Summary: National Alliance for Medical Image Computing (NA-MIC): A National Center for Biomedical Computing

NA-MIC has championed a modular set of interoperable free open source software (FOSS) packages, managed under a collaborative, high quality software engineering methodology. This common infrastructure allows new concepts, emerging from algorithmic research in computer science, to be directly and efficiently deployed into the hands of clinical researchers trying to solve difficult clinical problems. Once embodied as NA-MIC Kit components, such innovations are available to the community at large for use across a range of compute platforms and datasets. Closing the gap between idea and implementation, supporting rapid iteration, and providing a stable dissemination mechanism lie at the core of the NA-MIC software approach. This brief overview highlights notable contributions that mark NA-MIC’s place in the field of biomedical image analysis, discusses important activities and functions that differentiate NA-MIC as a center, and cites NA-MIC’s most pre- eminent achievements as illustrations of the quality of its work and productivity.

Statistical Modeling of Genetic and Imaging Data for COPD and Huntington’s Disease

Imaging biomarkers are an essential component of modern approaches to understanding heritable diseases because they provide powerful tools to interpret genetic information in the context of their clinical manifestation. NA-MIC has established a pattern of scientific research that integrates genetic testing with large scale, statistically sensitive disease-specific image quantification. The NA-MIC collaboration with the NIH-funded COPDGene effort (www.copdgene.org) has enabled statistical modeling of genetic profiles of the at-risk population by correlating imaging derived airway, parenchymal, and vascular phenotypes with a spectrum of established pulmonology diagnostic metrics. A recent study has revealed new genetic associations at the loci near CHRNA-3/5 in chromosome 15 and MMP-12/13 in chromosome 11 based on CT-quantified emphysema patterns using a local histogram classifier, establishing that these genes can determine the genetic predisposition of an individual to develop COPD.

The same statistical approach is being used in collaboration with the PREDICT-HD, a Huntington's disease (HD) consortium led by the University of Iowa. The goal is to provide early detection of HD progression using image, genetic, and clinical data from 786 gene-positive but undiagnosed subjects. People afflicted with HD can be identified well in advance of symptom onset based on a reliable genetic test, but genetics alone cannot predict when they will transition into the acute phase of the disease. The PREDICT-HD consortium is seeking quantitative medical imaging biomarkers for use as surrogate endpoints in their drug treatment trials aimed at delaying the onset and/or progression of disease. These more accurate predictions will ultimately help inform clinical decisions about the timing and use of therapies such as implantable devices that can deliver genetically engineered neurotrophic factors directly to the brain. The NA-MIC Kit is being used to identify early changes in white matter architecture and atrophy of subcortical brain structures including caudate, putamen, and thalamus. These biomarkers correlate with the known genetic test for HD in presymptomatic patients.

Mobilizing an International Open Source Development Community

NA-MIC takes seriously the responsibility of representing US medical imaging software development activities in the national and international community. Through our collaborations and outreach programs, we have mobilized like-minded scientists to contribute to open source software development for biomedical image analysis. Attracted to the concept of sharing software development resources, leading international groups have adopted NA-MIC’s engineering framework in lieu of undertaking the costly and redundant option of developing their own. These collaborative efforts have greatly raised awareness of the benefits of open science, and as a result, government-funded efforts that complement NA-MIC are now in place in Canada, Germany, Spain, France, and Italy.

In 2011, Canadian funding was awarded to the Ontario Consortium for Adaptive Interventions in Radiation Oncology (OCAIRO) to develop a shared framework for radiation therapy, called Software Platform and Adaptive Radiotherapy Kit (SPARKit). SPARKit’s goal is to enable oncologists to monitor, assess response to, and adapt radiation therapy in individual patients. Recognizing the quality and value of NA-MIC’s open source model, software imaging scientists at OCAIRO decided to adopt 3D Slicer as the platform for SPARKit. OCAIRO has contributed substantially to 3D Slicer by adding specific functionality in adaptive radiotherapy data format support and dose visualization and processing.

In a similar vein, NA-MIC investigators have been leaders in establishing Common Toolkit (CTK), a multi-institution international collaboration to share software development resources in medical imaging applications. The inspiration for this project grew from informal discussions between NA-MIC scientists and investigators from the German Cancer Research Center (DFKZ) during a NA-MIC hosted outreach event in Munich. CTK’s initial focus was on user interfaces and core technology around DICOM networking and related standards to be shared to the mutual benefit of individual investigators and has further adapted and extended the NA-MIC Kit.

