from 11 participants diagnosed with CAA-related intracerebral hemorrhage and 13 matched healthy control participants. Spatially normalized maps of diffusion anisotropy (fractional anisotropy; FA) were compared using voxel based t-test and region of interest analyses. FA was reduced in CAA in a number of white matter regions, including temporal white matter and the splenium of the corpus callosum. FA was increased in CAA in the posterior limb of the internal capsules and subthalamic gray matter regions (likely including the red nucleus and the substantia nigra). FA was not statistically reduced in the anterior corpus callosum or anterior limb of the internal capsule, consistent with the predominantly posterior distribution characteristic of CAA. FA reduction was bilateral and did not depend on the hemisphere of the cerebral hemorrhage. These findings suggest that white matter degeneration is a regional feature of CAA and not an epiphenomenon related to post hemorrhagic degeneration. As seen in Figure e), there was an increase in FA in subthalamic gray matter nuclei as well as portions of the posterior and anterior limb of the internal capsule. The colorscale shows regions of increasingly significantly reduced FA in CAA in the red to yellow

range (yellow indicates greatest reduction from p = .05 to p = .001), and significantly increased FA in CAA in the dark to light blue range (light blue indicating greatest increase from p = .05 to p = .001).

Diffusion and Behavior

Humans exhibit significant interindividual variability in cognitive performance ability, yet little is known about the underlying neural mechanisms for such variability. It has been proposed that interindividual variations in white matter (WM) composition may play a role in individual cognitive performance differences, although such a relationship has never been shown in young healthy adults. Using diffusion tensor MRI (DTI) we sought to test whether the diffusion tensor fractional anisotropy (FA), a marker of WM microstructural integrity, is correlated with behavioral reaction time (RT) on a self-paced choice RT task. In young healthy adults, choice RT performance was found to be highly correlated with FA in specific WM pathways including the right optic radiation, right superior parietal gyrus, cerebellum, bilateral superior temporal gyrus, and left frontal WM. The right laterality of the correlation in the visual pathway is consistent with the right lateralization of visuospatial attention. The localization of the correlation to the occipital, parietal, and frontal cortex, but not to motor cortex or the callosum argues that the predominant factors affecting performance on the choice RT task are visuospatial attention and action selection as opposed to motor performance or interhemispheric transmission. The correlation between RT and FA suggests that WM physiology may be a key factor in behavioral performance ability (see Figure f).

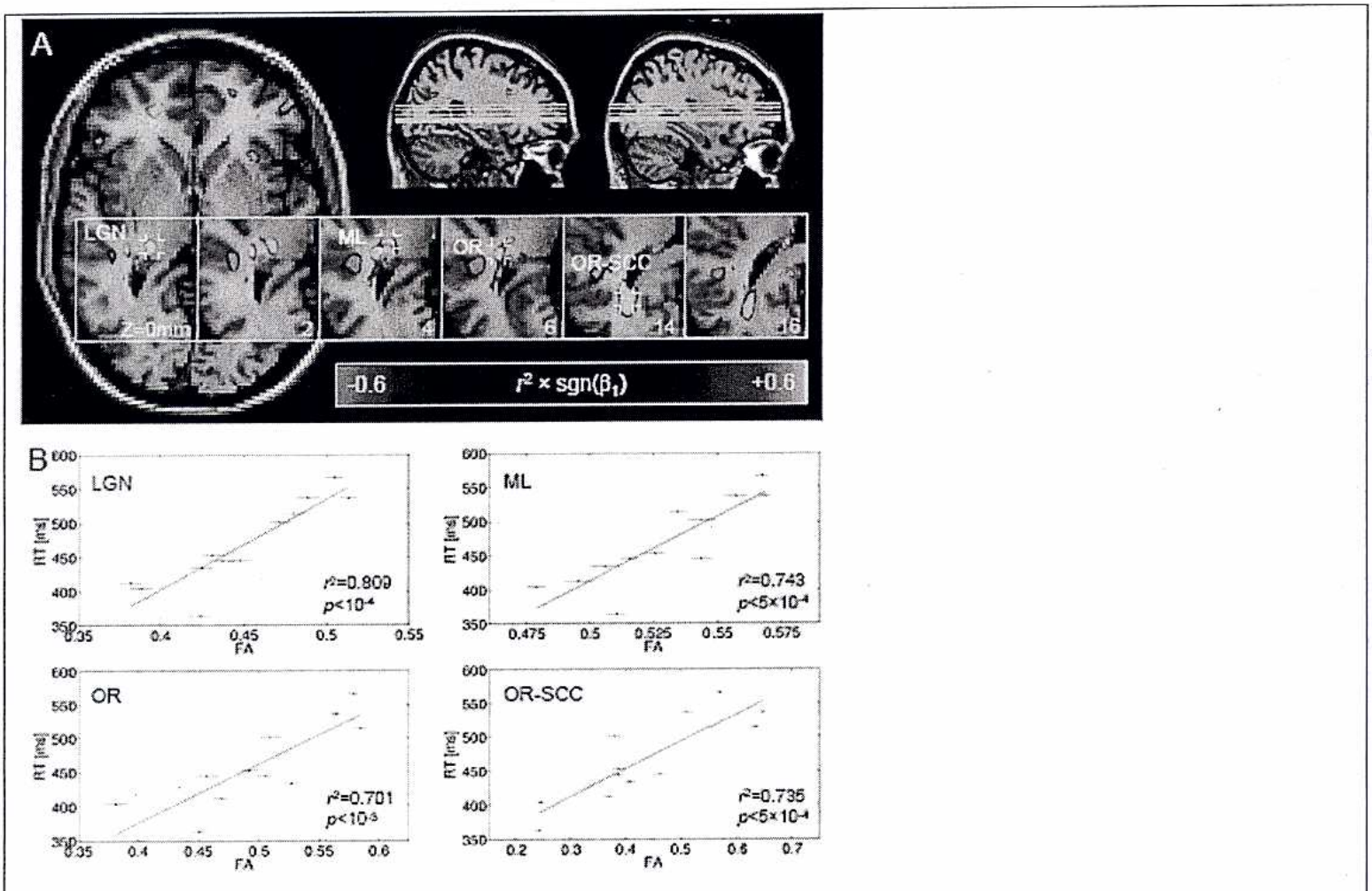

Fig e) Map of correlation between diffusion anisotropy and reaction time shows right optic radiation. (A) The small frames show the correlation maps from 6 axial slices through the optic radiation. The superior-inferior level of the axial slices is indicated by the yellow lines in the sagittal images at top right and by the MNI/Talairach Z-coordinate at the bottom-right of each frame. The RT-FA correlation map shows the trajectory of the right visual pathway from lateral geniculate nucleus (lgn) through Meyer's Loop (ml) to optic radiation (or) to the junction between the optic radiation and the splenium of the corpus callosum (or-scc). (B)

RT and FA values for the ROIs designated by the crosshairs above. The FA values were taken from 3×3×3 voxel ROIs centered on the peak of the correlation. The FA error bars are SEM over each subject's ROI.

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NAMIC-enabled Papers and Conference Abstracts

Papers

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Salat DH, Smith EE, Tuch DS, Benner T, Schwab K, Rosas HD, Rosand J, Greenberg SM. CAA-related alterations in brain white matter measured by diffusion tensor imaging. 2005 (in review)

Tuch DS, Salat DH, Wisco JJ, Hevelone ND, Zaleta A, Rosas HD. Choice reaction time performance correlates with diffusion anisotropy in white matter pathways supporting visuospatial attention. 2005 (in review)

Tuch DS, Wisco JJ, Khachaturian MH, Ekstrom LB, Kotter R, Vanduffel W. Q-ball imaging of macaque white matter architecture. *Philos Trans R Soc Lond B Biol Sci.* 2005 (in press).

Conference abstracts

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Da Silva AFM, Snyder J, Tuch DS, Hadjikhani N. Diffusion tensor imaging (DTI) of migraine patients. 34th Annual Meeting of the Society for Neuroscience, San Diego, CA, 2004.

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Salat DH, Yu P, Tuch DS, Hevelone ND, Fischl B, Rosas HD. Detailed Analysis of Age-Related Changes in the Corpus Callosum: Combined DTI and Morphometric MRI. 11th Annual Meeting of the Organization for Human Brain Mapping, Toronto, Canada, June 2005.

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Whitcher B, Tuch DS, Wang L. The wild bootstrap for quantifying variability in DTI. 13th Scientific Meeting of the International Society for Magnetic Resonance in Medicine, Miami, FL, 2005.

Yu P, Salat DH, Golland P, Tuch DS, Rosas HD, Fischl B. Subdividing the Corpus Callosum Based on Morphometry and Diffusion Anisotropy. 13th Scientific Meeting of the International Society for Magnetic Resonance in Medicine, Miami, FL, 2005.

Ziyan U, Wisco JJ, Tuch DS. Hierarchical segmentation of thalamic nuclei using spectral clustering. 13th Scientific Meeting of the International Society for Magnetic Resonance in Medicine, Miami, FL, 2005.

Progress Report 2005, Year 1
National Alliance for Medical Image Computing
Core 1 at Georgia Tech

A) Progress in Core 1 at Georgia Tech

We have described a new framework for white matter tractography in high angular resolution diffusion data. A direction-dependent local cost is defined based on the diffusion data for every direction on the unit sphere. Minimum cost curves are determined by solving the Hamilton-Jacobi-Bellman using an efficient algorithm. Classical costs based on the diffusion tensor field can be seen as a special case. While the minimum cost (or equivalently the travel time of a particle moving along the curve) and the anisotropic front propagation frameworks are related, front speed is related to particle speed through a Legendre transformation which can severely impact anisotropy information for front propagation techniques. Implementation details and results on high angular diffusion data show that this method can successfully take advantage of the increased angular resolution in high b-value diffusion weighted data despite lower signal to noise ratio. See Figure 1 below for an illustrative example..

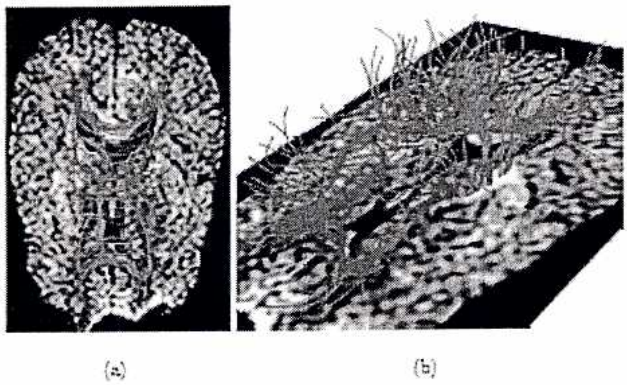


Figure 1: Fiber tracking from high resolution data set. (Taken from NA-MIC supported work: E. Pichon, C.-F. Westin, and A. Tannenbaum, ``A Hamilton-Jacobi-Bellman approach to high angular diffusion tractography," submitted to *Proceedings of MICCAI*, 2005.)

We have also done work on shape analysis. Our approach is motivated by the observation that shape variation in a population that is localized in space and scale cannot be well described by standard PCA analysis. In addition, PCA suffers from poor approximation properties when the training set is small. To address these issues, we have developed a novel algorithm that learns the shape variation at ***multiple scales and locations*** based on a training set. Our technique uses spherical wavelets to generate a multiresolution description of surfaces and spectral graph partitioning to adaptively discover independent shape variations at multiple scales. Our results show that our algorithm significantly improves the approximation of shapes in a testing set over PCA that tends to oversmooth the data. We also use our technique as a shape prior in a segmentation task and compare it to PCA. Figure 2 below illustrates some results on prostate data.

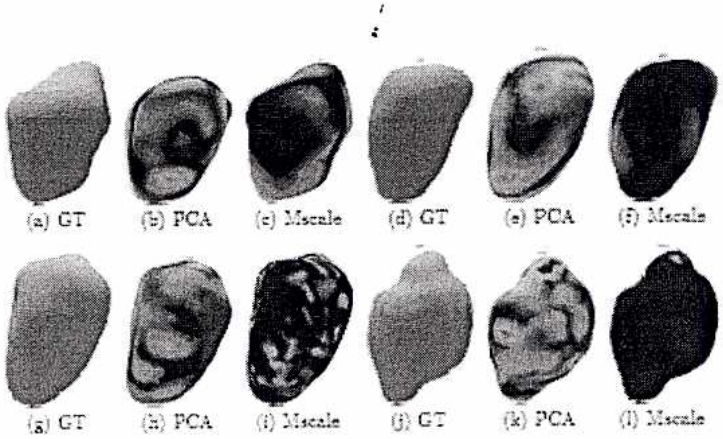


Figure 2: Ground Truth (GT) and Reconstructed (R) Shape using the PCA a nd Multiscale (Mscale) priors for (a-f) 5 training samples (g-l) 30 Training Samples. Color is error from blue (lowest) to red (highest). (Taken from NA-MIC supported work: D. Nain, S. Haker, and A. Tannenbaum, ``Multicale shape analysis using spherical wavelets," submitted to *Proceedings of MICCAI*, 2005.)

We have also described a model of stochastic snakes based on the theory of interacting particle systems. This is based on some previous work in which we described a stochastic interpretation of curve shortening flows. This brought together the theories of curve evolution and hydrodyNA-MICal limits, and as such impacted on the growing use of joint methods from probability and partial differential in the image processing and computer vision. This theory has now been implemented in order to forge a novel stochastic curve evolution algorithm that may provide an alternative to level set techniques for various medical imaging tasks including segmentation and registration.

B) Two Highlights

Highlights 1 [Algorithmic Development and Software Transfer]:
(a) Software transfer is a key part of the NA-MIC mission. Accordingly, we have already transferred two key pieces of software to the ITK platform. The first is a new algorithm for 3D medical image segmentation. The algorithm is based on minimizing a global energy defined from a learned non-parametric estimation of the statistics of the region to be segmented. The source code is freely available as part of the NA-MIC program. The method is now available as part of ITK and preliminary versions are also available on 3D Slicer.

(b) We have also put our knowledge-based segmentation algorithm on ITK. The idea is that we can augment segmentation approaches with knowledge of object shape to guide segmentation in uncertain regions. A natural way of doing this which combines

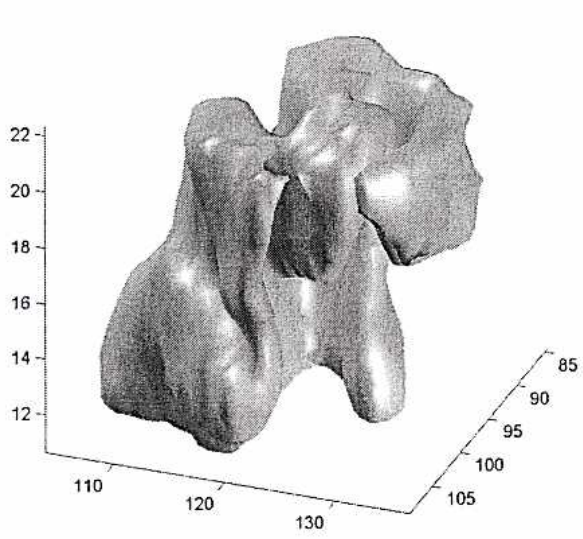
statistical and curvature driven is to smooth the posterior probabilities and then extract a maximal a posteriori (MAP) classification in segmenting the given image. More precisely in the Bayesian framework, we can calculate the posteriors $P^c_i = Pr(C_i = c|V_i = v)$ (the C's are the possible classes and the V's the intensities) and smooth by evolving P^c according to the affine geometric heat flow equation, under which the level sets of P^c undergo affine curve shortening whilst preserving edges. This approach has a very strong connection to Markov random field (MRF) techniques. Indeed, the prior smoothing of the posterior probabilities gives the MAP solution to a discrete MRF with a non-interacting, analog discontinuity field. The combination of a discontinuity field with a discrete MRF can have some important consequences since it allows the disabling of clique potentials across discontinuities. This is in contrast to the isotropic (linear) smoothing of the posterior probabilities, which corresponds to computing the MAP solution of a single discrete MRF using continuous relaxation labeling.

