TECHNICAL PORTION

Simple ITK multi-atlas registration and segmentation: Methods and tutorials

Purpose

Two fundamental segmentation approaches in medical imaging are:

- Multi-atlas labeling/segmentation and
- Bayesian segmentation with priors (anatomical or Markov Random Fields (MRF)).

Whereas the latter has a significant developmental history spanning 30+ years, the former has seen extreme interest in the medical imaging community recently due to the general success of crowdsourcing solutions to problems. Although other segmentation approaches are well-represented within the Insight Toolkit and SimpleITK (e.g., region growing and level sets), these popular segmentation approaches are glaringly absent. This proposal aims to remedy this deficiency.

Multi-atlas labeling (MAL). MAL is the current state-of-the-art for propagating expert labelings from a reference atlas library onto new instances of unlabeled data. Image registration is used to align the atlas library (images + segmentations) to a common space. A statistical model is then used to combine the "guesses" from all the normalized atlas labels to provide a "best guess" estimate of the target labeling. Several such algorithms have been developed and much effort has been devoted to determining relative performance levels. See, for example, the recent MICCAI 2012 Grand Challenge and Workshop on Multi-Atlas Labeling).

The joint fusion (JF) algorithm of [1, 2] is one of the top performing MAL algorithms. JF is capable of predicting anatomical labels with accuracy that rivals expert anatomists [3]. It has proven its effectiveness in lung [4], cardiac data, the human brain [5], and in multiple modality canine MRI.

Bayesian segmentation with anatomical and/or MRF priors. Early statistically-based segmentation work appropriated NASA satellite image processing software for classification of head tissues in 2-D MR images [6]. Following this work, many researchers adopted statistical methods for n-tissue anatomical brain segmentation. The Expectation-Maximization (EM) framework is natural [7] given the "missing data" aspect of this problem. The work described in [8] was one of the first to use EM for finding a locally optimal solution by iterating between bias field estimation and tissue segmentation. Core components of this type of work is the explicit modeling of the tissue intensity values as statistical distributions [9, 10] and the use of MRF modeling [11] for regularizing the classification results [12]. A more formalized integration of generic MRF spatial priors was employed in the work of [13], commonly referred to as FAST (FMRIB's Automated Segmentation Tool), which is in widespread use given its public availability and good performance. Recently, researchers have begun to rely on spatial prior probability maps of anatomical structures of interest to encode domain knowledge [14, 15] by providing spatial prior probability maps and an initial segmentation. Although this particular segmentation framework has significant application

in the neuroimaging domain, it has also applicable to other domains such as breast MRI [16, 17] and functional ventilation of the lung [18].

However, despite the numerous algorithms and other developments which have been proposed over the years, there are an extremely limited number of software implementations to perform these types of segmentations *including within the Insight Toolkit and SimpleITK*. This lack within the segmentation community inspired us to create our own Bayesian-based segmentation framework [19] (denoted as Atropos) which we made publicly available within our own ANTs repository. The modular nature of this particular implementation would fit within the parameters of the ITK library.

Deliverables

The core contributions of this proposal will include the following deliverables:

1. **A multivariate implementation of the MAL approach described in [1].** Given the voxelwise estimation of the optimal labeling, it will be multi-threaded. It will also handle multi-modal data as described in [2]. Also, as the original description did not constrain the optimal weights to be strictly positive, a non-negative least squares solution will be provided as a user-selected option. This functionality will be encapsulated in the ITK filter `itk::WeightedVotingFusionImageFilter`.