NA-MIC’s ‘center’ mandate for outreach, a feature of every National Center for Biomedical Computing, has been a crucial catalyst to international collaborations such as OCAIRO/SPARKit and CTK. Such collaborations attract international funding that benefits not only NA-MIC, but also other NIH initiatives.
2. NA-MIC Top-10 Publications List

NA-MIC has published 456 papers since its inception. A list is provided in Appendix A. Below we highlight ten publications that represent the breadth and depth of recent activity in NA-MIC.

DBP Science


2. Kubicki M., Styner M., Bouix S., Gerig G., Markant D., Smith K., Kikinis R., McCarley R.W., Shenton M.E. Reduced Interhemispheric Connectivity in Schizophrenia- Tractography Based Segmentation of the Corpus Callosum. Schizophr Res. 2008 Dec;106(2-3):125-31. PMID: 18829262. PMCID: PMC2630535. This paper, published in one of the prime schizophrenia journals, highlights the integration of shape analysis on the corpus callosum and NA-MIC DTI processing with Slicer. It is one of the first publications to report reduced interhemispheric connectivity in schizophrenia via callosal fiber tracts. Schizophrenia Research Impact Factor: 5.1 Paper citations: 43

3. Van Horn J.D., Irimia A., Torgerson C.M., Chambers M.C., Kikinis R., Toga A.W. Mapping Connectivity Damage in the Case of Phineas Gage. PLoS ONE 7(5): e37454. PMID: 22616011. PMCID: PMC3353935. This paper models and examines the extent of white matter damage experienced in the case of Phineas Gage, undoubtedly the most famous case of neurological injury in medical history. Mr. Gage, a railroad construction foreman was severely injured when a large iron crowbar was driven completely through his head, destroying much of his left frontal lobe and markedly altering his personality. This work has been featured on CNN, LA Times, NPR, among other media, and will soon be featured in Discover Magazine. PLoS ONE Impact Factor: 4.092, Paper citations: 1


Computational Science

7. Rathi Y., Vaswani N., Tannenbaum A., Yezzi A. Tracking deforming objects using particle filtering for geometric active contours. IEEE Trans Pattern Anal Mach Intell. 2007 Aug;29(8):1470-5. PMID: 17568149. This paper was the first to combine statistical estimation theory with geometric models of active contours for the dynamic segmentation of noisy imagery that may undergo large deformations. By decoupling the affine part from the elastic part of the deformation, one may drastically reduce the number of particles in the particle filter necessary for a given task. The method has been applied already to several of our DBPs including the robotic prostate biopsy and the left atrial fibrillation projects. (2011 Thomas Reuter’s Web of Knowledge; Second Highest Among All Computer Science Journals). TPAMI Impact Factor: 4.908, Paper citations: 100


9. Gerber S., Tasdizen T., Fletcher P.T., Joshi S., Whitaker R.T. Manifold Modeling for Brain Population Analysis. Med Image Anal. 2010 Oct;14(5):643-53. PMID: 20579930. PMCID: PMC3020141. This paper describes a method for building efficient representations of large sets of brain images. The basic hypothesis is that the space spanned by a set of brain images can be captured to a close approximation by a low-dimensional, nonlinear manifold. This paper presents a method to learn such a low-dimensional manifold from a given dataset. The manifold model is generative. Brain images can be constructed from a relatively small set of parameters and new brain images can be projected onto the manifold. Medical Image Analysis Impact Factor: 4.424, Paper citations: 23.

10. Lankton S., Tannenbaum A. Localizing region-based active contours. IEEE Trans Image Process. 2008 Nov;17(11):2029-39. PMID: 18854247. PMCID: PMC2796112. This paper proposes a framework that allows any region-based segmentation energy to be re-formulated in a local way. Thus, we consider local rather than global image statistics and evolve a contour based on local information. Such localized contours are capable of segmenting objects with heterogeneous feature profiles that would be very challenging to capture using a standard global statistically based method. Such heterogeneity is very typical in much medical imagery. TIP Impact factor: 3.042, Paper citations: 174
3. Training

NA-MIC has trained 35 students, of whom 8 are now pursuing academic careers (5 faculty positions 3 research fellows) and 10 are in industry (3 in leadership positions and 7 in engineering roles).

NA-MIC has also trained 20 fellows, of whom 9 are now in faculty positions around the world, and the rest are in leadership positions in industry or research laboratories.

In addition, NA-MIC has employed nearly 60 engineers from academic and industry laboratories, many of whom are thought leaders in the international free and open source software community.