Highlights 2 [Progress in Medical Imaging Research]:

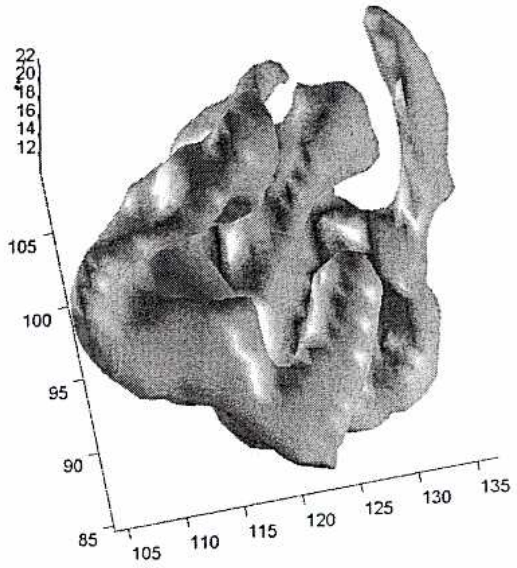
(a) We have made some theoretical progress that will impact our NA-MIC related work. First of all, we have put directionality explicitly into the conformal geometric active contour framework for our work in DTI tractography.

(b) Further using a new basis based on spherical wavelets and a conformal flattening technique, we are developing a new statistical way of describing anatomical shape. We are particularly interested in applying this technique to the caudate nucleus as part of our NA-MIC supported research.

(c) Finally, we have developed a new ruled-based procedure for the segmentation of DLPFC. Specifically, we have incorporated rules formulated by our Core 3 collaborator, Professor James Fallon of UCI, into a semi-automatic segmentation module that cuts the segmentation time by about 60%. We are planning to incorporate this as well first into ITK, and then the 3D Slicer after further validation of the results. An example of the result of this procedure is given in Figure 3 below.



Side-Anterior-Inferior View



Anterior View

Figure 3: Results of Semi-Automatic Segmentation Procedure Based on Fallon's Rules (Work of NA-MIC supported researcher Ramsey Al-Hakim.)

C) Details of Federally Funded Researchers

Allen Tannenbaum (PI at Georgia Tech)
Delphine Nain (Graduate Student)
Eric Pichon (Graduate Student)
Ramsey Al-Hakim (Undergraduate Research Assistant)

D) List of Papers that Acknowledge NA-MIC Support

1. Eric Pichon and A. Tannenbaum, ``Pattern detection and image segmentation with anisotropic
conformal factors" (with E. Pichon), to appear in *ICIP*, 2005.

2. A. Szymczak, K. Mischaikow, and A. Tannenbaum, ``Segmentation of blood vessels: a topological
approach" (with A. Szymczak and K. Mischaikow), *SPIE*, 2005.

3. E. Pichon, C.-F. Westin, and A. Tannenbaum, ``A Hamilton-Jacobi-Bellman approach to high angular diffusion tractography,'' submitted to *Proceedings of MICCAI*, 2005.

4. D. Nain, S. Haker, and A. Tannenbaum, ``Multicale shape analysis using spherical wavelets,'' submitted to *Proceedings of MICCAI*, 2005.

5. M. Niethammer, A. Tannenbaum, W. Kalies, and K. Mischaikow, ``Detecting simple points in higher dimensions," submitted for publication in *IEEE Image Processing*, 2005.

6. O. Michailovich and A. Tanenbaum, ``Fast approximation of smooth functions from samples of partial derivatives," submitted for publication to *IEEE Signal Processing,* 2005.

7. D. Nain, A. Tannenbaum, G. Unal, A. Yezzi, and O Zeitouni ``On a stochastic model of geometric snakes," to appear in *Mathematical Methods in Computer Vision: A Handbook*, edited by O. Faugeras and
N. Paragios, Springer-Verlag, 2005.

8. A. Angenent, A. Yezzi, A. Tannenbaum, and O. Zeitouni ``Curve shortening and interacting particle systems," to appear as a book chapter in a volume edited by Hamid Krim, 2005.

9. M. Niethammer, P. Vela, and A. Tannenbaum ``On the evolution of closed curves by means of vector
distance functions," to appear in *Int. Journal Computer Vision*, 2005.

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National Alliance for Medical Image Computing

Core 1 at UNC

STRUCTURAL ANALYSIS OF ANATOMICAL SHAPES AND OF WHITE MATTER TRACTS

PRINCIPAL INVESTIGATOR, Guido Gerig, UNC Chapel Hill

Co-Investigator DTI Processing: Isabelle Corouge, UNC Chapel Hill

A: Activities in Analysis of White Matter Tracts

A.1 General Description:

We are developing a NA-MIC toolkit for quantitative analysis of white matter tracts extracted from MR-DTI data. In year one, we are putting all necessary computing and user interaction components as standardized ITK modules into a stand-alone prototype environment (FiberViewer). Key modules go into the NA-MIC sand-box to be tested for integration into SLICER. The prototype FiberViewer will be tested on Core-3 data and will be given to clinical users for testing. Focus of scientific research, in close collaboration with partnergroup UTAH, is the systematic integration of modules for computations on tensors for interpolation, averaging and statistical analysis. This tool will complement common voxel- or region--based group tests as it will allow to analyze diffusion properties in a tract-oriented coordinate system, i.e. ask for fiber integrity in the uncinate fasciculus or cingulum by using tractography for definition of complex regions of interest.

A.2 Research and Development:

Whereas tractography on DTI is mostly used to study the white matter architecture, we extend this concept towards quantitative tractography. The development augments white matter bundle extraction by a set of methods that provide diffusion tensor analysis for individual tracts. The tool includes clustering of sets of streamlines into coherent bundles with outlier removal, interpolation of sets of curves by B-splines and arc-length parameterization, calculation of diffusion statistics in cross-sections and along bundles, and standardized output of statistics into files. User interaction is facilitated by a graphical user interface with fiber bundle editing and visualization options.

Tractography applied to DTI results in the extraction of sets of streamlines, either obtained by tracking from source to target regions or from source to whole brain. Clustering of sets of streamlines into compact bundles is performed by the normalized graph cut (NGC) algorithm which uses pair-wise Euclidean distance and angle difference between corresponding points as distance metric. The NGL algorithm with curve clustering features is implemented in ITK and made available to NA-MIC via the sand-box.

Quantitative analysis uses methodology developed by UTAH, in particular the non-linear Riemannian metric for interpolation and averaging of tensors across and along fiber bundles and the geodesic anisotropy (GA). Fractional anisotropy (FA), GA and mean diffusivity (D_{av}) as most common clinical parameters are finally calculated from the average tensors.

Scientific visualization makes use of the newly developed Spatial-Object-Visualization Toolkit (SOViewer) which complements the ITK SpatialObjects library (provided by our UNC partners Aylward/Jomier). Objects like curves, ellipsoids, vectors, tensors, and volume data can be efficiently combined into efficient displays.

Validation: We make use of a series of 6 scans of the same subject with small head position differences, and another series of 5 scans with no re-positioning. We tested repeatability of tractography and the resulting diffusion cross-sectional statistics along fibers (ISMRM 2005). We also developed a pair-wise tract-to-tract distance metric to calculate reproducibility of spatial regions covered by repeated tractography tests.

A.3 Results:

The FiberViewer prototype tool has been applied to data-sets (>100) from several clinical studies at UNC and Duke. Tests show that quantitative tractography serves as a method to analyze fiber bundles with complex

geometry and has superior sensitivity in comparison to region-based or voxel-based analysis. Using isotropic voxel data, we can efficiently extract a set of major bundles, including the uncinate fasciculus, cingulum, splenium and genu bundles, trans-callosal subparts, inferior and superior longitudinal fasciculus and even U-fibers between motor and sensory cortex. Clustering showed very efficient to separate joint bundles, e.g. the uncinate and longitudinal tract, and the left and right fimbria. User interaction includes supervised clustering with a choice of different metrics, definition of cut-planes and coordinate origins per bundle, and efficient visualization of 3D geometry attributed with user-defined diffusion properties (FA, GA, D_{av}, Eigenvalues etc.).

Tests with Core-3 data are in progress. Early tests clearly demonstrate the need for a well-designed data format standardization (NRRD) to accommodate the large variety of DTI protocols with different sets of gradient directions, patient orientation, variable B-values, and number of repetitions for averaging.

A.4 Publications:

Guido Gerig , Isabelle Corouge, Clement Vachet, Ranga Krishnan and James MacFall, Quantitative Analysis of Diffusion Properties of White Matter Fiber Tracts: A Validation Study, International Society of Magnetic Resonance ISMRM, May 2005 (peer reviewed long abstract)

Guido Gerig, Weili Lin, Sampath Vetsa, John Gilmore, Assessing White Matter Growth Trajectory of Early Neonatal Development by 3T MR-DTI, , International Society of Magnetic Resonance ISMRM, May 2005 (peer reviewed long abstract)

Submitted:
Isabelle Corouge, P. Thomas Fletcher, Sarang Joshi, John H. Gilmore, and Guido Gerig, Fiber-Tract-Oreiented Statistics for Quantitative Diffusion Tensor MRI Analysis, submitted to *Medical Image Computing and Computer Assisted Interventions 2005*

B: Activities in Statistical Shape Analysis:

B.1 Development and Design:

In collaboration with other members (MIT, GeorgiaTech, Utah and Kitware) in NA-MIC, we initiated and are heading a much needed standardization effort for a computation, IO and visualization framework in statistical shape analysis studies. The design of the framework is compatible with the NA-MIC toolkit. The IO framework has already been designed and implemented to a larger part and the computational and visualization framework will be finalized until the end of August this year. This framework will highly facilitate the exchange of algorithms and the development of subsequent clinical study tools, which are currently nearly non-existent in the shape analysis field. The advanced UNC shape analysis pipeline is being redesigned within this framework to allow other researchers within and outside of NA-MIC to use these methods. Several modules have already been redesigned such as the spherical parameterization method, which has been ported from a proprietary sparse matrix solver to a public domain solver. Several collaborators outside NA-MIC have already made use of this new non-proprietary parameterization. The initial sets of tools developed within the framework are tested using the UCLA LONI pipeline on datasets from Core 3.

We have also implemented a series of shape analysis tools which are now freely available for mesh extraction from binary images, mesh extraction from spherical harmonic surface descriptions, as well as for mesh analysis/validation. The mesh validation tool called MeshValmet allows comparing the similarity of a set of meshes with a series of different similarity measurements.

Additionally to the standardization and tool development efforts, we developed novel methods in shape analysis for a) the computation of local thickness maps at the surface using Voronoi skeletons and b) the parcellation of 2D and 3D boundary shape descriptions in order to measure regional effects of volume/area, shape and diffusion tensor properties. The statistical local shape analysis methods were extended to incorporate multivariate Hotelling T^2 size and significance maps, both raw and corrected for multiple comparison, as well as effect size and regression coefficient r^2 maps. These additional maps are crucial in the correct validation and interpretation of local shape statistics.

B.2 Studies:

The initial developments in shape analysis were tested and validated on in-house UNC studies. As the datasets from Core 3 became available to the NA-MIC network, we also incorporated the Brockton VA/Harvard structural caudate datasets. Specifically the shape analysis framework development pipeline with our redesigned shape analysis pipeline alongside the LONI pipeline will be tested on this datasets.
Using the existing pipeline as well as our MeshValmet tool, we studied in detail the stability of local and regional (parcellation based) shape analysis studies regarding the choice of surface correspondence. This topic has received much too little attention despite its relevance to the field. We showed in our studies that the influence of correspondence on the study results is non-trivial, as in one mid-powered study of hippocampal morphology in adolescent psychoses the regional results stemming from two different correspondence methods were virtually antipodal.

We also combined our foci of research within NA-MIC by employing DTI tractography for the computation of an inter-hemispheric connectivity based probabilistic parcellation method of the corpus callosum, the major commissural structure between the brain hemisphere. This parcellation was applied to a small scale study of healthy callosal growth from age 2 to 4, which showed that main callosal growth is found in regions associated with frontal lobe connections. We plan to apply this callosal parcellation to the regional analysis of DTI properties of Core 3 data.

B.3 Publications in progress:

We submitted two papers that to the Medical Image Computing and Computer Assisted Interventions conference and their reviews are pending (full paper, double blind review, acceptance rate in previous years < 35%). Journal article versions of these papers are in preparation.

M Styner, I Oguz, R Smith, C Cascio, M Jomier: Corpus Callosum Subdivision based on a Probabilistic Model of Inter-Hemispheric Connectivity, submitted to *Medical Image Computing and Computer Assisted Interventions 2005*

M Styner, S Xu, M El-Sayed, G Gerig: Influence of Correspondence on Local Shape Analysis and Structural Subdivision, submitted to *Medical Image Computing and Computer Assisted Interventions 2005*

C. Project-Generated Resources

We developed and enhanced several software packages that will be available as open source packages to NA-MIC and finally to the public. The *MeshValmet* tool for surface mesh validation and comparison, The *Spharm2Mesh* tool for the conversion of spherical harmonic descriptions to mesh surfaces, The *FiberTracking* for tractography from DTI images, The *FiberViewer* tool for the post-processing and statistical analysis of DTI fiber properties. Novel processing components like the new Normalized-Graph-Cut for curve clustering are transferred to the NA-MIC sand-box as an intermediate step towards integration into the NA-MIC toolkit. The spatial-object-visualization toolkit (SOViewer) is an integral part of our tools by augmenting ITK programming with efficient visualization. SOV is available as full open source for non-commercial use (http://caddlab.rad.unc.edu/software/SOViewer/index.htm).

All our tools can be downloaded by the public from our webpage http://www.ia.unc.edu/dev/. This web-site also includes comprehensive tutorials to support successful first steps efficient use of these tools.

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Core 1 at U of Utah

Research

We have been developing methods for statistical analysis and image processing of diffusion tensor MRI. These methods should benefit clinical researchers in Core 3 by helping them answer questions about how diseases such as schizophrenia affect the white matter structures of the brain. Our research is based on treating diffusion tensors as nonlinear entities, which we have shown preserves the integrity of the diffusion tensor data as a valid model of diffusion. As classical multivariate statistics only handles linear data, we are generalizing statistical methods to handle nonlinear diffusion tensor data.

The image processing methods we are working on, include interpolation and anisotropic filtering of diffusion tensor images. These are essential preprocessing steps that are required before further analysis is done. The statistical analysis methods we are developing include summary statistics such as the mean, covariance, and modes of variation of a collection of diffusion tensors. We are also building statistical hypothesis tests that are based on the full diffusion tensor, rather than a derived measure such as FA. The hope is that by utilizing the full information from the diffusion tensor, clinical researchers will be able to find significant group differences in diffusion tensor data that are not obtainable with current methods.

Software Development

The following progress has been made in software development of the DTI methods.

- Code for performing the nonlinear geometric operations on tensors has been written and tested. This serves as a foundation for the rest of our methods.
- We have developed and tested software for computing the mean, covariance, and modes of variation of a collection of diffusion tensors.
- We have implemented the hypothesis test for diffusion tensors. This code is currently being tested on data from Core 3 (Brockton VA/Harvard dataset).
- Prototypes of the interpolation and filtering methods have been implemented, and further development is in progress to make them available.

All of our software development is being done within ITK. These methods were built using our own diffusion tensor data structures. We are in the process of modifying them to use the new diffusion tensor data structures that were recently added to ITK.