2. **A generic architecture for MAP-MRF Bayesian multivariate image segmentation with optional spatial priors**. The proposed framework will encode a family of Bayesian segmentation techniques that may be configured in an application-specific manner based on developments dating back 30+ years [19]. The main ITK filter coordinating this framework will be denoted as `itk::AtroposSegmentationImageFilter` or some varient thereof. Additional contributed ITK classes will allow for a variety of options including:

   - *Initialization:* Initialization options will allow for 1) ITK-based K-means initialization, 2) ITK-based Otsu thresholding, 3) labeled prior image, and 4) prior probability images.
   - *Likelihood or observation models:* Bayesian paradigms for image segmentation employ a user selected observation model defining the likelihood term and one or more prior probability terms. The likelihood term has been previously defined both parametrically and non-parametrically. Possible options would include Gaussian modeling and various Parzen windowing schemes. The parent class for such models will be the `itk::ListSampleFunction` with the following child classes:
     - `itk::GaussianListSampleFunction`
     - `itk::HistogramParzenWindowsListSampleFunction`
     - `itk::JointHistogramParzenWindowsListSampleFunction`
     - `itk::JointHistogramParzenShapeAndOrientationListSampleFunction`
     - `itk::LogEuclideanGaussianListSampleFunction`

– `itk::ManifoldParzenWindowsListSampleFunction`
– `itk::PartialVolumeGaussianListSampleFunction`

- *Posterior probability models:* Application-dependent segmentation needs (fully vs. semi-automated) dictate different posterior formulations. The proposed implementation would permit different formulations.

- *Outlier handling:* For improved observation model estimation, data is often *winsorized* to minimize the influence of outliers (parent class: `itk::ListSampleToListSampleFilter`). Possible options for winsorising the sampling would include a robust box-plot strategy `itk::BoxPlotQuantileListSampleFilter` and the Grubbs-Rosner method (`itk::GrubbsRosnerListSampleFilter`).

- *Partial-volume accommodation:* Discretization often leads to confounds such as partial volume effects. The proposed architecture would include partial-volume handling for minimizing such effects (`itk::PartialVolumeGaussianListSampleFunction`).

3. **ITK test code and documentation for the new functionality.** This proposal may appear ambitious given the modest budget. However, our proposal builds upon existing work within ANTs to make these goals achievable. These classes were written in ITK-style format so integrating these classes into the ITK library using the gerrit review system will be straightforward. However, we will need to write individual tests for these classes ensuring proper code coverage and function testing.

4. **SimpleITK integration and generation of tutorial material.** We will implement appropriate wrapping, documentation and metadata for SimpleITK. Beyond these first steps, we will also (most importantly, perhaps) implement step-by-step tutorial material based on the Simple ITK platform.

Benefits

The proposed effort will allow users of ITK, SimpleITK and ITK-based end-user applications access to fundamental and state-of-the-art segmentation algorithms and corresponding components which are currently unavailable in a widely distributed platform such as the Insight Toolkit. Additionally, the accompanying documentation and tutorial materials will be of significant benefit for facilitating the accessibility of this new functionality.

Advantages derived from the use of ITK

We are excited about the opportunity to port these segmentation frameworks into the core of ITK. Our prior experience has shown that the quality and lifespan of such algorithms is greatly improved when they are merged within the ITK ecosystem. ITK also provides one of the best crowdsourcing mechanisms for software debugging and performance-enhancements. The deep testing, consistent use of valgrind to find memory defects and cross-platform CMake-based ctests are all integral to the further improvement of the C++ backbone of these methods.

Differences from related prior work

There is a substantial level-set framework within ITK. There also exists a relatively under utilized statistical framework that allows methods such as K-means clustering followed by Markov random field regularization to be implemented. However, both of these frameworks lack the ability to implement truly Bayesian statistical models that incorporate spatial probability maps and maximize the posterior probability of a segmentation map explicitly.

Personnel and resources

The personnel that will implement this plan has extensive background in general innovative software development with a collective extensive ITK contribution history. The project team comprises the following persons:

- Brian B. Avants (PI, 0.6 c.m. effort) is an Assistant Professor of Radiology at the University of Pennsylvania. He has a Ph.D. in Biongineering and Masters in Computer Science from the University of Pennsylvania with expertise in the development of analysis stems for multidimensional medical datasets that include imaging with a particular emphasis on open-source dissemination. He is the founder and lead developer for the ITK-based Advanced Normalization Tools (ANTs) toolkit which is considered by many to be the premier medical image registration toolkit in the world. He is also the founder and lead developer for the ANTsR project—an R interface to the ANTs package enabling integration of state-of-the-art medical image transformation methods with advanced statistical and visualization methods. Among these qualifications for the proposed project, Dr. Avants is also a found and lead developer of the Insight Toolkit. Despite his personal contributions to code, Dr. Avants has contributed perhaps the most through his leadership of the ITKv4 development team. Specifically, his team implemented a full refactoring of the ITK registration framework. A few contributions of this framework include thread safety, the ability to implement composite transformations, multi-channel registration, extensibility and addition of cutting edge diffeomorphic transformation models as well as image similarity metrics for both intensity and point set features. In addition, an early version of GPU-based registration was implemented with OpenCL.

- James C. Gee (??, 0.24 c.m. effort) is an Associate Professor of Radiologic Science in Radiology at the University of Pennsylvania where he currently serves in several directorships including that of the Penn Image Computing and Science Laboratory (PICSL). Dr. Gee's major area of interest is biomedical image analysis and computing, with active research in all of the quantitative methods represented, including segmentation, registration, morphometry and shape statistics, as applied to a variety of organ systems and all of the major and emerging modalities in biological/biomaterials imaging and in vivo medical imaging. Dr. Gee has an extended history of software development for medical image analysis. Most relevant for this proposal is that Dr. Gee was part of the original ITK development core. More recently he was the PI on the ITKv4 registration refactoring efforts. He has also obtained several A2D2 grants in collaboration with Drs. Avants and Tustison.

- Paul Yushkevich (??, 0.24 c.m. effort) is an Associate Professor of Radiology at the University of Pennsylvania. His Ph.D. is in Computer Science and he has published over 90 papers on computational medical image analysis and led in the development of a broad range of methods including continuous medial representation, joint label fusion for multi-atlas segmentation, learning-based segmentation error correction, structure-specific analysis of human medial temporal lobe, fusion of dense MRI and histology, tract-specific analysis of diffusion MRI, bias-free longitudinal MRI analysis, and others. His unique qualifications for this project arise from his role as the lead developer of ITK-SNAP since 2003. A company that he started as a graduate student was the recipient of one of the first-round ITK-A2D2 contracts. This contract funded the development of ITK-SNAP on the base of the SNAP and IRIS tools developed at UNC Chapel Hill by his mentor Guido Gerig. In the last decade, he has grown the ITK-SNAP codebase manyfold, and obtained NIH R01 and R03 grants to support continued ITK-SNAP development and maintenance. Despite his research, teaching and mentoring responsibilities, he continues to dedicate at least a third of his time to programming, most of it in C++ and utilizing ITK. Besides ITK-SNAP, he has developed and contributed to several other widely used GUI and command line applications, including Convert3D, ANTs, DTI-TK, ASHS, and HistoloZee. He has expertise in XNAT obtained by setting up, maintaining, and developing advanced image segmentation pipelines for the XNAT server at the Penn Center for Functional Neuroimaging, which hosts data from multiple large neuroimaging research projects.

- Nicholas J. Tustison (consultant, ?? effort) is an Assistant Professor of Radiology and Medical Imaging at the University of Virginia. Dr. Tustison has been involved in various aspects of ITK development since he arrived at PICSL in 2004. He was initially charged with fulfillment of the requirements of a 2004-2005 A2D2 grant where he designed and coded a set of classes to handle graph data types and an implementation of the popular "graph cuts" segmentation algorithm [20]. Other widely-used contributions include generic scattered data approximation using B-splines [21], N4 bias correction [22], and an RGB faux-colormapping framework [23].

Budget.

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BUSINESS PORTION

Cost

The cost for this project is $99,995, as specified in the budget. All direct costs will go towards salaries of personnel involved in software development.