A list of all NA-MIC funded personnel is provided in Appendix B.
4. Milestones of a Successful National Infrastructure Resource

Grant funding mechanisms have a substantive impact on the development efforts a project may undertake. The National Center for Biomedical Computing program was chartered to create infrastructure to enable focused research. In contrast to this, R01s typically support discrete, specified, circumscribed projects. As a result, where investment in cross-cutting and broadly applicable technologies can be difficult or impossible to justify in the context of an R01, NA-MIC investigators routinely identify commonality across a range of use-cases in order to implement general purpose tools and techniques. For example, NA-MIC has undertaken numerous projects in image registration, shape analysis, segmentation, and visualization that are now applied across multiple imaging modalities and used in dozens of clinical domains.

The principled use of software engineering science inside the NA-MIC effort has resulted in a robust, modular, and maintainable software environment embodied in the NA-MIC Kit. The infrastructure created in this open source software allows collaborating R01s to focus on their own core science without having to re-create redundant commodity capabilities. More importantly, the stability of an infrastructure maintained by a dedicated group of engineers facilitates the long-term viability and accessibility of the results of R01 research. Likewise, requirements of the driving biological projects and collaborating R01s shape the extension of NA-MIC functionality. With continued funding, the medical image computing community will benefit from NA-MIC’s foundational investment in high quality software engineering methodology and common infrastructure that promote open and reproducible science. As more projects adopt the tools and methodologies provided by the center, maintaining the continuity of this infrastructure will be critical to sustaining its productivity.

Network of External Collaborations. NA-MIC has powered 31 funded collaborations using the NA-MIC Kit; 25 funded by NIH grants (8 active, 17 completed) and 6 by international governments (5 active, 1 completed). A list of these collaborations is provided in Appendix C. Collectively, these collaborations address a broad range of organ systems and pathologies: diagnosis and therapy of schizophrenia, lupus, autism, lung disease, cancer of the liver, colon, and prostate, and musculoskeletal disorders. Recognizing the value of developing new techniques that integrate with the NA-MIC Kit, the collaborating PIs and their respective teams have gained efficiency by bypassing the time-consuming tasks associated with custom software development, including distribution, training, and routine maintenance.

Driving Biological Projects (DBPs). Synergistic with but distinct from our external collaborations, NA-MIC’s 11 DBPs have provided the strong push-pull relationship needed to drive the NA-MIC portfolio. These address neurodegenerative disorders including schizophrenia and autism, lupus, Huntington’s disease, heart disease (atrial fibrillation), radiotherapy for prostate and head and neck cancer, and traumatic brain injury. The NA-MIC Kit now contains detailed tutorials and test datasets that can be used to solve specific clinical research problems in each of these clinical domains.

NA-MIC Kit. The first FOSS biomedical computation platform of its magnitude, the current configuration of the NA-MIC Kit is the culmination of 6 years of effort. The Kit and its various components have been and continue to be widely disseminated as measured by the center’s download statistics. Our flagship end-user application, Slicer, was downloaded 31,717 times in the past 12 months. CMake, along with its associated software process tools (CTest, CDash, CPack), continues to be one of the most popular pieces of the NA-MIC Kit, with more than 2,000 known downloads per day (not counting the various Linux distributions). Used to build, test, and deploy software in a cross-platform manner, CMake has become the industry standard for cross-platform development way beyond the medical image computing community. Finally, NA-MIC’s user and developer mailing lists now contain 829 and 483 members, respectively. Membership is distributed globally, and the high level of daily activity is a testament to the ability of open-source software to leverage development efforts across a broad community, at little additional cost to project sponsors.

Training Compendium and Workshops. Using the NA-MIC Kit, we have created an online training compendium, consisting of 88 detailed tutorials with step-by-step instructions and pre-computed datasets that are freely available to the scientific and clinical community. Additionally, we have taught 2,090 investigators worldwide through 63 instructor-led hands-on workshops (ranging from 12-120 participants per event). These workshops are customized to the needs of specific audiences composed of clinical researchers, radiologists, neuroscientists, neurosurgeons, computer scientists, and biomedical engineers. We also provide training to the translational and clinical research communities, through the organization of grand challenge workshops at premier conferences, such as our pioneering initiative on the standardized evaluation of diffusion tensor imaging tractography algorithms for neurosurgical planning offered at MICCAI and RSNA.