Meetings and Visits

- Attended NA-MIC Kickoff Meeting, Boston, Oct. 15, 2004.
- Participated in DisseminationWorkshop, UCSD, Feb. 17-18, 2005. This meeting was a working tutorial for learning to program with ITK and Slicer.
- Attended NA-MIC All-Hands Meeting, Salt Lake City, Feb. 20-22, 2005. During the "Day 0" DTI workshop, we presented the proposed framework for DTI statistics and processing, and we reported on current progress of software development.

• Visited Brigham and Women's Hospital, Mar. 25, 2005. This meeting set up our collaboration with Dr. Shenton and Dr. Kubicki on DTI.

Collaborations

We are currently working together with Dr. Martha Shenton and Dr. Marek Kubicki from Brigham and Women's Hospital (Core 3) on DTI statistics. They are providing us with the Brockton VA/Harvard DTI data sets and with driving problems. It is our goal to provide them with statistical tools for analyzing diffusion tensor data, including statistical tests of group differences utilizing the full diffusion tensor. We have built the infrastructure to read and process the DTI data, and we have reproduced the results on this data reported by Kubicki et al. that analyzes group differences based on FA. We are in the process of testing our new group test methods on the full tensor data to see if it gives promising results.

Another collaboration we have developed is with Dr. Guido Gerig at the University of North Carolina at Chapel Hill (Core 1). We are working together to combine fiber tract analysis with the diffusion tensor statistics we are proposing. This involves pointwise analysis of diffusion tensor data along important white matter fiber tracts, where the analysis is done using our new statistical methods. The diffusion tensor data is sampled along a fiber using our new interpolation methods. This collaboration has resulted in a paper submission to MICCAI by Corouge et al.

Data Downloaded

We have downloaded the DT-MRI data from Brockton VA/Harvard. This includes 80 diffusion-weighted images, 72 segmentations of the cingulum bundle, and 55 segmentations of the fornix.

Papers Written

1. I. Corouge, P. T. Fletcher, S. Joshi, J. H. Gilmore, and G. Gerig. Fiber Tract-Oriented Statistics for Quantitative Diffusion Tensor MRI Analysis. Submitted to Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI) 2005.

2. P. T. Fletcher and S. Joshi. Riemannian Geometry for the Statistical Analysis of Diffusion Tensor Data. Submitted to Signal Processing, Special Issue on Tensor Signal Processing, May 2005.

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National Alliance for Medical Image Computing

Core 2 at General Electric Global Research

The role of Core 2 is to establish software architectures and software processes that will empower the Core 1 algorithm developers to create robust, well-designed software and interfaces. In addition to enhancing the new software from Core 1, Core 2 will build interfaces to existing software and data sources. The Core 3 end-users will define the requirements for the applications developed by Core 2. During the first year of NA-MIC, the GE Core 2 team worked in three areas: Software Architecture, Software Process and Software Quality Control.

Software Architecture:

There are three major components in NA-MIC's software application. The Visualization Toolkit, VTK; the Insight Toolkit, ITK; and the end-user interface, Slicer.

Early in the year, Core 2 identified two gaps in the Insight Toolkit, ITK, that needed immediate attention. The first, toolkit support for image orientation, was identified by the Core 2 Slicer developers. The second, toolkit support for tensors, was identified by Core 1 scientists.

Image Orientation

Medical images are acquired with a variety of radiological sensors including MRI and CT. These two modalities can produce cross-sectional images (slices) in a variety of acquisition schemes. CT normally acquires axial data from head-to-toe or toe-to-head. MRI is more flexible and can, in addition to axial slices, acquire the data from left-right, right-left, front-back, back-front or arbitrary oblique slices. It is critical that end-user applications respect the order of slice acquisition. If the correct order is not used, left-right flipping can occur. In the past, Slicer has handled the image acquisition order as part of its application code base. A more robust solution is to do this within the ITK and VTK toolkits. Working with the Core 2 Slicer developers and the ITK software community, GE has defined an approach for implementing slice orientation within the ITK Image class. An initial implementation has been placed in the ITK code base. In addition to keeping a consistent image orientation, software has been developed to create compatible slice orientations regardless of the initial acquisition protocol.

Tensor Support

Tensor support is a Core 1 requirement of the algorithm developers doing MRI Diffusion Weighted Imaging. This was identified and discussed at a full day Core 1-2 NA-MIC workshop prior to the All Hands Meeting at Salt Lake City. ITK has no direct support for tensors. There are two aspects to tensor support: basic tensor data structures and tensor algorithms. The Kitware Core 2 team has provided a "strawman" implementation of the tensor data structures. GE has investigated tensor estimation from

diffusion weighted magnetic resonance (DW-MR) images, as well as computation of the quantities of diffusion tensors, including eigenvectors, fractional anisotropy (FA), apparent diffusion coefficient (ADC), and relative anisotropy (RA). GE also investigated fiber tractography using the streamline method to follow the principal eigenvectors of tensors and methods for segmenting brain white matter using information from DW-MR images. The current work is largely implementing existing methods using ITK/VTK to reproduce results that have been published. GE is working with Core 1 developers from UNC to develop methods for quantitatively analyzing fiber tracts reconstructed from DW-MR images.

Software Process:

Core 2 defines and provides tools to support a lightweight software engineering process for NA-MIC. The process combines object-oriented design techniques with the Extreme Programming development methodology. The Core 2 goal is to encourage algorithm developers to adhere to the process principles without restricting innovation and productivity.

GE and other Core 2 developers established a software process based on the successful Insight Toolkit experience. This process includes periodic software workshops, weekly telephone conferences and nightly software dashboards. In addition to these proven communication techniques, we are using the NA-MIC Wiki established by the Kitware in Core 4.

NA-MIC Wiki and T-Cons

The Wiki, a web-based collaboration tool, is used to collect documents and discussion for all of NA-MIC. Core 2 uses the Wiki to communicate with the other NA-MIC Cores. After the Salt Lake City All Hands Meeting it was apparent that NA-MIC would benefit from more frequent communication between the distributed Core 2 team members. GE established a weekly telephone conference (t-con) to discuss issues and report problems and progress. The t-cons are driven from the Wiki. During the week, Core 2 members can populate the next week's t-con agenda. During the t-con, an appointed scribe takes notes and posts them to the Wiki after the call. Core 2 folks are encouraged to edit and add material to the t-con minutes.

SDIWG

Bill Lorensen, Core 2 PI, has been active in the NCBC Software and Data Integration Working Group (SDIWG). He is working with NIH and other NCBC PI's to establish communication and software process exchange between the Centers.

Software Quality Control:

GE, working with Kitware, has established automated software quality assurance mechanisms. These facilities use a daily and continuous build/test environment that reports software defects as soon as they enter the system. The initial software quality system is based on DART, a distributed automatic regression

testing system. DART was developed by GE as part of the National Library of Medicine ITK contract.

Dart 2

Early in the grant period, GE worked with Kitware to establish requirements for the next generation QA system, Dart 2. Dart 2 provides a cleaner separation between the developer (client) and the dashboard reporting system (server). GE took ownership of the server, Dart 2, and Kitware took ownership of the client, CTEST. An initial version of Dart 2 has already been distributed and is under evaluation by NA-MIC. Dart 2 is entirely written in Java. This simplifies distribution and installation. A document describing Dart 2 was also created and is accessible from the NA-MIC Wiki.

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Core 2 ISOMICS Activity Report

Core 2 Activities as part of Dissemination Events

1. Attended NA-MIC Dissemination Workshop at SPL, BWH on Dec 9-10, 2004 (Alex Y.).

2. Participated in Jan 24-25, 2005 Dissemination Workshop at MIT CSAIL. Presented a talk: Slicer and ITK I/O factory generic readers module describing ITK/VTK/Slicer architecture of a new Generic Image Reader module in Slicer (Alex Y.).

3. Steve P. attended all Dissemination events as part of his role as Dissemination Core PI but also provided an engineering perspective and collected feedback from algorithm and biological collaborators.

4. Participated in Feb 20-22, 2005 All Hands Meeting in Salt Lake City, Utah (Alex Y. and Steve P.).

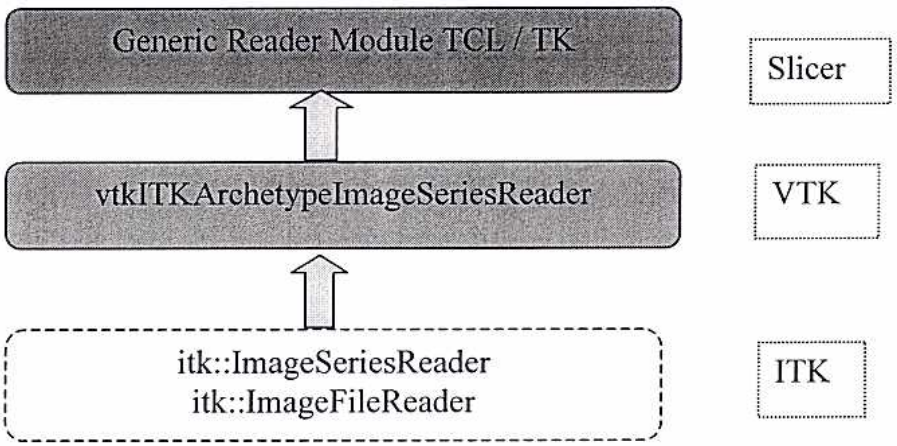
Core 2 Engineering Activities

1. Worked with DBP researchers in Core1 on gathering and formalizing requirements for brain image data import, analysis, and visualization in Slicer in particular:
   - Requirements for image file formats and readers in ITK and Slicer – resulted in vtkNRRDReader and Generic Readers (see below).
   - Requirements for patient base coordinate system representation in ITK image file readers – worked with GE and ITK community on ongoing implementation.
   - Requirements for transformation support in ITK Image classes – ongoing developments in ITK.
   - Requirements for re-sampling different images in common physical space and common slice ordering for further registration and segmentation– resulted in TransformVolume Module (see below).
   - Requirements for registration modules in Slicer – resulted in registration class hierarchy proposal (see below).

2. Implemented Generic Image Reader module in Slicer based on ITK's extensible IO Factory mechanism. The Slicer module was implemented using vtkITKArchetypeImageReader implemented by GE Core 2 group. The module supports multiple image file formats, many of which are new to Slicer:
   a. Meta

b. PNG
c. VTK
d. Gipl
e. Analyze
f. Stimulate
g. JPEG
h. TIFF
i. Nrrd
j. BMP
k. DICOM2

Generic Image Reader Module Architecture:



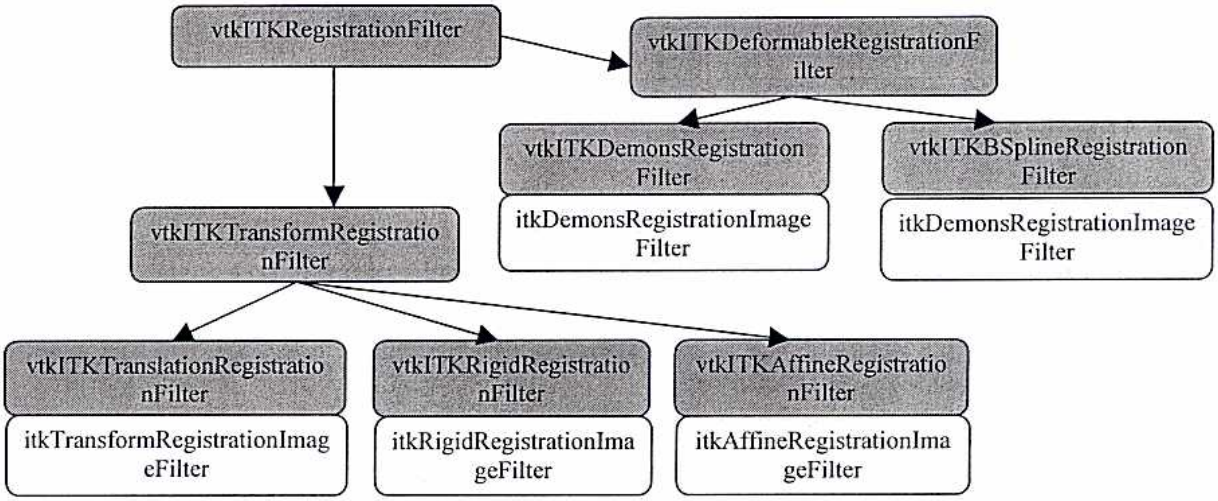
A current limitation of vtkITKArchetypeImageReader is that it does not provide the information about patient coordinate system and slice order. It also does not support multi component DTI image data files.

3. Created Nrrd file format reader in Slicer that was capable of preserving scan order and reading DTI images in interleave volume format required by Slicer DTI module. Nrrd file format has become a de facto standard for NA-MIC data repositories. Having a Nrrd reader in Slicer addresses a short term need for reading both structured MRI and DTI MRI data in a specified patient coordinate system. In the long term Generic Image Reader module will extent it's capability to provide information about patient coordinate system and scan order.

4. Designed and implemented Slicer TransformVolume module for re-sampling and transforming volume images into common physical space and common scan order. The module allows the results of multiple differing modality scans obtained with different scan ordering to be transformed to the same physical space and orientation for further registration and segmentation.

5. Designed a software framework for ITK based registration classes to be used in VTK/Slicer architecture. The registration framework is design to support

translation, rigid, affine, and deformable forms of registration between images. A hierarchy of VTK classes is designed for this purpose as shown on the diagram below. The leaves of the hierarchy implement registration algorithms using ITK registration wrapper classes. The ITK registration wrapper classes include registration pipelines consisting of multiple ITK components. They inherit from itk::ImageToImageFilter class.



6. Worked to support DTI tractography in Slicer in collaboration with UCI DBP and the mBIRN project.

Progress Report 2005, Year 1
National Alliance for Medical Image Computing

Core 2 at UCLA

The analysis of raw data in neuroimaging has become a computationally entrenched process with many intricate steps run on increasingly larger datasets. Many software packages exist that provide either complete analysis or specific steps in an analysis. These packages often possess diverse input and output requirements, utilize different file formats, run only in particular environments, and have limited abilities with certain types of data. The combination of these packages to achieve more sensitive and accurate results have become a common tactic in brain mapping studies, but require much work to ensure valid interoperation among the programs. The handling, organization, and storage of intermediate data can prove difficult as well. The LONI Pipeline is a simple, efficient workflow execution environment that manages these difficulties for the user by coordinating all the various programs and datasets.

The inclusion of the LONI Pipeline into the NA-MIC Toolkit, along with other tools such as ITK, VTK, and Slicer, and the integration of the Pipeline with these tools provide a synergy to both NA-MIC and LONI products and improves research support for users of the products. ITK/VTK/Slicer users get the benefit of a complete workflow execution environment, while Pipeline users benefit from the vast library of well-validated and effective image processing modules.

Research Highlights.

During the first year of funding, we have initiated a multi-pronged effort at integrating the LONI Pipeline with various components of the NA-MIC software infrastructure, including components of the NA-MIC toolkit.

For integration with NA-MIC toolkit component ITK, we developed a pipeline module that allows for users to download, setup, and build ITK in a single step (Figure 1). There is a version of the pipeline module for both Windows and UNIX variants, so that users on either platform can take advantage of our efforts.

As with ITK, for integration with NA-MIC toolkit component VTK, we developed a pipeline module that allows for users to download, setup, and build VTK in a single step. There is a version of the pipeline module for both Windows and UNIX variants, so that users on either platform can take advantage of our efforts.