Institution

The University of Pennsylvania, located in Philadelphia, has a proud tradition of intellectual rigor and boundary-breaking scientific innovation that dates back to its founder, Benjamin Franklin. Penn is one of the world's most powerful research and teaching institutions, with a research budget last year topping $850 million and more than 4,300 active faculty members. The scale and interdisciplinary character of research and teaching sets Penn apart, and the highly ranked Perelman School of Medicine is one of the top recipients of NIH funding in the country. As a leading institution for research in medical image analysis techniques, Penn provides an ideal environment to host the proposed image processing software development. There is a wealth of medical imaging focused collaboration across laboratories in the Departments of Neurology, Psychology, Radiology and Psychiatry. More specifically, there is a long standing and highly productive collaboration between the Penn Computing & Science Laboratory (PICSL) and the Center for Functional Neuroimaging (CfN). Together, these facilities will provide the necessary resources to execute the proposed work.

The University of Pennsylvania has a wealth of resources and facilities that will contribute to the success of the proposed work. In addition to PICSL and CfN, there are multiple institutes and research centers that are relevant to the proposed work as their reliance upon image processing techniques provides an ideal user-base and source of heterogeneous data to help ensure the generalized utility and robustness of the software:

- The Center for Advanced Magnetic Resonance Imaging & Spectroscopy (CAMRIS)
- The Neuroscience Neuroimaging Center (NNC)
- Center for Cognitive Neuroscience (CCN)
- Institute on Aging (IOA) Center of Clinical Epidemiology & Biostatistics (CCEB)
- Institute for Translational Medicine & Therapeutics (ITMAT)
- The Mahoney Institute of Neurological Sciences

A recent initiative to consolidate research in neuroimaging and brain function on the Penn campus will result in nearly all neuroimaging investigators at Penn being located in newly renovated space in the Richards and Goddard Laboratories Buildings, a designated National Historic Landmark designed by the renowned architect Louis Kahn to facilitate research interactions. Although the Penn campus is already very compact, consolidating the many faculty members involved in neuroimaging research will facilitate broader participation in projects, seminars, workshops, and interdisciplinary training, and will provide an outstanding environment for trainees to interact with faculty and with each other. PICSL will occupy one floor in the D wing of the Richards building.

Performance site

The proposed software development effort will take place at the Penn Image Computing and Science Laboratory (PICSL). Housed in the Department of Radiology, PICSL is a major research resource in biomedical image analysis and computing at the Schools of Medicine and Arts and Sciences of the University of Pennsylvania. PICSL is led by James Gee, Ph.D., and its faculty members are Brian Avants, Ph.D. and Paul Yushkevich, Ph.D., Over the past two decades, the laboratory has collaborated with numerous investigators, including dozens from extramural organizations, and have provided them with comprehensive support in cutting-edge image analysis and processing. PICSL is also part of the graduate groups of the Departments of Computer and Information Science, Applied Mathematics and Computational Science, and Bioengineering. It is affiliated with the Centers for Functional Neuroimaging, for Bioinformatics, for Cognitive Neuroscience and for Human Modeling and Simulation, the Institutes for Medicine and Engineering and for Translational Medicine and Therapeutics, the General Robotics, Automation, Sensing and Perception Laboratory, and the Leonard Davis Institute of Health Economics, and is a founding member of the Center for Health Informatics at Penn, the Penn Center for Musculoskeletal Disorders, and the National Library of Medicine Insight Consortium. PICSL was the inaugural collaboration partner of the National Centers for Biomedical Computing, which are specifically charged to foster translational research in biomedical computing.

PICSL has a long track record of methodological innovation in medical image analysis as well as a strong commitment to translational research. In addition to its founding role and continuing support of the Insight Toolkit (ITK), PICSL leads the development of several significant open-source tools, including ITK-SNAP, ANTs/ANTsR, Convert3D, PipeDream and DTI-TK, and serves as as a key contributor to Camino and VoxBo.

