Research Portfolio

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I. Research Statement

As research support faculty in the Department of Radiology and Medical Imaging at UVa, my primary research focus is the development of high quality and robust software for processing of medical imaging data and corresponding analysis strategies for these data. To put it simply and generally, I am a data scientist who operates at the nexus of "big data", statistical science (including machine learning), and software development for gaining insight into human systems (specifically brain, lung, and heart).

A. Major Contributor to The Insight Toolkit

Addressing the deficiency of image processing tools for analyzing the Visible Human Project in 1999, the National Library of Medicine (NLM) of the National Institutes of Health (NIH) funded the Insight Toolkit (ITK) initiative bringing together such academic institutions as the University of Pennsylvania and the University of North Carolina, along with various industrial partners, such as GE Research. This effort resulted in the Insight Toolkit—a comprehensive, open-source suite of codified algorithms for medical image analysis. Development and expansion continues to the present and is heavily utilized by industry and academia worldwide and, due to its generalizability, has been adopted by the French space agency (CNES) for the processing of remote-sensing imagery.

Open source software contributions. I have provided several key developments to the Insight Toolkit which is one of the primary venues for my software contributions and influence in the field. These contributions are listed in the accompanying CV in Section IX, Subsection C *Open-Source Software Short Communications*. Starting from my first contribution in 2005 (*N-D C^k B-Spline Scattered Data Approximation*), I have continued to provide open-source algorithmic implementations to the Insight Toolkit including my latest contribution made recently on August 27, 2016 (*Two Luis Miguel fans walk into a bar in Nagoya —> (yada, yada, yada) —> an ITK-implementation of a popular patch-based denoising filter*). Other important contributions include operations for image convolution (*Image Kernel Convolution*), faux Colormapping (*Meeting Andy Warhol Somewhere Over the Rainbow: RGB Colormapping and ITK*), and fundamental measures for evaluating segmentation results (*Introducing Dice, Jaccard, and Other Label Overlap Measures To ITK*). These software classes have been downloaded over 67,413 times (average = 2,931 downloads).

N4 for MRI bias correction. Of all these contributions, perhaps my most significant is a method for removing the low frequency inhomogeneity artifacts common to MR images as an important preprocessing step for MR image analysis. This algorithm is commonly referred to in the literature as "N4" or "Nick's nonparametric nonuniform intensity normalization" which is described in the following publication:

Tustison NJ, Avants BB, Cook PA, Egan A, Zheng Y, Yushkevich PA, and Gee JC. N4ITK: Im-

proved N3 Bias Correction, *IEEE Trans Med Imaging*, 29(6):1310–1320, June 2010. Cited 367 times; IF = 3.390; Rank 5 out of 100 computer science, interdisciplinary applications, 12 out of 76 biomedical engineering, 18 out of 249 electrical & electronic engineering, 3 out of 24 imaging science & photographic technology, 21 out of 125 radiology, nuclear medicine & medical imaging.

It is a significant extension of the popular N3 algorithm[1] (introduced in 1998 with currently ~3,000 citations). Prior to the N4 formal publication, it was provided as open-source software to the ITK community:

Tustison NJ, Gee JC: N4ITK: Nick's N3 ITK Implementation for MRI Bias Field Correction, *Insight Journal*, 2009, http://hdl.handle.net/10380/3053.

where it has been downloaded over 10,000 times.

ITKv4 Image Registration Refactoring. Image registration (or the alignment of corresponding features between two images) is a fundamental component in medical image processing and analysis. In 2011 the NIH-NLM sponsored a large-scale funding effort to "modernize" the Insight Toolkit. One of the three major contracts was to provide modern image registration techniques requiring a complete refactoring of the existing image registration framework. This contract was awarded to a joint team consisting of myself and collaborators from the University of Pennsylvania (under the direction of Professor James C. Gee):

Sponsor: NIH-NLM
Title: *Fundamental Refactoring of Deformable Image Registration in ITK with Distributed Computing and GPU Acceleration*
Role: Principle investigator of UVa subcontract
Period: 7/1/2011 – 6/30/2012

This team provided several major image registration upgrades to the algorithmic toolkit where I wrote a significant portion of the actual software code. Not only did we implement current image registration technologies for inclusion but we also developed new and innovative techniques which were also included:

Tustison NJ and Avants BB. Explicit B-spline regularization in diffeomorphic image registration. *Front Neuroinform*, 7:39, 2013. Cited 21 times; IF = 3.261; Rank 8 out of 57 mathematical & computational biology, 105 out of 252 neurosciences.

Avants BB, Tustison NJ, Stauffer M, Song G, Wu B, and Gee JC. The Insight ToolKit Image Registration Framework. *Front Neuroinform*, 8:44, 2014. Cited 29 times; IF = 3.261; Rank 8 out of 57 mathematical & computational biology, 105 out of 252 neurosciences.

[1] Sled JG, Zijdenbos AP, and Evans AC. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans Med Imaging*, 17(1):87-97, Feb 1998.