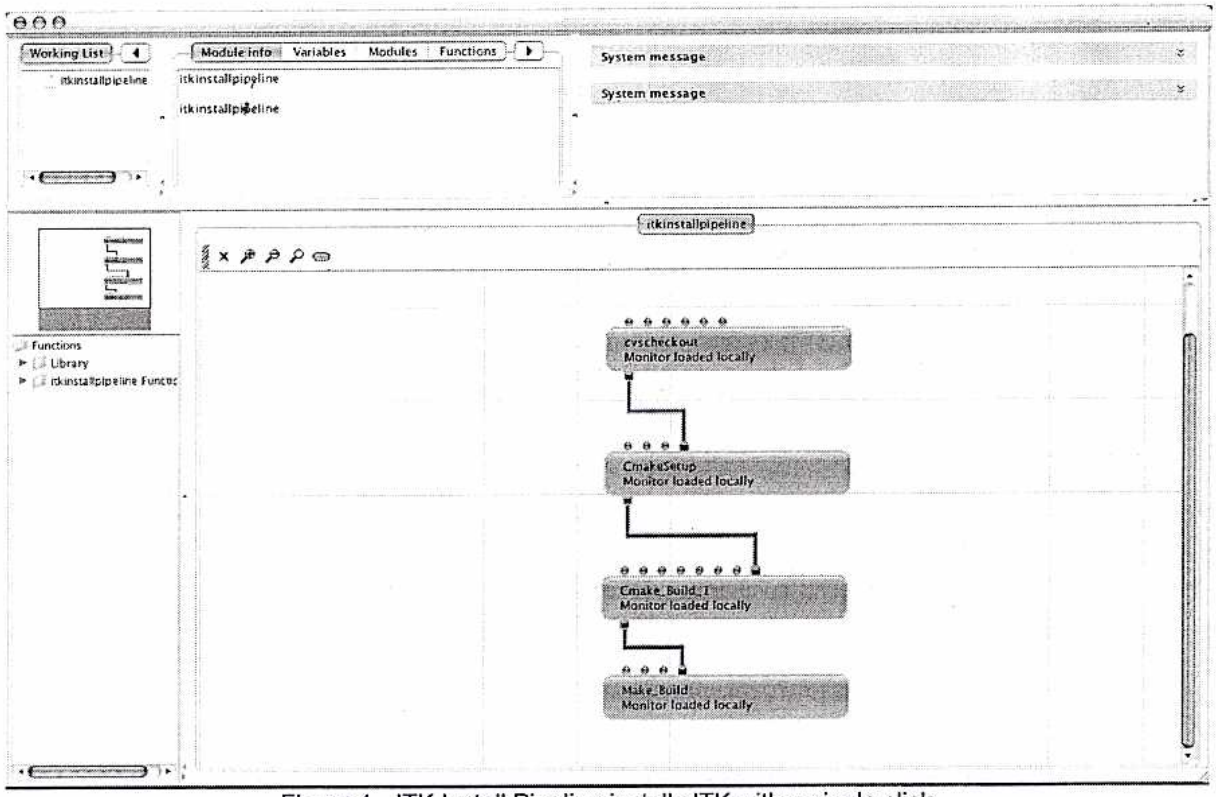


Figure 1 - ITK Install Pipeline installs ITK with a single click

Both modules were provided to the attendees of the NA-MIC Toolkit dissemination meeting held in San Diego in February 2005. Also, the modules can be found on NA-MIC's Wiki page, http://www.na-mic.org/Wiki/index.php/InstallationPipelines. We have also developed pipeline modules for all of the 22 ITK tutorial exercises used in the disseminations (http://www.na-mic.org/Wiki/index.php/ITKExercisePipelines).

We are currently in the process of doing the same (i.e. building a one step installation) for *Slicer2* and other NA-MIC Toolkit components. This has proven to be more difficult for a variety reasons, including software and platform incompatibilities. A more successful effort in terms of *Slicer/Pipeline* integration has been the integration of Slicer as a viewer for files stored in Slicer's MRML format. Properly configured, a user can now select to view these files anywhere in the Pipeline workflow, at any point in time in the workflow execution. This feature (see Figure 2) was presented to NA-MIC collaborators at the NA-MIC AHM in Salt Lake City in February 2005.

Additionally, we are currently in the process of integrating UCSD's Supercomputing Center (SDSC)'s Storage Resource Broker (SRB) protocol in the Pipeline. This would enable NA-MIC researchers to access data stored on the distributed archive. The feature has been implemented, but remains untested due to various technical issues at SDSC.

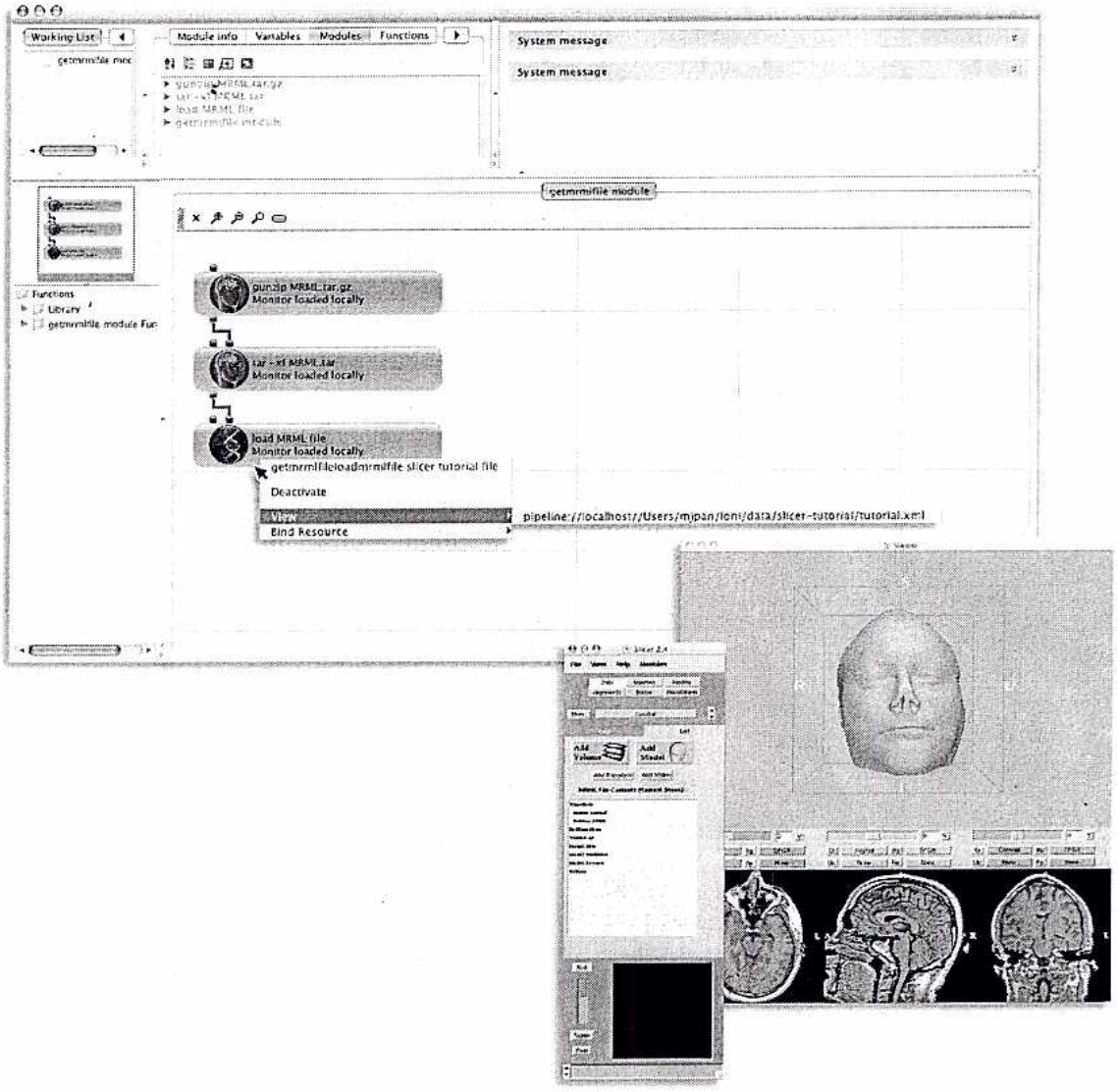


Figure 2 - Slicer can be launched from the Pipeline as a preferred viewer for various file types such as MRML files

Coordination Between Sites:

In Year 1, the Pipeline development team has established, and continues to foster, strong working relationships with other NA-MIC collaborators. In addition to frequent telephone and video conferences we have participated in several face-to-face meetings with the NA-MIC software and science researchers and developers. In December 2004, we attended the NA-MIC Toolkit dissemination workshop held at the Surgical Planning Lab (SPL) of Harvard's Brigham and Women's Hospital (BWH). There we were immersed in the details of the other components of the NA-MIC toolkit- ITK, VTK, and Slicer. In return, we introduced the attendees to the LONI Pipeline and discussed its role within the NA-MIC Toolkit.

In February 2005, we attended another dissemination workshop, this time held at the Biomedical Informatics Research Network (BIRN) Coordinating Center, at the University of California San Diego (UCSD). At that meeting, our newly hired NA-MIC-LONI point

person was introduced to various NA-MIC collaborators and exposed to NA-MIC's engineering practices, which includes *Extreme Programming* paradigms such as *DartBoard*, in addition to the other components of the NA-MIC toolkit.

Also in February 2005, we attended the NA-MIC All Hands Meeting held at the Hotel Monaco in Salt Lake City. There we met with more NA-MIC collaborators and furthered discussions on possible collaborative efforts, including the use of the new Java enabled Dart2 testing framework (and in return identifying and submitting bug reports and feature requests) for continued improvement of the software development process for all involved.

In April 2005, NA-MIC Principal Investigator Ron Kikinis visited LONI, and we met with, and held a long and fruitful discussion on mutual goals for even closer collaboration.

In June 2005, we will attend NA-MIC's Programmers' Retreat, to be held at MIT from 27 June to 1 July. At this meeting, we will provide support to NA-MIC programmers to integrate their programs into the LONI Pipeline as pipeline modules, allowing for these programs to be part of massive scientific workflows. Additionally, we will demonstrate how the Pipeline can provide users with distributed computing support in a grid engine.

In addition to the face-to-face meetings described above, we continue to participate actively in 2 regularly held NA-MIC teleconferences. One of them is the main Engineering Core teleconference, held weekly. The other is the NA-MIC Toolkit Grid Integration Interest Group teleconference, also held weekly.

Progress Report 2005, Year 1
National Alliance for Medical Image Computing

Core 2 at UCSD

A. Specific Aims

The following specific aims were described in the University of California, San Diego's (UCSD) contribution to the National Alliance for medical Image Computing (NA-MIC):

Specific aim 1: *Provide researchers with access to a computing environment that supports their natural working paradigm while taking advantage of Grid-based infrastructures.* We will build this environment through the incorporation of Grid middleware that is fully compliant with emerging Grid standards; the "Grid-enabling" of applications and algorithms being developed within NA-MIC; and the "Grid-enabling" of NA-MIC contributions to workflows, through the integration of application-linking tools like the LONI pipeline (see Core 2:4).

Specific Aim 2: *Enable NA-MIC researchers to store large collections of federated data within a distributed data grid.* We will ensure the compatibility of NA-MIC tools with the BIRN virtual data grid to ensure the ability of NA-MIC researchers to seamlessly access distributed data caches and enable the use of NA-MIC developed applications and algorithms within the BIRN environment.

Specific Aim 3: *Deploy a data mediation environment within NA-MIC that will enable researchers to retrieve, integrate and better understand data stored at distributed sites.* We will help to deploy the BIRN data mediation environment within the NA-MIC driving biological projects and integrate NA-MIC databases (e.g. see the description of DTI database in Core 1:2) and related knowledge sources.

In the first year of the proposal, the majority of the effort has focused on specific aims 1 and 2. The most immediate goal has been to enable researchers within NA-MIC to be able to share their data effectively within the consortium. Work has also focused on providing NA-MIC a Grid computing environment. The following section details these accomplishments.

B. Results during the current period of support (09/17/04-07/31/05)

The following progress report represents the work accomplished by the University of California, San Diego in conjunction with the National Center for Microscopy and Imaging Research and the BIRN Coordinating Center over the past year in support of the National Alliance for medical Image Computing. Emphasis on the major accomplishments will highlight several of the reasons for the success of UCSD in supporting the NA-MIC consortium.

Infrastructure Support for Data Sharing

A core effort in the first year of this project has been to support NA-MIC researcher's need to share data (data provided from the Driving Biological Projects in Core 3 to the algorithm developers in Core 1). In order to support this requirement the following activities were required:

- Provided custom project space for the NA-MIC consortium on the BIRN Portal
- Assisted and supported in the account generation and registration of NA-MIC users
- Hosting of NA-MIC data utilizing data grid that is accessible to all NA-MIC participants

The data grid and Portal environment provide an intuitive interface and single sign-on to all NA-MIC data sets (see Figure 1). Once, the core infrastructure for the sharing of data had been deployed, we worked closely with Isomics and the core 3 sites in uploading their data (once the proper IRB approvals had been granted). This support included the definition of the proper data hierarchies and the necessary upload routines required for uploading data. Utilizing the audit functionality of the BIRN data grid, utilization of data sets within NA-MIC is being tracked. Monthly utilization statistics have been collected since March 2005 and are listed in the following table (Table 1).

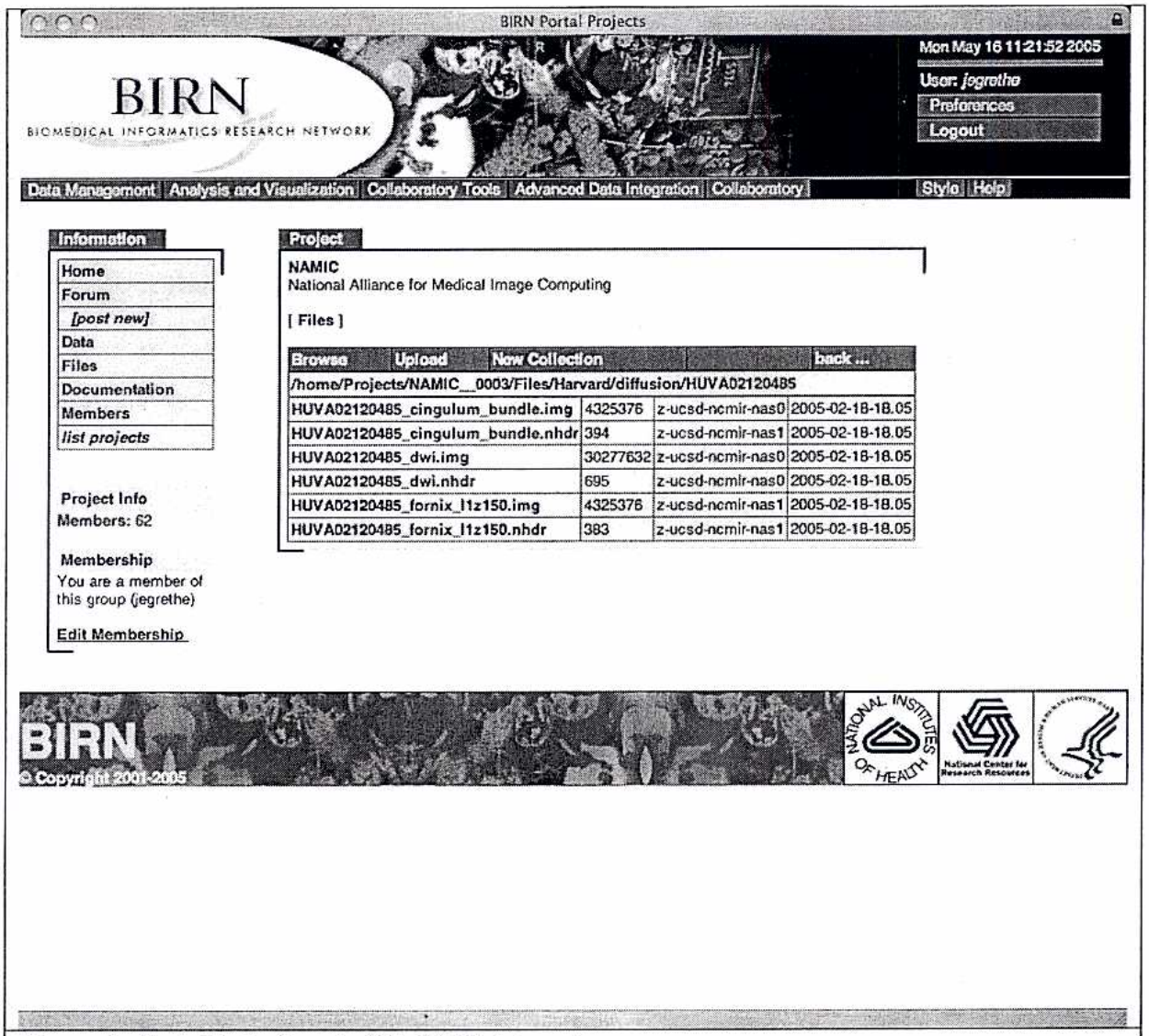


Figure 1: Portal interface to NA-MIC data sets

	March 2005	April 2005
Num. of NA-MIC users	56	60
Num. of subject data sets uploaded	320	320
Num. of downloaded data sets (duplicates allowed)	541	662
Num. of unique data sets downloaded	269	310

Table 1: Usage statistics for NA-MIC data

A core development in supporting the sharing of data within NA-MIC has been the deployment of a service allowing for access to data resources from sites (e.g. GE research) that have very strict firewall policies (i.e. they don't allow client initiated connections to the required data services). In order to support GE, we researched, tested, and deployed a newly configured data grid server for NA-MIC that allows for the tunneling of all data grid commands via SSH. This tunneling has been tested with all current clients, including command line Scommands, the Java (JARGON) library, and platform specific clients (e.g. InQ). The NA-MIC tunneling server is now hosted in a production server environment at UCSD.