Extensive computer facilities for software development and large-scale data processing are available at PICSL and the CfN data analysis facility, which houses the computing resources for the NIH funded Neuroscience Neuroimaging Center (NNC), whose Informatics Core is managed by Dr. Yushkevich, the PI, and Michael Stauffer is the primary engineer and system administrator for the Core. The facility includes a high performance 576-core compute cluster with more than 200TB of on-line RAID storage with a dedicated tape backup system. The cluster is located in a University-run commercial-grade server room with redundant power supplies, UPS power backup systems, fire suppression system and 24-hour restricted access and security. The cluster provides access to a variety of commercial and customized software packages are available for statistical analysis, scientific computing, code development, and data visualization. Additionally, PICSL is equipped with a large number of dual-processor workstations, all networked via gigabit Ethernet to the computing cluster and the Internet. A standalone server with multiple virtual machines, is dedicated to performing automated nightly software builds for open-source projects. The build system uses the CMake/CTest/CDash architecture with binaries uploaded to SourceForge and NITRC. This automated build architecture will be leveraged by the proposed project.

The NNC Informatics Core operates an XNAT server housed on a modern multi-core computing server with 32 GB of memory and a dedicated 20TB RAID. The XNAT server currently houses 3,000 imaging sessions from multiple projects including large cohorts from

the Penn Memory Center, Penn Epilepsy Center and Penn Frontotemporal Neurodegeneration Center. The XNAT server is configured as the DICOM send destination for the Siemens 3T and 7T research MRI scanners operated by CAMRIS. The XNAT server includes in-house pipelines for data conversion and automatic multi-atlas brain structure segmentation.

Open-source software track record

The University of Pennsylvania and PICSL in particular have an extensive track record of contribution to open-source projects, including numerous previous contributions to ITK.

- PICSL is a major contributor to ITK. Between 1999 and 2015, PICSL members have been PIs on four NLM Visual Human Insight Toolkit contracts. In each case, PICSL all acquisition objectives within the original delivery and cost schedules. All source code developed by PICSL under these contracts was released under appropriate open-source licenses and remains a major part of ITK and related ITK-based applications. These NLM contracts were:
    - The original NLM ITK contract to Dr. Gee, the head of PICSL, in 1999, under which the first-generation ITK image registration and FEM frameworks were developed. The 2002
    - ITK-A2D2 contract to Cognitica, Inc., a small company started by Dr. Yushkevich, under which ITK-SNAP was first created by integrating research software tools SNAP/IRIS developed by Dr. Gerig at the University of North Carolina with ITK.
    - The 2002 ITK-A2D2 contract to Dr. Gee to develop a surface-based analysis and image normalization environment in ITK.
    - The 2003 ITK-A2D2 contract to Dr. Gee to develop graph-based segmentation algorithms in ITK.
    - The 2008 ITK-ARRA contract to Dr. Gee to develop the registration framework in ITKv4. This very large effort completely redesigned the registration pipelines, introduced efficient diffeomorphic registration algorithms, and included GPU accelerated algorithms.
- PICSL has been awarded three NIH Continued Development and Maintenance of Software grant awards for its open-source projects. These awards are:
    - Grant 1R03-EB008200 (PI: Yushkevich) awarded in 2007 to continue the development of ITK-SNAP and integrate it into the NITRC environment.
    - Grant 1R03-EB009321 (PI: Gee) awarded in 2009 to continue the development of DTI-TK, a toolkit for diffusion tensor MRI registration and tract-based analysis.
    - Grant 1R01-EB014346 (PI: Yushkevich) awarded in 2010 to continue the development of ITK-SNAP. Under this grant, ITK-SNAP was almost completely rewritten, ported to the Qt GUI platform, and extended to support visualization and semi-automatic segmentation of multi-modality and multi-component images.

- PICSL members (Gee, Tustison, Avants, Yushkevich) have authored 25 Insight Journal articles, including the top-downloaded Insight Journal article N4ITK: Nick's N3 ITK Implementation For MRI Bias Field Correction.
- PICSL members are involved in the development of multiple large image-related software tools released under open source licenses which, for the most part, follow ITK software architecture and coding guidelines. These are summarized below.