Hands-on Project Events. We practice the best principles of collaborative science through our semi-annual Project Week events. To date, we have held 15 consecutive events. Experts and students from inside and outside of NA-MIC gather at these hands-on workshops to address current research problems. The events have grown over the years, now attracting more than 100 participants per workshop and they have been recognized and adopted by several other centers including NCI GT (P41EB015898) and NAC (P41 RR13218; and P41 EB015902).
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<td>Kennedy Consulting, Neuromorphometrics, UCSD</td>
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| **20** | U24RR021992 | fBIRN | **Institution:** University of California Irvine  
**PI:** Steven G. Potkin  
**NA-MIC:** R Kikinis, S Pieper  
**Funding Duration:** 02/08/2006-11/30/2010  
**Status:** Completed |
| **21** | U41RR019703 | NCI GT | **Institution:** Brigham and Women's Hospital  
**PI:** Ferenc Jolesz, Clare Tempany  
**NA-MIC:** R Kikinis, T Kapur, N Hata, H Liu, S Pieper  
**Funding Duration:** 09/29/2005-07/31/2010  
**Status:** Active |
| **22** | U54LM008748 | I2B2 | **Institution:** Harvard University  
**PI:** Isaac Kahane  
**NA-MIC:** R Kikinis, R Gollub  
**Funding Duration:** 09/15/2004-7/31/2010  
**Status:** Completed |
| **23** | U24RR021382 | mBIRN | **Institution:** Massachusetts General Hospital  
**PI:** Bruce Rosen  
**NA-MIC:** R Kikinis, S Pieper  
**Funding Duration:** 09/30/2004-05/31/2010  
**Status:** Completed |
| **24** | P41RR013218 | NAC | **Institution:** Brigham and Women’s Hospital  
**PI:** R Kikinis  
**NA-MIC:** W Wells, C-F Westin, S Pieper, M Halle  
**Funding Duration:** 09/30/1998-05/31/2013  
**Status:** Active |
| **25** | UI1RR025758 | Catalyst Translational Imaging Consortium | **Institution:** Massachusetts General Hospital  
**PI:** Bruce Rosen, Director; R Gollub Co-Director  
**NA-MIC:** C Tempany, R Kikinis, C Guttmann, T Perlstein, G Williams  
**Funding Duration:** ?  
**Status:** Completed |
|   |   | Teragrid neurosurgery | **Institution:** College of William and Mary  
**PI:** Nikos Chrisochoides  
**NA-MIC:** A Fedorov  
**Status:** Active |
|   |   | Pediatric cardiology | **Institution:** Stanford/SCI/SPL/Boston Children’s Hospital/Northeastern  
**PI:** John Triedman, Matthew Jolley, Dana Brooks  
**NA-MIC:** S Pieper, K Pohl  
**Status:** Active |
| **1** | International | OCAIRO/SPARKit | **Institution:** Ontario Consortium for Adaptive Radiation Oncology  
**PI:** Gabor Fichtiger, Terry Peters  
**NA-MIC:** R Kikinis, S Pieper  
**Status:** Active |
| **2** | International | CO-ME (COME) Image-Guided Brain Tumor Surgery | **Institution:** The National Centre of Competence in Research, Zurich, Switzerland  
**PI:** Network of leading clinics and engineering sites  
**NA-MIC:** R Kikinis, S Pieper  
**Status:** Active |
|   | International | NA-MIC collaboration for neurosurgical intervention | **Institution**: University Hospital of Marburg, Germany  
**PI**: Jan Egger, Bernd Freisleben, Christopher Nimsky  
**NA-MIC**: R Kikinis, R Colen, A Golby  
**Status**: Active |
|---|---|---|---|
| 4 | International | CTK Multi-institution international collaboration to share development of a common toolkit for medical image analysis | **Institution**: International consortium  
**Leadership**: Ron Kikinis, NA-MIC and Hans-Peter Meinzer, German Cancer Research Center, Heidelberg, Germany  
**NA-MIC**: R Kikinis, S Pieper, S Aylward, W Schroeder, J-C Fillion-Robin, J Finet, J Jomier  
**Status**: Active |
| 5 | International | Soft tissue organ deformation for computer-assisted Surgery (Australia) | **Institution**: University of Western Australia  
**PI**: Karol Miller  
**NA-MIC**: R Kikinis  
**Status**: Active |
| 6 | International | AIST Japan Research and development project on intelligent surgical instruments | **Institution**: Consortium of Japanese Universities and Companies  
**PI**: Kiyoyuki Chinzei  
**NA-MIC**: N Hata, R Kikinis  
**Funding Duration**: 04/01/2007-12/31/2011  
**Status**: Completed |
| 7 | International | Vascular Modeling Toolkit (Italy) | **Institution**: Mario Negri Institute, Italy  
**PI**: Luca Antiga  
**NA-MIC**: R Kikinis, S Pieper  
**Status**: Completed |