Additional infrastructure assistance is also being provided to NA-MIC as is required (e.g. worked with BWH to configure and deploy NA-MIC servers utilizing high speed network connection available through the BIRN rack co-located at BWH).

Infrastructure Support for Distributed Computation

In addition to supporting the data sharing needs of the NA-MIC consortium, UCSD is actively involved in providing infrastructure and support for the utilization of distributed computation resources. Activities are currently focused on two activities. First, UCSD is configuring and deploying a computational cluster to support NA-MIC activities. As part of these activities, configuration for job submission and scheduling (i.e. utilizing Condor; http://www.cs.wisc.edu/condor/) is being done taking into account requirements from the Engineering Core. The first training and production use of this resource is scheduled to occur during the upcoming 'Programming Week in Boston'. Secondly, we are actively working with core 2 partners in developing guidelines and requirements for grid-enabling applications within NA-MIC.

UCSD support in NA-MIC dissemination

UCSD has also been actively supporting NA-MIC dissemination activities. As part of these activities, UCSD hosted the NA-MIC west coast dissemination event (February 17-18; http://www.na-mic.org/Wiki/index.php/Dissemination:Workshop_Feb17-18_2005). As part of this event, we taught a data grid course to familiarize NA-MIC participants with the data grid and associated tools. On-line help and instructions have also been provided via the NA-MIC Wiki (http://www.na-mic.org/Wiki/index.php/DataRepository) and the BIRN Portal. We continue to support NA-MIC dissemination events and are currently actively involved in preparations for the Programming Week in Boston, to be held June 27 - July 1 2005.

C. Results Obtained and Their Significance to the Field

The results from this current funding period have been mainly related to the development and deployment of the infrastructure necessary for core 1 developers to have access to the necessary core 3 data sets. The results from this funding period are significant in that they support and enable the work of NA-MIC developers.

D. Plans for Next Year

In the coming year we will continue to support the data grid infrastructure and data sharing needs of NA-MIC. In addition to this core activity (i.e. specific aim #2) we will work closely with Core 1 and Core 2 groups in the increased utilization of distributed computational resources (i.e. specific aim #2). This will build on our initial work in the current funding period described above.

Progress Report 2005, Year 1
National Alliance for Medical Image Computing

Kitware: Core 2 Progress Report May 2005

Summary

Initial Core 2 activities have focused on shorter-term technical tasks to support start-up activities in Cores 1 through 3. In particular we have added basic functionality to support DTI; are extending the software testing process, and are engaged in the design of the Slicer 3.0 product.

Highlights

The following list highlights Kitware's contributions to the NA-MIC community in Core 2. These highlights are categorized as *design, implementation,* and *testing*.

- *Design*. We have designed a series of ITK classes to support diffusion tensor imaging (DTI). These classes support symmetric tensors, 3D diffusion tensors, and filters for computing fractional anisotropy, relative anisotropy and Hessian matrices (as tensors). We are also participating in the design of the next generation Slicer 3.0 software system. This includes providing input on the build process, GUI design and implementation (via KW Widgets), and the underlying parallel, large-data computing engine.

- *Implementation*. Besides implementing the DTI classes mentioned above, we also extended ITK's image I/O facility to support symmetric tensors and diffusion tensors. Other implementation activities include implementing a thread-safe (for parallel processing) eigenvalue calculator, and assisting other Core 2 team-mates to implement an ITK statistical classifier filter and perform deformable registration of EPI (echo-planar) images.

- *Testing*. Working with our GE Research partners, we have participated in gathering requirements for the next generation testing server DART2. We have also adapted our CMake/CTest testing client to interface with this server. We are currently hosting a DART2 server and dashboards.

Resource Usage

We have engaged in several positive collaborations with outside parties. Because the foundation of NA-MIC is open software and data, we have been able to engage outsiders in technical discussions. For example, Jeffrey Duda from the University of Pennsylvania and Torsten Rohlfing at SRI International have helped design the DTI classes in ITK. We also have at least one known group already beginning to use the DART2 testing server. This group (Andrew Maclean is the contact point) is located in Australia and is adopting NA-MIC's software process to their robotics research center.

Progress Report 2005, Year 1
National Alliance for Medical Image Computing

Core 3 at Harvard/VA

(A) NARRATIVE OF PROGRESS FOR CORE 3.1:

The work accomplished in Core 3.1 over the last funding period includes:

(1) Medical image data sets from published Brigham/Harvard studies have been collected and organized and made available to our computer and engineering Cores (**Core 1 and 2**) for tool development. These data sets include well-delineated neuroanatomical regions of interest, as well as diffusion tensor imaging data with brain regions of interest delineated. Specifically, raw structural images and regions of interest have been uploaded to the NA-MIC website and include the following structures: a) amygdala-hippocampus, b) super temporal gyrus, c) middle temporal gyrus & inferior temporal gyrus, d) caudate nucleus, and e) insular cortex & temporal pole. There are a total of 188 morphology cases and 80 diffusion tensor cases. The cases have a unique identifier and a great deal of time was spent in converting the data sets to formats that would be easily accessible to our U54 collaborators. Information about diagnosis, data parameters and labels associated with the Region of Interests (ROI) can be found on the NA-MIC website at: http://www.na-mic.org/Wiki/index.php/DataRepository#Brockton_VA.2Fharvard_Structural_and_DTI_Images

(2) We have worked with **Core 5** to provide them with resources we have developed such as an informal manual with instructions for using 3D slicer software that was developed by our research assistants. This has been given to **Core 5** for further development and refinement.

(3) We have worked with **Core 5** on their tutorial for the 3D slicer at Dartmouth on May 26-27, 2005. As our research group is one of the heaviest users of the 3D slicer, Sylvain Bouix, Ph.D., a computer scientist from our group as well as three Research Assistants, were involved in the tutorial with **Core 5**.

(4) We have worked with **Core 2** to add functionalities to the Slicer. The DTMRI analysis module has been improved by NA-MIC collaborators and tested by us. We also have initiated the addition of a resampling module in the Slicer and extensively tested the linear and non-linear registration as well as the automatic segmentation modules. Furthermore, we have pushed for the addition of more flexible file format readers in the Slicer. These components are all part of the latest version of the software and were presented at the dissemination seminar in Dartmouth, May 26-27.

(5) In addition to raw images, and regions of interest, we have also provided data for software testing on the NA-MIC Wiki website (http://www.na-mic.org/Wiki/index.php/DBP:Harvard:Software:Testing). Structural volumes for three cases are now available for the following brain areas and structures: 1) intracranial contents, 2) gray matter, 3) white matter, 4) CSF, 5) superior temporal gyrus, 6) amygdala, 7) hippocampus, and, 8) parahippocampus. The

purpose of providing these data is so that computer scientists who are developing new tools can check the validity of volume measures using these data. Additionally, we have provided software-testing data for DTI variables in order to ensure that the data are reliable using the fractional anisotropy and other dependent DTI measures. Thus far we have observed inconsistencies that we have reported so that they can be addressed.

(6) In an effort to keep track of the development of analysis modules in the 3D Slicer, we have created an interactive website interface on the NA-MIC Wiki page, where researchers can report "bugs" they notice while using the software (http://www/na-mic.org/Wiki/index.php/DBP:Harvard#Software_Testing). These problems are then discussed at weekly DTI/Slicer development meetings, and the website is then updated, weekly. In addition, the website also contains a wish list, so that researchers can suggest tools or functions they feel would be useful in Slicer. This use of the NA-MIC Wiki website has proven extremely helpful for communication between researchers and developers, and it provides an excellent interface whereby software developments can be organized, tested, and disseminated.

(7) We also met with investigators from Utah, Drs. Ross Whitaker and Tom Fletcher, in March, to review possible collaborations. One of the topics discussed was the comparison of old and new anisotropy measures in schizophrenia. Dr. Fletcher also presented a non-linear statistical approach to tensors for the schizophrenia and neuroscience investigators.

(8) In summary, we believe that the work we have done on the U54 over the previous grant period has been most productive in setting up the infrastructure, in setting up the alliances among collaborators, and in setting up the data to be used by the computer scientists and engineers. We have also assisted in the teaching elements of the U54. With respect to a time line of events, the following is a capsulized summary of our efforts over this time period.

Timeline of important events:

10/2004 Kickoff Meeting

11/2004 Introduced Project to the Schizophrenia Lab Personnel

- Research Assistants involved in collecting data and updating site on patient recruitment
- Sylvain Bouix, Ph.D. is designated as the point person for Core 3.1 at Harvard, in place of Hae-Jeong Park, Ph.D., who returned to Korea to accept an academic position. Charges to a grant cannot be made until IRB approval. IRB approval is more complicated because it involves multiple sites and the VA as well as Harvard Medical School as institutions of record.

12/2004 Software Development Meeting.

- Tina Kapur & Steve Pieper: Intro on the NA-MIC project.
- Presentations of existing software from the different institutes (Core 1 and 2):
- Presentations on Software Development within the NA-MIC framework using NA-MIC specific tools (ITK,VTK,Slicer).

2/2005 Utah All Hands Meeting.

- Our schizophrenia group prepared and presented the data.
- Our group participated in the DTI engineering workshop.

3/2005 Visit from Ross Whitaker and Tom Fletcher from U. of Utah.

- Presentation of non-linear statistics for tensors by Tom Fletcher.

- Possible collaboration on comparing new and old anisotropy measures in the context of Schizophrenia.
- Highlighted for Ross and Tom the work we are doing on DTI that is also updated weekly on the NA-MIC website.

5/2005 User Training and Dissemination Workshop at Dartmouth.

- Our group gave a presentation on User Experiences and Applications with Slicer.
- Our group participated in hands-on training sessions with Core 5.

B) A MINIMUM OF TWO "HIGHLIGHTS."

1) Core 3.1 prepared data for the NA-MIC community. This involved a great deal of effort on the part of Core 3.1. Over 20 gigabytes of data was put on the website for collaborators. Over 200 subjects underwent different types of morphological MR scans with at least one region of interest (ROI) drawn for each subject. Approximately 80 subjects also underwent a diffusion MR scan in which at least one ROI was drawn. That data set will be used extensively by **Cores 1 and 2**.

2) One paper used the 3D slicer to evaluate diffusion tensor imaging in subjects diagnosed with schizotypal personality disorder. This investigator, Moto Nakamura, M.D., works with Core 3.1 investigators at Harvard. His paper entitled "Fronto-temporal Disconnectivity in Schizotypal Personality Disorder: A Diffusion Tensor Imaging Study" has been accepted for publication in *Biological Psychiatry*. This paper would not have been possible without the assistance of the 3D slicer for evaluating fronto-temporal connections in white matter as quantified on diffusion tensor images. Dr. Nakamura also received the Neil Mysell Award for the best poster presentation by a fellow at the Harvard Research Day. This work was based on using tools from the 3D slicer.

C) The Details of the Federally Funded Investigators that Used the Resources in the NIH NCBC During the Preceding Fiscal year; and

Investigators in Core 3.1 are active users of the resources in NA-MIC. For example, Drs. Shenton, Marek Kubicki, Moto Nakamura, James Levitt, Min Seong Koo, Sylvain Bouix, Khang Uk Lee, Chandlee Dickey, as well as 7 research assistants in our laboratory, and collaborators Carl-Fredrik Westin, and members of his laboratory, have all used the 3D Slicer as well as improvements in the slicer for their research studies.

D) A List of Papers that Acknowledge Support from the NIH NCBC as Well as a List of Publications that Used the Center But Did Not Acknowledge Support. These Two Lists of Publications Should be Presented Separately.

The paper cited above, under **B.**, entitled "Fronto-temporal Disconnectivity in Schizotypal Personality Disorder: A Diffusion Tensor Imaging Study" by Moto Nakamura is from Dr. Shenton's laboratory and is in press now in *Biological Psychiatry* (see attached paper). This paper acknowledges the support of the NA-MIC. There are no papers from our group that used support from NA-MIC that did not acknowledge this grant support.

Progress Report for Core 3.1 (Dartmouth Site, PI: Saykin)

A. Specific Aims

There are no changes in Specific Aims planned for the next funding period. Our goals remain targeted to MRI-based assessment of neuroanatomical and functional connectivity with a focus on the pathophysiology of schizophrenia. Key connectivity pathways for investigation continue to include the corpus callosum, internal capsule, arcuate fasciculus, cingulate fasciculus and uncinate fasciculus. Examination of volume and shape abnormalities in ROIs interconnected by these pathways remains an important objective, as is analysis of fMRI activation patterns in these circuits. Our component of Core 3.1 will continue to work closely with other Core 3 investigators as well as with Core 1 (Computer Science),Core 2 (Engineering), and the training and dissemination cores.

B. Studies and Results

Progress at the Dartmouth Core 3.1 site during the initial funding period is summarized below. Please note that this work was primarily completed during the six months after all IRB issues were resolved and staff and equipment were fully in place (11/04-5/05). There is significant carry over of support requested and work has been accelerated to catch up with initial benchmarks over the next 12 months.

(1) IRB protocols for medical image data sharing were submitted, revised as needed and approved for data utilization by NA-MIC affiliated tool developers and investigators.

(2) Protocols for scan and other data de-identification were developed and implemented.

(3) An additional 3 Terabytes of RAID server capacity, a tape library backup system and an isolated secure upload/download server were implemented in the Brain Imaging Laboratory at DHMC.