ITK-Lung: A Software Framework for Lung Image Processing and Analysis. Consistent with our previous work, Professor James C. Gee and I recently submitted an NIH R01 grant for the development of ITK-Lung, a set of open-source software tools for CT, PET, MRI pulmonary image analysis based on the Insight ToolKit. Specifically, we plan to provide core algorithms for specific pulmonary image analysis tasks across multiple modalities, many of which I have included with previous publications. These basic tasks include intra- and inter-modal pulmonary image registration, template building for cross-sectional and longitudinal (i.e., respiratory cycle) analyses, functional and structural lung image segmentation, perfusion analysis, and computation of quantitative image indices as potential imaging biomarkers. These efforts would facilitate other NIH-sponsored projects which interface specific pulmonary algorithms (e.g., CT nodule detection) with clinical and research applications. Over the course of this 5-year project, the following UVa faculty and staff will be engaged:

- Nicholas J. Tustison, DSc, Principal Investigator (50% / year)
- Kun Qing, PhD, Co-investigator (15% / year)
- Y. Michael Shim, MD, Co-investigator (2% / year)
- W. Gerald Teague, MD, Co-investigator (2% / year)

B. Co-Founder and Developer of the Advanced Normalization Tools (ANTs)

In the late 2000s my longtime colleague, Dr. Brian Avants, and I co-founded the Advanced Normalization Tools (ANTs). ANTs is popularly considered a state-of-the-art medical image registration and segmentation toolkit based on ITK. It is used by multiple academic institutions, research facilities (e.g., the Allen Brain Institute, the Montreal Neurological Institute, the Laboratory of Neuroimaging at the University of Southern California), and industry leaders (e.g., IBM Watson, GE Research). In addition to providing well-performing basic processing components, we have also engineered advanced pipelines for obtaining key biomarkers for specific applications. For example, measuring the thickness of the cortical gray matter of the brain from MRI has long been used for assessing various neuropathologies and normal longitudinal changes in the brain. For a long time, the only publicly available resource for performing this type of measurement was a software program called "FreeSurfer" which is developed and made available from Mass General Hospital of Harvard University. Recently, however, I (along with several colleagues) created an ANTs-based pipeline which outperformed FreeSurfer on a large, publicly available data set. This work is described in

> Tustison NJ, Cook PA, Klein A, Song G, Das SR, Duda JT, Kandel BM, van Strien N, Stone JR, Gee JC, and Avants BB. Large-Scale Evaluation of ANTs and FreeSurfer Cortical Thickness Measurements. *NeuroImage*, 99:166-179, Oct 2014. Cited 46 times; IF = 6.357; Rank 1 out of 14 neuroimaging, 24 out of 252 neurosciences, 3 out of 125 radiology, nuclear medicine & medical imaging.

All resulting quantities and corresponding scripts and analyses were made publicly available for other people to use. In fact, these measurements were used recently for investigating other hypotheses:

Hasan KM, Mwangi B, Cao B, Keser Z, Tustison NJ, Kochunov P, Frye RE, Savatic M, and Soares J. Entorhinal cortex thickness across the human lifespan. J of Neuroimaging, 26(3) :278-82, May 2016. Cited 0 times; IF = 1.734; Rank 128 out of 192 clinical neurology, 12 out of 14 neuroimaging, and 65 out of 125 radiology, nuclear medicine & medical imaging.

Competitions. Over the years our ANTs-based tools have won several international competitions:

- finished in the first rank in the Klein 2009 international brain mapping competition,[2]
- finished first overall in the EMPIRE10 international lung mapping competition,[3]
- was the standard registration tool for the MICCAI 2013 segmentation competitions,[4]
- finished first in the BRATS 2013 challenge,[5] and
- won the best paper award at the STACOM 2014 challenge.[6]

We have provided these winning protocols to the public as open-source for continued development.

Tutorials and Other ANTs Informational Fora. I have given several in-person workshops at the request of various research groups so that they can better understand the various algorithms and pipelines of the ANTs toolkit. These include the following:

- ANTs workshop, MD Anderson, Houston, TX, USA. August 2016.
- ANTs Workshop for the Chronic Effects of Neurotrauma Consortium (CENC), Baylor College, Houston, TX, USA. October 2015.
- SimpleITK tutorial, MICCAI, Munich, Germany. October 2015.
- ANTs workshop, Laboratory of Neuroimaging, Marina Del Rey, USA. July 2015.
- CREATE-MIA Summer Workshop, ANTs Workshop, Montreal, Canada. May 2015.
- SPIE Medical Imaging Workshop, Open source tools for medical image analysis, San Diego, USA. February 2012.

In addition to these workshops, I typically answer 3–4 ANTs inquiries per day originating from our Sourceforge or Github ANTs repositories. These inquiries range from instructions for specific programs to providing analysis guidelines for large-scale studies.

ANTsR

C. Provide support for UVa faculty

- Tumor work with Max Wintermark
- Hyperpolarized gas work

[2] Klein et al., Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration. *NeuroImage*, 46(3):786-802, Jul 2009.

[3] Murphy et al., Evaluation of registration methods on thoracic CT: the EMPIRE10 challenge. *IEEE Trans Med Imaging*, 30(11):1901-20, Nov 2011.

[4] http://www.miccai2013.org

[5] http://martinos.org/qtim/miccai2013/

[6] http://www.springer.com/us/book/9783319146775

- Cardiac work with Mike Salerno
- fMRI processing for Jonathon Kipnis and Mark Beernhaker (also mention pending grants)

D. External collaborations

- Work with Jim
- Work with Martha
- Work with Mike