Tool	Lead Developer	Description	License
ITK-SNAP	Yushkevich	GUI tool for 3D image volume visualization, manual and semi-automatic segmentation.	GPL
ANTs	Avants	Diffeomorphic image registration, tissue classification, thickness analysis.	BSD
ANTsR	Avants	Multivariate statistical analysis and data visualization in R.	BSD
DTI-TK	Zhang	Diffusion MRI registration, visualization, tract-based statistical analysis.	GPL
Convert3D	Yushkevich	Multi-purpose command line tool for 2D/3D/4D image processing, format conversion, and analysis.	GPL
ASHS/AHEAD	Yushkevich	Pipelines for automatic segmentation of anatomical structures in MRI scans using multi-atlas joint label fusion.	GPL
HistoloZee	Adler	GUI tool for visualization, alignment and segmentation of dense histology stacks and MRI volumes.	GPL

Commitment to open-source software

Given PICSL's level of involvement in open-source projects closely aligned with ITK, and its track record of releasing and maintaining open-source software, we can confidently commit to making all products of the proposed development open source. Specifically, the following open-source commitments are made:

- To make all ITK and SimpleITK source code described in the Technical Portion of the proposal available as part of the ITK repository, and released under the BSD license.
- To use standard technologies for distribution of source code. This includes the use of Git/Gerrit/GitHub (for ITK components).

- To adhere to ITK coding, software build, and software testing practices for all components developed in this project.
- To ensure that all algorithms and technologies integrated into ITK are not protected by patents that would preclude their inclusion in ITK.

References

1. Wang, H., Suh, J. W., Das, S. R., Pluta, J., Craige, C., and Yushkevich, P. A. "**Multi-Atlas Segmentation with Joint Label Fusion**" *IEEE Trans Pattern Anal Mach Intell* (2012): doi:10.1109/TPAMI.2012.143

2. Wang, H. and Yushkevich, P. A. "**Multi-Atlas Segmentation with Joint Label Fusion and Corrective Learning-an Open Source Implementation**" *Front Neuroinform* 7, (2013): 27. doi:10.3389/fninf.2013.00027

3. Yushkevich, P. A., Wang, H., Pluta, J., Das, S. R., Craige, C., Avants, B. B., Weiner, M. W., and Mueller, S. "**Nearly Automatic Segmentation of Hippocampal Subfields in in Vivo Focal T2-Weighted MRI**" *Neuroimage* 53, no. 4 (2010): 1208–24. doi:10.1016/j.neuroimage.2010.06.040

4. Tustison, N. J., Qing, K., Wang, C., Altes, T. A., and Mugler, J. P., 3rd. "**Atlas-Based Estimation of Lung and Lobar Anatomy in Proton MRI**" *Magn Reson Med* (Accepted):

5. Tustison, N. J., Cook, P. A., Klein, A., Song, G., Das, S. R., Duda, J. T., Kandel, B. M., Strien, N. van, Stone, J. R., Gee, J. C., and Avants, B. B. "**Large-Scale Evaluation of ANTs and FreeSurfer Cortical Thickness Measurements**" *Neuroimage* 99, (2014): 166–79. doi:10.1016/j.neuroimage.2014.05.044

6. Vannier, M. W., Butterfield, R. L., Jordan, D., Murphy, W. A., Levitt, R. G., and Gado, M. "**Multispectral Analysis of Magnetic Resonance Images**" *Radiology* 154, no. 1 (1985): 221–4. doi:10.1148/radiology.154.1.3964938

7. Dempster, A., Laird, N., and Rubin, D. "**Maximum Likelihood Estimation from Incomplete Data Using the EM Algorithms**" *Journal of the Royal Statistical Society* 39, (1977): 1–38.

8. Wells, W. M., Grimson, W. L., Kikinis, R., and Jolesz, F. A. "**Adaptive Segmentation of MRI Data**" *IEEE Trans Med Imaging* 15, no. 4 (1996): 429–42. doi:10.1109/42.511747

9. Cline, H. E., Lorensen, W. E., Kikinis, R., and Jolesz, F. "**Three-Dimensional Segmentation of MR Images of the Head Using Probability and Connectivity**" *J Comput Assist Tomogr* 14, no. 6 (): 1037–45.