(4) Structural MRI data and associated manual segmentation of 16 ROIs from a published study of prefrontal subregions in schizophrenia was de-identified and uploaded to the secure NA-MIC data site. This set will be used for shape analysis, testing automated parcellation, and to enhance interoperability with BRAINS, another widely used morphometric analysis package with which we completed the manual ROI traces. Discussions were held with Core 2 regarding the need for a Slicer application to read BRAINS ROI definition files into Slicer for further processing and interoperability.

(5) A sample set of newer data on six healthy older controls was also de-identified and uploaded. This set is important in that each participant underwent a high resolution structural scan for ROI volume and shape analysis, a diffusion tensor scan for anisotropy/diffusivity mapping and tractography, as well as an event related fMRI memory task for examining functional activity. Hippocampal segmentations were performed on these subjects using BRAINS and made available. These data were used for Slicer testing, development and training (see Dissemination Event, below).

(6) Dr. Saykin visited the Brigham/Harvard (Core 3.1) and MIT (Core 1, Golland and Wells Labs) NA-MIC groups over two days in April 21-22, 2005 to present data and discuss needs for tool development and potential innovative approaches to integrating

fMRI and DTI connectivity analyses. Related discussions were also held by telephone in April with David Tuch at MGH regarding field map correction for warping in DTI scans and integration strategies for fMRI and DTI connectivity measures.

(7) NA-MIC Dissemination Event at Dartmouth. On May 26-27, 2005, a 2-day Slicer Training workshop was held on the Dartmouth College campus. Thirty-eight participants attended including all of the Dartmouth Brain Imaging Laboratory faculty and staff. Dr. Kikinis and investigators and staff from multiple NA-MIC Cores, the Brigham/Harvard SPL group, as well as representatives from the Core 3.2 UC Irvine and Toronto sites attended. Graduate students from the Dartmouth Cognitive Neuroscience Program and fMRI Data Center were also present. A topical summary and list of participants is available on the NA-MIC Wiki:

http://www.na-mic.org/Wiki/index.php/Dissemination:Workshop_May_26-27_2005.

In brief, image analysis theory/algorithms and current Slicer 3D version 2.5 software functionality were addressed in the areas of ROI analysis, DTI and fMRI. This was a highly successful "hands-on" training event. All participants brought computers and learned to perform analyses of raw DTI data collected at Dartmouth, as well as fMRI data collected at BWH. Significant user feedback was provided and approaches to overcome current limitations and plans for new feature sets were discussed.

(8) A series of new participants with psychosis and controls were screened, recruited, clinically and neuropsychologically assessed and scanned. This included 10 patients with schizophrenia and 5 healthy controls as well as 5 patients with bipolar disorder as a clinical contrast group. All participants underwent volumetric and functional MRI probes and most received a DTI scan during the same session.

"Highlights" of Progress in Initial Funding Period

(1) Two data sets of brain images from the Dartmouth Site were de-identified, documented and successfully uploaded to NA-MIC to facilitate collaborative tool development and training.

(2) A NA-MIC Dissemination Event was held May 26-27, 2005 at Dartmouth. Thirty-eight participants from Dartmouth and other NA-MIC Sites and Cores attended this highly successful two day Slicer 3D Training workshop.

C. Significance

The progress to date directly advances the Specific Aims of DBP Core 3.1 by facilitating acquisition and analysis of connectivity and related data on patients with schizophrenia and controls. There are also broader computational, biomedical and neuroscience implications in that we are already beginning to apply the techniques being developed by NA-MIC for studies of schizophrenia to other diseases including preclinical Alzheimer's disease/MCI, cognitive effects of cancer treatment, traumatic brain injury, multiple sclerosis, epilepsy and substance abuse. Thus the NA-MIC tools will directly benefit ongoing neuroimaging research projects in our laboratory sponsored by NIA, NCI, NICHD, NINDS, NIDA and several foundations. In turn, user feedback and feature requests from the Dartmouth faculty and staff working on these clinical projects will enhance the functionality and generalizability of NA-MIC tools.

D. Plans

We expect the development, deployment and testing/user feedback of NA-MIC technology to accelerate over the next funding period both for schizophrenia research and studies of the other above-referenced clinical populations. We also plan to test the NA-MIC Slicer 3D tool for analysis of large animal fMRI data through a piglet brain injury model NICHD-sponsored grant (PI: A.C. Duhaime).

We have been preparing for our new NCRR sponsored, research-dedicated Philips Achieva 3.0T MRI scanner due to be installed in the Dartmouth Neuroimaging Research Center by early Fall 2005. We are evaluating optimized pulse sequences for T1-volumetric, DTI and fMRI data acquisition that will enhance the quality of scan data available for tool development in NA-MIC and for hypothesis testing for DBP Specific Aims.

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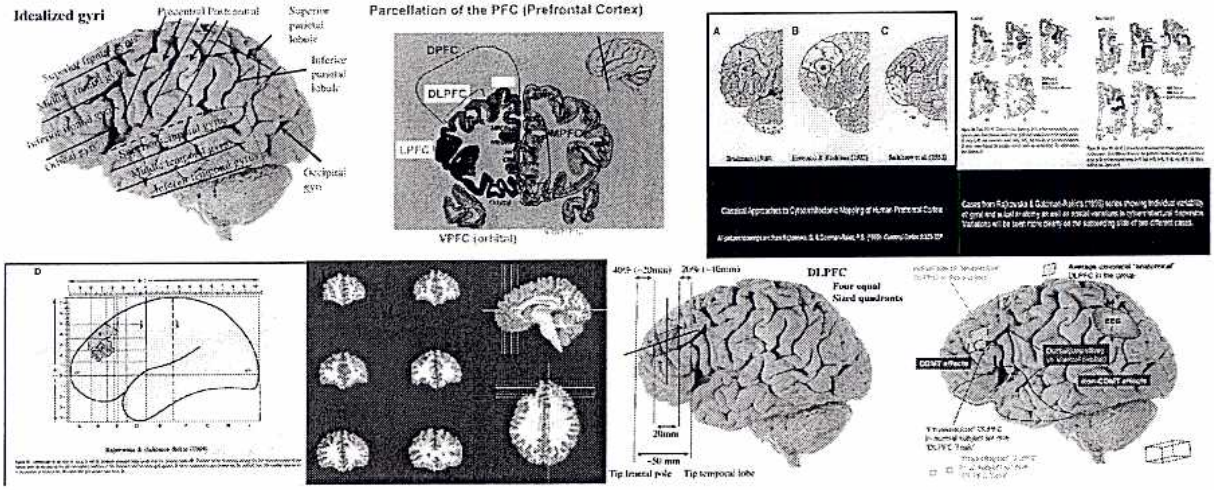
Core 3.2 at UCI and U of Toronto

Significant progress has been made in testing the hypotheses related to our specific aims during this early stage of the project. Due to the intensive interactions with other cores, some materials may overlap with other reports.

1. Creating custom brain segmentations using semi-automated techniques

The UCI Core 3.2 (Fallon) and Georgia Tech Core 1 (Tannenbaum) team has successfully developed a method for taking lengthy and complex neuroanatomical rules for defining a cortical area (Fallon) and creating a new semiautomated segmentor program that is anatomically accurate, but takes only a fraction of the time to carry out.

First, Fallon chose a highly variable and complex-shaped cortical area involved in executive brain functions and short-term memory, the dorsolateral prefrontal cortex (DLPFC). We then created both quantitative and qualitative distance and shape 'rules' (based on neuroanatomical expertise and the literature) for defining its boundaries in different subjects. The rules for outlining the DLPFC were outlined in seven pages of text and twelve figures (a few examples are shown below):



This information was then tested in a series of subjects using manual segmentation techniques to create the most realistic 2-D and 3-D models of DLPFC. For each manual reconstruction carried out locally by a postdoctoral student (Dr. Sandy Kindermann) with some neuroanatomical expertise, then checked post hoc by Fallon for precision and accuracy. Each subject's manual reconstruction of DLPFC took about one full day. The rules were then sent to the Tannenbaum lab for adapting the neuroanatomical rules into a semiautomated algorithm program.

Ramsey Al-Hakim, an undergraduate research student working in Allen Tannenbaum's lab then developed a semi-automatic segmentation program based on domain specific (qualitative and quantitative neuroanatomy) rules formulated by the Core 3 researcher, James Fallon. The motivation of the DLPFC semi-automatic segmentor was to minimize segmentation time of the

DLPFC by incorporating the Fallon rules into an algorithm, while still giving the user control of the segmentation process. The time to segment the DLPFC was reduced from over an hour or more to approximately 5 minutes. The algorithm requires a knowledge of Fallon's rules, and thus extensive knowledge of the entire human brain. The algorithm was originally developed in Matlab and returned a VTK file that is a 3D model of the DLPFC. Future work is to implement the algorithm into 3D Slicer of Brigham and Women's Hospital. Below are two models of the DLPFC from the same MRI case. Figure1 shows a model that was created by the semi-automatic segmentor (in under 5 minutes) and figure 2 shows a model of the same case that was created by manual segmentation (over an hour). Both models are viewed in Slicer with the same right side-anterior-superior view.

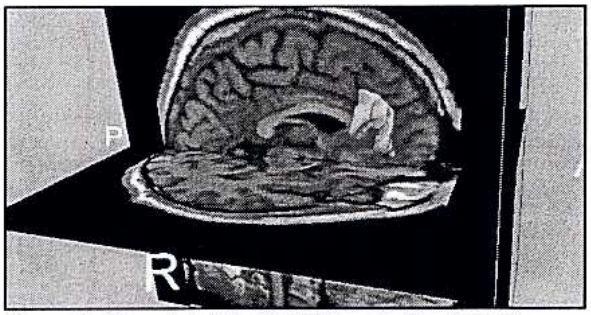


Figure 1. 3D model of the DLPFC created by the semi-automatic segmentor and viewed in SLICER. This is a right anterior-superior view.

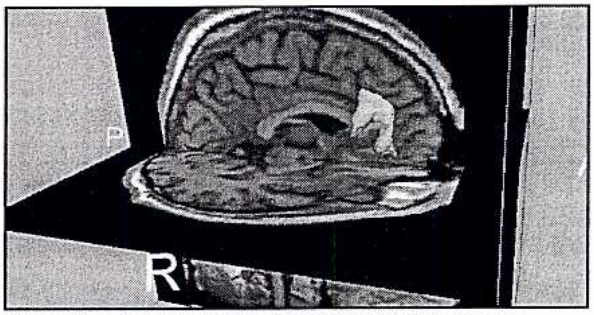


Figure 2. 3D models of the DLPFC created by manual segmentation in SLICER. This is a right side-anterior- side-superior view (same view as Fig 1).

This NA-MIC Core 1-Core 3 collaboration was completed through two face-to-face conversations and presentations at two NA-MIC meetings, and through individual and conference calls, and email. In June of 2005, Allen Tannenbaum and Ramsey Al-Hakim will travel to Fallon's lab for four days to expand and deepen the Core 1- Core 3 interaction in order to determine how the neuroanatomical rules, i.e., both the quantitative definitions but importantly the more qualitative and intuitive features of the neuroanatomist's perceptions, estimations and determinations of location, shape, 'neighborhood' rules can be automated in such a way that retains the precision, accuracy, (and variability) of neuroanatomical expertise but which requires undergraduate level expertise at only a fraction of the time necessary for the manual segmentation.

2. Functional connectivity of the DLPFC investigated using partial least squares correlation

Drs. Lisa Kilpatrick and James Fallon investigated the functional connectivity of the DLPFC using partial least squares (PLS), PLS is a multivariate analytical technique used to summarize large neuroimaging datasets in such a way as to correlate patterns of activation with a variable(s) of interest (i.e. DLPFC activity). PLS works on the assumption that the focus of analysis is on which aspects of the signal in one dataset (neuroimaging data) are related directly to signals in another dataset (DLPFC activity). PLS computes a matrix that defines the relation between the two datasets then analyzes that "cross-block" matrix through singular value decomposition. PLS, as applied here, enables us to derive commonalties and differences among experimental conditions in DLPFC functional interactions with other brain regions. Drs. James Fallon and Lisa Kilpatrick hold weekly meetings (in person) to discuss the results and interpretation of the partial least squares analyses.

The functional connectivity of the DLPFC during performance of the Sternberg working memory task under a low memory load and a high memory load condition was examined. Areas displaying positive correlation with activity in the DLPFC during both low and high load conditions included other prefrontal areas such as the orbitofrontal cortex. Areas displaying a

more positive correlation with activity in the DLPFC during the high load condition than during the low load condition included inferior parietal cortex.

An additional partial least squares analysis to investigate relationships between DLPFC functional connectivity and accuracy performance during the working memory task was performed. In this analysis, both DLPFC activity and accuracy were simultaneously entered as variables of interest. Prefrontal areas were positively correlated with DLPFC and negatively correlated with accuracy during both low and ligh memory load conditions (Figure 1). Parietal areas were positively correlated with both DLPFC and accuracy during the high memory load condition (Figure 2). These results support the view that prefrontal dysfunction underlies working memory deficits in schizophrenic patients and suggest that there may be more dysfunctional and functional aspects of DLPFC networks in terms of supporting working memory performance. The dorsolateral prefrontal cortical networks will be further investigated using structural equation modeling. Structural equation modeling allows the examination of memory load-related changes in the direct influence of the DLPFC onto other brain regions, providing more specific information about the relationships between regions in the DLPFC network. This analysis complies with Specific Aims #1 and #2 by investigating the role of the DLPFC through interactions with other regions in prefrontal and extended networks. This analysis provides information about a general working memory network expressed in schizophrenic patients within which differences among subtypes of schizophrenia may exist.

Figure 1

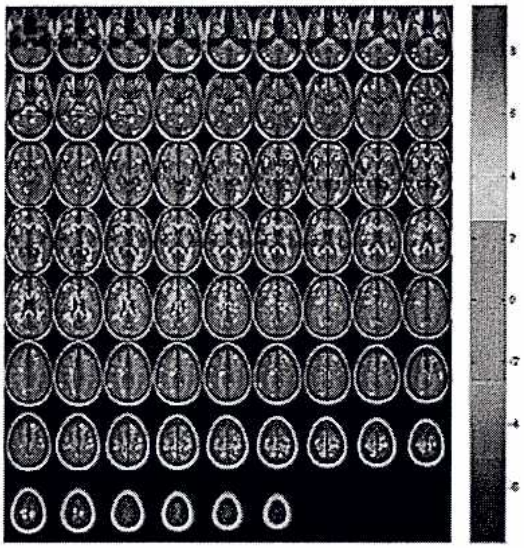


Figure 2

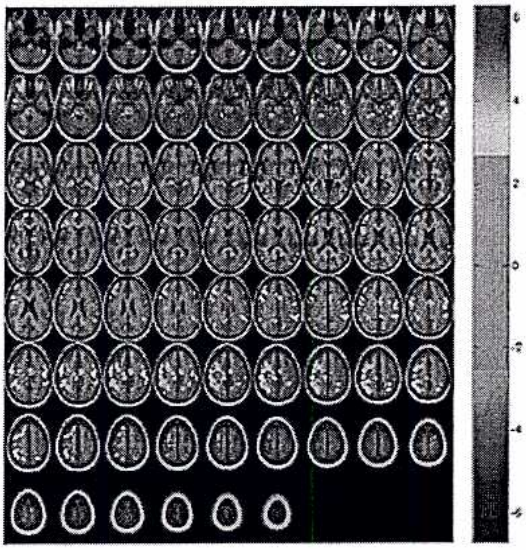


Fig.1. Hot areas are associated with a positive correlation with DLPFC activity and negative correlation with accuracy during low and high memory load conditions. Cool areas are associated with a negative correlation with DLPFC activity and positive correlation with accuracy during low and high memory load conditions. Fig. 2. Hot areas are associated with a positive correlation with both DLPFC activity and accuracy during the high load memory condition. Cool areas are associated with a negative correlation with both DLPFC activity and accuracy during the high load memory condition.

3. Preliminary analysis on genetic allelic variation of schizophrenia at UCI

We have genotyped 27 polymorphisms and tested for Hardy Weinberg Equilibrium across all the SNPs that had 2 alleles. We have also calculated the relative distance from consecutive polymorphisms (e.g., all the SNPs in the DRD2) and build their maps with the LD

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Kitware: Core 4 Progress Report May 2005

Summary

Initial Core 4 activities have focused on establishing the initial collaboration infrastructure for NA-MIC. This includes putting in place resources such as web pages, Wiki, mailing lists, and other supporting software services. We have also established the computing infrastructure (both hardware and software resources) necessary to research, develop, test and deploy the NA-MIC software tools and data. Finally, we have participated with Cores 5 & 6 to disseminate the necessary information to enable the NA-MIC community to use these resources.

Highlights

The following list highlights Kitware's contributions to the NA-MIC community in Core 4. These highlights are categorized as *hardware, software,* and *collaboration*.

- *Hardware*. We have purchased six systems dedicated to NA-MIC. The NA-MIC server is located at Brigham to leverage their high-bandwidth internet connectivity (Internet 2). Five other systems are located at Kitware. These systems are rack mounted with high-speed gigabit Ethernet connectivity. They are dedicated to testing ITK and Slicer on Linux and gcc compilers, Windows XP with MS Visual Studio Versions 6.0, 7.0, and 7.1 compilers, and Windows with the mingw tools.

- *Software*. We have installed and configured many supporting software packages. This includes the compilers and operating systems mentioned previously; the testing framework with DART, DART2 and CMake; dashboards for Slicer; Slicer bug tracker; CVS (for source code control), and various web servers. We have also installed many collaboration tools as described below.

- *Collaboration*. One of our most significant impacts has been the installation, configuration and maintenance of the NA-MIC Wiki. We have also setup and maintain dozens of mailing lists. We also host many of the NA-MIC web pages and other web resources. Finally, we are working with the dissemination and training cores (Cores 5 & 6) to organize and teach dissemination workshops.

Resource Usage

Core 4 provides basic infrastructure to the NA-MIC community. However, since many NA-MIC software tools are open-source, we indirectly benefit the many users of these tools. For example, we have extended the testing process for ITK and Slicer, thereby improving the quality of these tools to the medical imaging community at large.

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Core 5 at MGH

A) Report

At the NA-MIC Kick-Off meeting in October 2004, the members of the NA-MIC Training Core established means of coordinating our efforts, identified and prioritized our initial work. Working within Core 5 and jointly with Core 6, we have used email, teleconference calls, our own lab web sites and our NA-MIC Wiki pages (http://www.na-mic.org/Wiki/index.php/Training:Main) to communicate and to disseminate our Training materials. Face-to-face meetings at NA-MIC and other events (e.g. MICCAI) supplement this long distance communication. Notably at the February NA-MIC AHM the Core 5 team agreed upon plans to focus training efforts in the domain of DTI acquisition and calibration with a goal of improving the quality of image data acquired by all our co-investigators, collaborators and the wider scientific community. See the next section for our first efforts towards this goal. As outlined in our grant proposal, we have focused our initial training efforts within the NA-MIC community as they provide excellent beta testers for the materials to be shared with the scientific community when completed. Importantly, these materials are available to the scientific community now, however, we have not yet worked to promulgate them widely as they are still under development.

Synergies with other funded research and educational initiatives with overlapping goals are being exploited to maximize the federal investment in these projects. For example, the Morphometry Biomedical Informatics Research Network test bed (mBIRN) has a mandate to calibrate DTI data across scan platform and field strength, minimizing distortion and other sources of variance in the data. Strategic partnerships with colleagues in that project are being established to enable joint development of training materials as well as access to benchmark calibration data sets to be used for tutorials (Core 5 activity) as well as by the Core 1 algorithm developers.

Development of training materials

The Training Core Wiki pages will be used to curate both NA-MIC and non-NA-MIC web based medical imaging educational materials. In addition, each of the Training investigators hosts the materials they develop on their own web site.

The UNC group has developed a set of training and teaching tools to explore and understand diffusion tensor image data. The main purpose is to give users a hands-on experience with tensor data and some basic analysis and visualization options. These tools can be used in combination with other teaching material like overview presentations, book chapters, and papers describing fundamental issues. The first three tools (Glyph, Fiber, Conn) read in a

volumetric tensor dataset (vtk standard format) and offer the opportunity to explore the 3-D tensor information in combination with orthogonal slice display. The tools can be downloaded at www.cs.unc.edu/~gerig/NA-MIC/DTI-Training-Tools. The fourth tool (MriWatcher) serves for a simultaneous visual inspection of all gradient channels of a DTI dataset:

A) **Glyph**: Representation of multi-planar orthogonal slice display of DTI fractional anisotropy and overlay of tensors displayed as ellipsoids. The size of the tensors reflects the magnitude of the apparent diffusion and the color coding reflects the directionality of the anisotropy. Users can define bounding boxes, minimum FA to display tensors, location and number of orthogonal planes, and a 3D rendering of the white matter surface.

B) **Fiber**: The "Fiber" tool offers the same visualization features as the "Glyph" tool, but demonstrates the basic idea of fiber tracking. A user interactively specifies a source location and can visually inspect the resulting streamline obtained by tracking the principal direction vector field.

C) **Conn**: The "Connectivity" tool is a re-implementation of the concept of Riemannian flow as developed by Lauren O'Donnell et. al., at MIT (NA-MIC Core 1). Based on the selection of a seed point, e.g. placed in a strongly structured bundle, the program calculates the tensor warped distance as a 3D volume. The color-coded distance maps from the original DTI volume are displayed side by side with multi-planar slice visualization. Users can interactively change slice locations and explore the 3D nature of the result.

D) **MriWatcher**: This is a display tool designed for simultaneous visualization of sets of volumetric image data. An arbitrary number of volumetric datasets, e.g. baseline DTI and gradient directions, or co-registered structural images and segmentation results, can be displayed simultaneously. This tool supports visual inspection for quality assurance checks for expert users as well as exploration to aid more novice users in understanding these complex image data. Users can zoom and pan images, change their intensity range, switch between axial, coronal and sagittal views, and even overlay existing multi-label segmentations with user-selected transparency. Download this tool at http://www.ia.unc.edu/dev/download/mriwatcher/index.htm.

The BWH/Brockton/MGH sites have worked separately and together to gather existing training materials for 3D Slicer, and develop updated materials to support the new release of Slicer version 2.4 (January 2005). Some of the development has been specifically tailored to fulfill the needs of Core 3 investigators, such as management of file formats from all Core 3 sites, visualization of 3D shapes/volumes- specifically hpc, tractography, co-registration of multi-modal datasets. This is being done in conjunction with the Core 2 Engineers who are developing the new modules and capabilities for 3D Slicer. These materials are already in use for the support of the on-going Training and Dissemination Workshops, such as

the May Dartmouth Workshop (see http://www.na-mic.org/Wiki/index.php/Dissemination:Workshop_May_26-27_2005). These materials are being adapted for the broader scientific community. The Training Core Wiki is used to coordinate this effort (see http://www.na-mic.org/Wiki/index.php/Training:Slicer). Personnel from the Harvard sites (Randy Gollub, MGH and Sylvain Bouix, Ph.D., a computer scientist as well as three Research Assistants, Brockton) are all providing the expertise required for the 1:1 training effort at the Workshop.

MGH site has continued to work on the development of the web based interactive fMRI tutorial. This is the one project that is a few weeks behind schedule due to file format management issues. We have upgraded the server hardware to support expected use. This effort addresses the stated need among Core 3 personnel for attention to fMRI training.

Personnel from the Utah site have also participated in several training Workshops locally (see Feb17-18 2005: ITK Segmentation, http://www.na-mic.org/Wiki/images/0/0b/Insight-Segmentation.ppt and Summer 2005 Workshop: Object population description and general feature analysis framework (Martin Styner - UNC, Tom Fletcher - Utah, Jim Miller - GE Research) http://www.NA-MIC.org/Wiki/index.php/Engineering:Project:Feature_Analysis_Framework).

Future plans

1. Develop metrics to determine the impact of our Training efforts and mechanisms to obtain user feedback for improvements.
2. Further customization and elaboration of Slicer training including additional Workshops to be offered summer 2005 at MGH, October 2005 at the BIRN AHM in San Diego.
3. Development of DTI image acquisition, distortion correction methods, and post-acquisition processing tutorial materials in collaboration with Allen Song (Duke) and Susumu Mori (Johns Hopkins) both members of the Morphometry BIRN testbed. Importantly, for both the Training Core and the Engineering Core, the m BIRN is working on improving DTI image acquisition methods and will have benchmark DTI calibration data sets that will be made available to be shared with NA-MIC. These will be used for the future development of tutorial materials. Next meeting of this group in San Diego Oct. 18-19 at the BIRN All Hands Meeting.
4. Development of a tutorial at MICCAI is under consideration.

B) Highlights

Set of DTI visualization and training tools (Glyp, Fiber, Connectivity, MriWatcher) developed by the UNC Core-5 partner group and made available to NA-MIC researchers to support teaching and training programs.

Publications/Presentations

During the first funding period, the training Core did not generate papers specifically addressing the training efforts of NA-MIC.

One presentation was made at an international meeting, the 2005 Association of University Radiologists conference in Montreal. The Core 5 software developer, Sonia Pujol and her mentor, Dr Kitt Shaffer, made a presentation and then ran a hands-on training session for Radiology educators in the use of 3DSlicer as a teaching tool during the Educational Exhibit Session on Friday May 6 and during the Medical Education Workshop on Saturday May 7. The slides from that presentation are posted at http://www.na-mic.org/Wiki/index.php/Training:Slicer.

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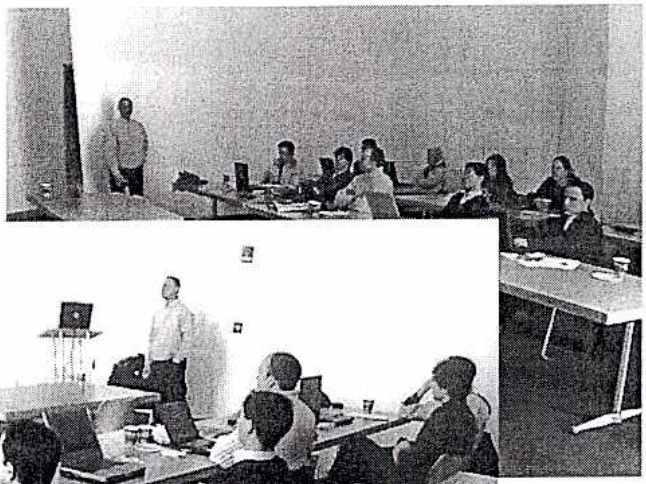
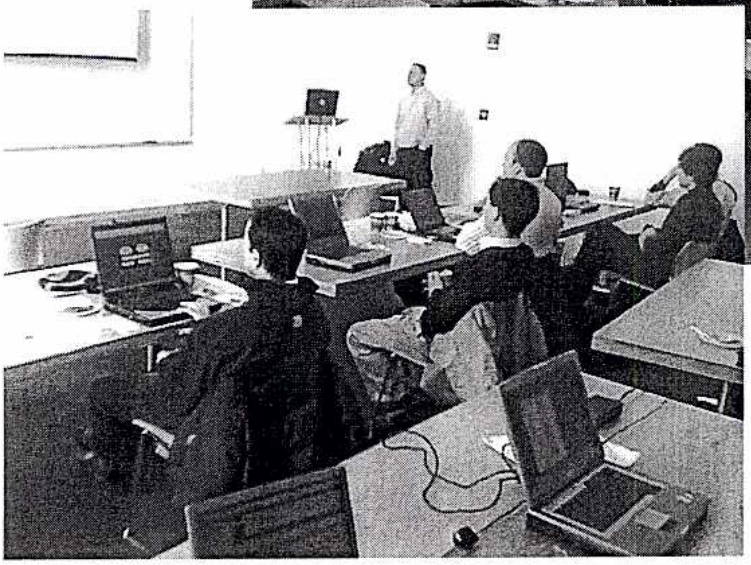
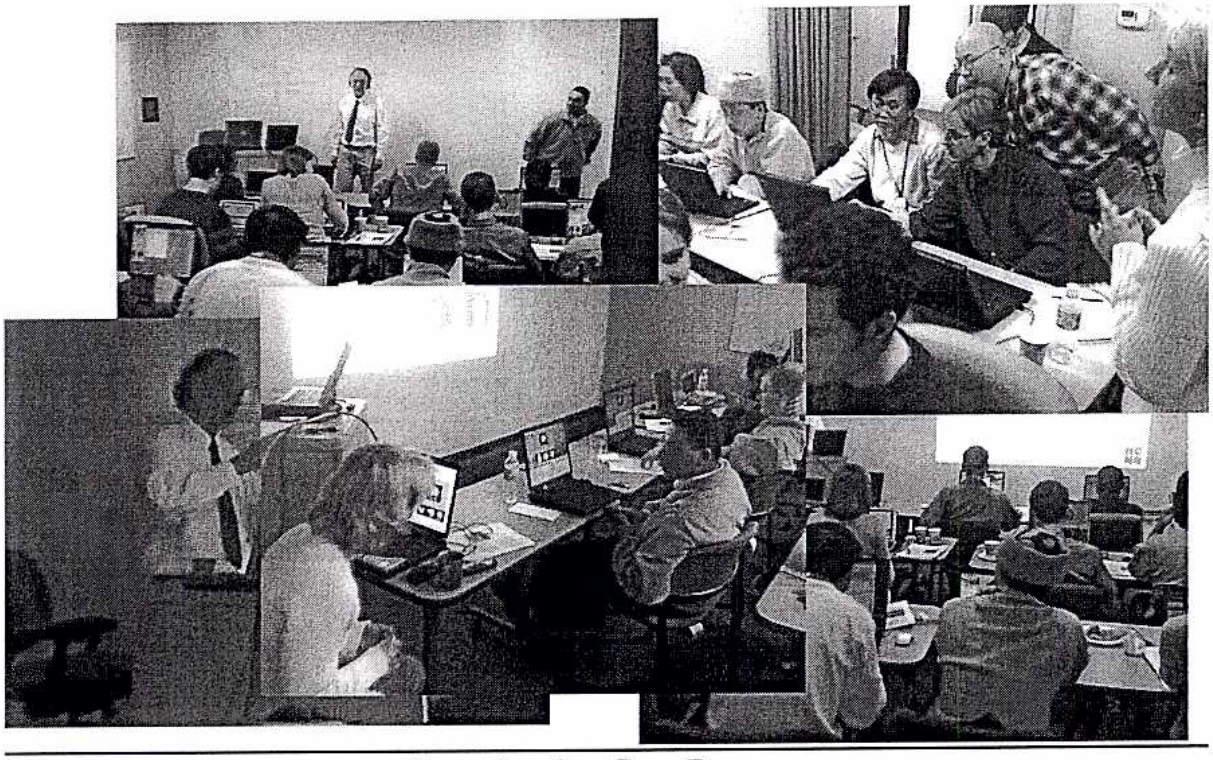
Core 6 at Isomics

Dissemination Core Highlight

The highlight of the Dissemination core's activities in the first year of the center has been to disseminate the mission and software infrastructure of NA-MIC to over 150 participants through personalized, highly interactive workshops held around the country, and to engage these participants in creating a collaborative web-based community of over three hundred pages that have been viewed over fifty thousand times in the last seven months.