10. Kikinis, R., Shenton, M. E., Gerig, G., Martin, J., Anderson, M., Metcalf, D., Guttmann, C. R., McCarley, R. W., Lorensen, W., and Cline, H. "**Routine Quantitative Analysis of Brain and Cerebrospinal Fluid Spaces with MR Imaging**" *J Magn Reson Imaging* 2, no. 6 (): 619–29.

11. Geman, S. and Geman, D. "**Stochastic Relaxation, Gibbs Distributions, and the Bayesian Restoration of Images**" *IEEE Trans Pattern Anal Mach Intell* 6, no. 6 (1984): 721–41.

12. Held, K., Rota Kops, E., Krause, B. J., Wells, W. M., 3rd, Kikinis, R., and Müller-Gärtner, H. W. "**Markov Random Field Segmentation of Brain MR Images**" *IEEE Trans Med Imaging* 16, no. 6 (1997): 878–86. doi:10.1109/42.650883

13. Zhang, Y., Brady, M., and Smith, S. "**Segmentation of Brain MR Images Through a Hidden Markov Random Field Model and the Expectation-Maximization Algorithm**" *IEEE Trans Med Imaging* 20, no. 1 (2001): 45–57. doi:10.1109/42.906424

14. Van Leemput, K., Maes, F., Vandermeulen, D., and Suetens, P. "**Automated Model-Based Tissue Classification of MR Images of the Brain**" *IEEE Trans Med Imaging* 18, no. 10 (1999): 897–908. doi:10.1109/42.811270

15. Ashburner, J. and Friston, K. J. "**Unified Segmentation**" *Neuroimage* 26, no. 3 (2005): 839–51. doi:10.1016/j.neuroimage.2005.02.018

16. Gubern-Mérida, A., Kallenberg, M., Mann, R. M., Martí, R., and Karssemeijer, N. "**Breast Segmentation and Density Estimation in Breast MRI: a Fully Automatic Framework**" *IEEE J Biomed Health Inform* 19, no. 1 (2015): 349–57. doi:10.1109/JBHI.2014.2311163

17. Ribes, S., Didierlaurent, D., Decoster, N., Gonneau, E., Risser, L., Feillel, V., and Caselles, O. "**Automatic Segmentation of Breast MR Images Through a Markov Random Field Statistical Model**" *IEEE Trans Med Imaging* 33, no. 10 (2014): 1986–96. doi:10.1109/TMI.2014.2329019

18. Tustison, N. J., Avants, B. B., Flors, L., Altes, T. A., Lange, E. E. de, Mugler, J. P., 3rd, and Gee, J. C. "**Ventilation-Based Segmentation of the Lungs Using Hyperpolarized (3)He MRI**" *J Magn Reson Imaging* 34, no. 4 (2011): 831–41. doi:10.1002/jmri.22738

19. Avants, B. B., Tustison, N. J., Wu, J., Cook, P. A., and Gee, J. C. "**An Open Source Multivariate Framework for n-Tissue Segmentation with Evaluation on Public Data**" *Neuroinformatics* 9, no. 4 (2011): 381–400. doi:10.1007/s12021-011-9109-y

20. Tustison, N. J. "**Graph Cuts, Caveat Utilitor, and Euler's Bridges of Konigsberg**" *The Insight Journal* (2008): Available at http://hdl.handle.net/1926/1503

21. Tustison, N. J. and Gee, J. C. "**N-d C^k B-Spline Scattered Data Approximation**" *The Insight Journal* (2005): Available at http://hdl.handle.net/1926/140

22. Tustison, N. J. and Gee, J. C. "**N4ITK: Nick's N3 ITK Implementation for MRI Bias Field Correction**" *The Insight Journal* (2009): Available at http://hdl.handle.net/10380/3053

23. Tustison, N. J., Zhang, H., Yushkevich, P., and Gee, J. C. "**Meeting Andy Warhol Somewhere over the Rainbow: RGB Colormapping and ITK**" *The Insight Journal* (2008): Available at http://hdl.handle.net/1926/1452