Dissemination Core Progress

The Dissemination core coordinated its efforts with the Service and Training cores to facilitate the exchange of information between the 14 participating institutions of NA-MIC as well as from NA-MIC to the broader research community. These efforts were concentrated on two fronts: Web Presence, and Workshops.

Web Presence: The main web site for the conference, http://www.na-mic.org was launched at the start of the project. Soon after, http://wiki.na-mic.org, a collaborative web site was created on October 18, 2004 as an experiment for communication within the center. In less than 9 months, with about 350 total pages created by over 150 unique users, this has become a critical communication tool within the center, as well as for outreach to the larger research community. The "NA-MIC Wiki" is used on a daily basis for the reporting of meeting minutes, organizing upcoming events, and as a repository for the various components of the NA-MIC kit. It is also used by collaborators from the NIH and BIRN project for similar purposes.

Another use of the Wiki emerged in communication with potential collaborators for NA-MIC. In response to PAR-05-063: Collaboration with NCBCs that was released in March 2005, the dissemination core actively worked to set up a process to inform and encourage investigators who were interested in applying for it. Again, like much of the rest of NA-MIC, along with phone and face-to-face communication as needed, a "Collaborator Resources" section was created on the Wiki and used to answer questions that were frequently asked by potential collaborators.

Workshops: Seven workshops were conducted at different NA-MIC sites in the first year of the project. Four of these focused on software-development (December: Brigham

and Women's Hospital, January: MIT, February: UC San Diego, February: University of Utah) and were taught jointly with the Service core. A total of about 80 participants attended these software development workshops (17,14,17, 35). Three workshops focused on training clinical users (January: Brigham and Women's Hospital, March: UC Irvine, May: Dartmouth) and were taught jointly with the Training core. About 70 attended these user workshops (16, 32, 30 estimate for Dartmouth). The target audience for the software-development workshops was computer scientists planning to write software using the NA-MIC software kit, while the target audience for the user training workshops was clinical researchers planning to use NA-MIC applications to address their scientific questions. The activity in each workshop started several weeks in advance of the workshop itself. As the first step, Dissemination core participants visited each of the sites to meet with the local teams and to gather a list of topics that the teams needed training in. Based on these face-to-face meetings, the rough scope of the workshops was defined and published on the Wiki. This preliminary scope was published on the Wiki, and refined using feedback from members of the Algorithms and Engineering Cores. Participants of the first few workshops were asked to provide information about their background, which was used to further customize the materials used. Shortly before the workshops, instructors provided instructions on the Wiki for the preparation the participants needed to do prior to the workshop (install software, download data, run examples). Mailing lists were set up for each workshop to allow the participants to communicate questions back to the instructors as they were preparing. Materials for the workshops were also made available on the Wiki prior to the actual event. The workshops themselves consisted of a mix of presentations by the instructors and hands-on training for the participants. After each of the workshops, feedback was gathered from users on the content and style of the workshops, and every effort was made to incorporate it in subsequent workshops.

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Core 7

The Management Core (Core 7) of NA-MIC has been responsible for some of the central functions as well some of the functions that require inter-Core coordination or extra-NA-MIC coordination. The following are some of the general activities as well as some of the key highlights of the first year of NA-MIC.

General Activities

1. Finance and administration

NOGA for NA-MIC was received on September 17, 2004. From this date onwards 17 subcontracts for 14 sites were prepared and sent out. In addition, at BWH, the accounts for all 7 Cores were created so that all invoices that arrived would be charged against the correct accounts. Core 7 members review all invoices coming through and recommend for approval by the PI, Ron Kikinis.

Invariably, some cores need to make changes to their subcontracts, which Core 7, coordinate with BWH Finance as well as the Finance departments of the corresponding institution.

In April 2005, Core 7 sent out reminder for the Progress Report and has coordinated the financial as well as science progress report collection for arrival at NIH by June 1, 2005.

2. IRB coordination

Early on, Core 7 coordinated efforts with Core 3 (the DBPs) to allow access to their retrospective data by NA-MIC members so that Core 1 and Core 2 could start their work. All 4 DBPs (Harvard/VA, Dartmouth, UCI and U of Toronto/CAMH) we able to amend their IRB protocols at their respective sites to allow sharing of their retrospective data to the NA-MIC community. After this was achieved, BWH approached the IRB committee at Partners Healthcare (IRB body for BWH) to allow secondary-use IRB protocol for all of NA-MIC—although the data was not collected at BWH, it was important to get the approval as BWH was a "transit" point and the NA-MIC contract with NIH was signed with BWH.

In March 2005, coordination for prospective data from the same 4 DBP sites was started. At the time of this writing all but Harvard/VA IRB for prospective data collection for NA-MIC was approved. After Harvard/VA prospective data IRB is approved, Core 7 will again approach Partners Healthcare for secondary-use IRB approval for sharing the prospective data.

Highlights

1. Secondary-Use IRB

Coordinating and securing secondary-use IRB approval from the 4 DBP sites as well as BWH for sharing retrospective data early on in NA-MIC's Year01 was critical. Until

some data was available, Core 1 could test their algorithms and Core 2 would not be able to make full use of the engineering/software processes and platform that they were building and as a result Core 3 (DBPs) would not be served and Dissemination and Training Cores would also be affected. Hence, the decision was made at the outset to get IRB approvals in two-steps: a) Retrospective data from other projects to be shared with NA-MIC and b) Prospective data specifically for NA-MIC.

The DBPs got secondary-use approval by early December 2004 and BWH got secondary-use IRB approval by late December, 2004, paving the way for upload of the data so all Cores were able to use it.

We decided to use BIRN infrastructure (also called SRB) as a repository for the retrospective data and uploads of data started in January-February 2005. By the time the AHM in Salt Lake City in late February 2005, other Cores were starting to use the data from repository.

2. All-Hands-Meeting at Salt Lake City, February 2005

Within 4 weeks of the NOGA, Core 7 brought all the Cores and participants together for introductions to each other and also to NA-MIC at a Kickoff Meeting on October 15, 2004. At the conclusion of the Kickoff Meeting the goal was to have an AHM within 6 months to start substantive coordination of science. The few months of the year was expended in setting up the finance/administrative infrastructures and securing IRB approvals and setting up processes—in the interim, all Cores and their PIs were also coordinating among themselves. Hence, in November 2004, Core 7 members picked late February 2005 in Salt Lake City to be date and venue of the AHM.

By all accounts, the AHM was a resounding success. We had 85 participants from all Cores as well as NIH. All the Core PIs presented their activities as well as goals for the year. Inter-Core workshops, primarily between Core 1 and Core 3, Core 1 and Core 2 as well as different sites within the same Core, e.g. sites from Core 1, sites from Core 2 and sites from Core 3 were able to discuss and coordinate their efforts. It was helpful to have NIH members as participants as much helpful feedback was gleaned from.

Logistically, the venue, the hotel and the date worked very well. Using the Wiki as the primary coordinating tool was invaluable. Our colleagues from University of Utah were very helpful in making local arrangements.

Face-to-face interactions with colleagues after months of email or teleconference were crucial for building a good foundation for the first year of NA-MIC. The AHM achieve its intended goal and we hope to have an annual AHM at a different collaborator's hometown.

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Leadership Core

The Leadership Core of NA-MIC has been responsible for setting the agenda for the first year and the planning future years. In addition, coordination among many disparate fields, researchers/experts was important from the starting blocks. Similarly, dialogue between NIH personnel were critical to better understand and deliver value of a U54 project. The following are some of the general activities as well as some of the key highlights of the first year of NA-MIC.

General Activities

1. Setting the priorities

Early on, the Leadership Core set the tone of transparency and mutual cooperation among the disparate disciplines and their researchers/experts. For instance, the publication policies and data share policies and conventions are quite different in the computer science world (mostly Core 1 and some Core 2 participants) from the clinical world (mostly Core 3 participants). The Leadership Core solicited feedback from all and led the way to create a policy that was clear and fair to all.

The Leadership Core set the priorities and deliverables for the first year and first months as well as anticipated the deliverables of the DBPs that were going to on the project for the first half of the project period. To that end, the Leadership Core delegated several tasks for the first few months:

a. Approval of the IRB in two steps. First getting easier IRB approval as secondary-use of old data, setting a precedent for getting full, prospective IRB approval by the close of the first year.
b. Frequent face-to-face meeting of experts. Kickoff Meeting (Oct 15; 2004), Dissemination Meeting (5 in the first year at various sites), All Hands Meetings (Feb 2005).

2. Finance and administration

With the help of the Management Core, the Leadership Core was instrumental in streamlining the financial processes so that the subcontractors' invoices are processed and signed off as quickly as possible and payments to them was distributed in equality timely manner. Any and all financial issues have been dealt with in a pro-active manner.

3. Inter-Core coordination

While, intra-Core coordination has been the responsibility of the Core PI (and that has worked satisfactorily), Leadership Core is typically involved in coordinating among Cores. Example of inter-Core work is answering the question posed by Core 3 members "How are Core 1 members using our data?" By getting the data access log from the SRB as well as talking with Core 1 members, Core 7 was able to provide the answer to Core 3 members.

Another important inter-Core topic included the policies on publication and data sharing. Since NA-MIC is a multi-discipline effort the conventions for publications, authorship and data sharing and acknowledgements are quite different. Leadership Core was able to provide a draft guideline that Core 1, 2 and 3 members were able to craft a version that everyone was comfortable with. This draft was finalized by all members during the AHM at Salt Lake City.

Highlights

1. Regular meeting with Key Personnel

The first year of any new, complex project requires investment of many hours in coordination among key personnel. As such, Ron Kikinis spent much of his time in coordination between the different cores and regular discussions with the core PI's and initiation and participation in the different teleconferences and events (Dissemination Meetings, All Hands Meeting).

In addition, Dr Kikinis spent time with different NIH personnel including monthly meetings with Program Officer, Grace Peng, and the Lead Science Officer, Karen Skinner.

The DBPs got secondary-use approval by early December 2004 and BWH got secondary-use IRB approval by late December, 2004, paving the way for upload of the data so all Cores were able to use it.

We decided to use BIRN infrastructure (also called SRB) as a repository for the retrospective data and uploads of data started in January-February 2005. By the time the AHM in Salt Lake City in late February 2005, other Cores were starting to use the data from repository.

2. Extra-NA-MIC Coordination

a. Leadership Core members have also been in contact with other U54 projects as per NCBC guidelines. At the time of this writing, contact has been made with 2 U54 projects, i.e., I2B2 of BWH and Simbios of Stanford University. Ron Kikinis visited the Stanford U54 twice and we have an emerging potential project doing patient specific segmentation of muscles from MRI for subject specific modeling. With I2B2 we have two projects: one about Chronic Obstructive Pulmonary Disease (COPD), where we will use our technology to analyze bronchi from CT data, the second is about velocardiofacial syndrome (VCF).

b. Leadership Core members have also actively participated in the NCBC evaluation bi-weekly conference calls since January 2005. There will be a NCBC-wide evaluation meeting in July 7-8, 2005. There will be four members of NA-MIC attending, including Ron Kikinis, the PI, Bill Lorensen, PI of Core 2, Stephen Pieper, PI of Core 6, Stephen Wong, PI of Core 7 and the Co-PI.

Principal Investigator/Program Director (Last, first, middle): Kikinis, Ron

GRANT NUMBER
U54 EB005149

CHECKLIST

1. PROGRAM INCOME ***(See instructions.)***
All applications must indicate whether program income is anticipated during the period(s) for which grant support is requested. If program income is anticipated, use the format below to reflect the amount and source(s).

Budget Period	Anticipated Amount	Source(s)

2. ASSURANCES/CERTIFICATIONS ***(See instructions.)***
In signing the application Face Page, the authorized organizational representative agrees to comply with the following policies, assurances and/or certifications when applicable. Descriptions of individual assurances/certifications are provided in Part III of the PHS 398. If unable to certify compliance, where applicable, provide an explanation and place it after this page.
• Human Subjects Research • Research Using Human Embryonic Stem Cells • Research on Transplantation of Human Fetal Tissue • Women and Minority Inclusion Policy • Inclusion of Children Policy • Vertebrate Animals

• Debarment and Suspension • Drug- Free Workplace *(applicable to new [Type 1] or revised [Type 1] applications only)*; • Lobbying • Non-Delinquency on Federal Debt • Research Misconduct • Civil Rights (Form HHS 441 or HHS 690); • Handicapped Individuals (Form HHS 641 or HHS 690) • Sex Discrimination (Form HHS 639-A or HHS 690) • Age Discrimination (Form HHS 680 or HHS 690); • Recombinant DNA Research, Including Human Gene Transfer Research • Financial Conflict of Interest (except Phase I SBIR/STTR) • Prohibited Research • Select Agents and Toxins
• STTR ONLY: Certification of Research Institution Participation.

3. FACILITIES AND ADMINSTRATIVE (F&A) COSTS
Indicate the applicant organization's most recent F&A cost rate established with the appropriate DHHS Regional Office, or, in the case of for-profit organizations, the rate established with the appropriate PHS Agency Cost Advisory Office.

F&A costs will ***not*** be paid on construction grants, grants to Federal organizations, grants to individuals, and conference grants. Follow any additional instructions provided for Research Career Awards, Institutional National Research Service Awards, Small Business Innovation Research/Small Business Technology Transfer Grants, foreign grants, and specialized grant applications.

☒ DHHS Agreement dated: November 4, 2004 ☐ No Facilities and Administrative Costs Requested.

☐ No DHHS Agreement, but rate established with _____ Date _____

CALCULATION*

Entire proposed budget period: Amount of base $ 363,063 x Rate applied 73.00 % = F&A costs $ 265,036

Add to total direct costs from Form Page 2 and enter new total on Face Page, Item 8b.

*Check appropriate box(es):

☐ Salary and wages base ☒ Modified total direct cost base ☐ Other base *(Explain)*

☐ Off-site, other special rate, or more than one rate involved *(Explain)*

Explanation *(Attach separate sheet, if necessary.):*

KEY PERSONNEL REPORT

Place this form at the end of the signed original copy of the application. Do not duplicate.

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All Key Personnel for the Current Budget Period (do not include Other Significant Contributors)

Name	Degree(s)	SSN (last 4 digits)	Role on Project (e.g. PI, Res. Assoc.)	Date of Birth (MM/DD/YY)	Annual % Effort
Ron Kikinis	M.D.	8836	PI	03/30/56	25.0
Mark Ellisman	M.A., Ph.D.		Investigator	11/15/48	2.0
Guido Gerig	Ph.D.		Investigator	09/24/54	19.4
Randy Gollub	M.D., Ph.D.		Investigator	01/24/59	10.0
W. Eric L. Grimson*	Ph.D.		Investigaor	04/25/53	100.0
David Kennedy	Ph.D.		Investigator	02/23/62	5.0
James L. Kennedy	M.D.		Investigator	05/24/55	10.0
William E. Lorensen	Ph.D.		Investigator	11/08/46	39.9
Steven Pieper	Ph.D.		Investigator	05/24/63	9.6
Steven Potkin	M.D.		Investigator	08/22/45	10.0
Andrew Saykin	PsyD, ABPP		Investigator	05/15/45	10.0
William J. Schroeder	Ph.D.		Investigator	03/12/57	32.5
Martha E. Shenton	Ph.D.		Investigator	11/11/52	15.0
Allen Tannenbaum**	Ph.D.		Investigator	01/25/53	10.0
Arthur W. Toga	Ph.D.		Investigator	07/19/52	2.0
Ross Whitaker	Ph.D.		Investigator	02/19/64	5.0
Stephen Wong	Ph.D.		Investigator	09/08/59	35.0

*budgeted for one month only
** budgeted for 5% for 9 months
& for 60% for 3 months