Research Statement

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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).

I. Principal Developer and Contributor of The Insight Toolkit (National Library of Medicine of the National Institutes of Health)

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 implemented 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.

A. Major developer of 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 number of downloads per publication = 2,931).

B. Inventor of the N4 method 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: Improved 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.

C. Co-investigator and principal developer of the 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.

D. Co-investigator and principal developer of *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

[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.

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)

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

In 2006 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.

A. The ANTs cortical thickness pipeline

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. Up until recently 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 have been made publicly available for external use. In fact, these measurements were used recently for investigating other hypotheses concerning the longitudinal development of the entorhinal cortex:

> 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.

B. Participant in international medical image analysis competitions

Over the years our ANTs-based tools have won several international competitions for a wide variety of applications involving several key UVa collaborators:

- 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.

C. Educator via tutorials and other ANTs informational fora

I have given several workshops to disseminate a better hands-on knowledge of the various algorithms and pipelines of the ANTs and ITK toolkits. 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 respond to several ANTs queries per week originating from our Sourceforge or Github ANTs repositories. These inquiries range from instructions for specific programs to providing analysis guidelines for large-scale studies.

Developer for the ANTsR project. ANTs (Advanced Normalization Tools) is designed to provide high performance image processing techniques for medical image analysis. During the evolution of the toolkit, it became clear that robust statistical machinery was lacking for making inferences from data produced from ANTs processing and visualization. As part of a collaborative effort, I am part of the ANTsR development team which provides an interface between ANTs and the R project for statistical computing and visualization thus providing a complete set of tools for multivariate image analysis. ANTsR intends to provide a modern framework for medical analytics, with a focus on imaging-assisted prediction and statistical power. The ANTsR package is publicly available on the github project hosting service

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[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

III. Research Support

As research faculty, I have played a supportive role for the various faculty research efforts. These include the following (with corresponding publications and other items of note):

A. UVa collaborations

- As part of the Hyperpolarized Gas group at UVa, I support efforts for quantitative assessment of functional lung imaging using hyperpolarized gases. Collaborators include Talissa Altes (now at University of Missouri, Columbia), John Mugler, Eduard de Lange, Kun Qing, Jaime Mata, Lucia Flors-Basco, W. Gerald Teague, and Mike Shim.
  - These collaborative efforts have resulted in several publications including the following:

    Flors L, Mugler JP, De Lange EE, Miller GW, Mata JF, Tustison N, Ruset IC, Hersman WW, and Altes TA. Hyperpolarized Gas Magnetic Resonance Lung Imaging in Children and Young Adults, *J Thorac Imag*, 31(5):285-295, Sep 2016. Cited 0 times; IF = 1.723; Rank 71 out of 124 radiology, nuclear medicine, and medical imaging.

    Tustison NJ, Qing K, Wang C, Altes TA, and Mugler III JP. Atlas-based estimation of lung and lobar anatomy in proton MRI. *Magn Reson Med*, 76(1):315-20, Jul 2016. Cited 1 times; IF = 3.571; Rank 20 out of 125 radiology, nuclear medicine & medical imaging

    Altes TA, Mugler JP, III, Ruppert K, Tustison NJ, Gersbach J, Szentpetery S, Meyer CH, de Lange EE, and Teague WG. Clinical Correlates of Lung Ventilation in Asthmatic Children. *J Allergy Clin Immun*, 137(3) :789-796, Mar 2016. Cited 2 times; IF = 11.476; Rank 1 out of 24 allergy, 6 out of 148 immunology.

    Qing K, Altes TA, Tustison NJ, Feng X, Chen X, Mata JF, Miller GW, de Lange EE, Tobias WA, Cates GD, Jr., Brookeman JR, and Mugler JP, III. Rapid Acquisition of Helium-3 and Proton 3D Image Sets of the Human Lung in a Single Breath-hold using Compressed Sensing. *Magn Reson Med*, 74(4):1110-5, October 2015. Cited 3 time; IF = 3.571; Rank 20 out of 125 radiology, nuclear medicine & medical imaging.

    Teague WG, Tustison NJ, and Altes TA. Ventilation Heterogeneity in Asthma. *J Asthma*, 51(7):677-84, Sept 2014. Cited 7 times; IF = 1.854; Rank 18 out of 25 allergy, 39 out of 58 respiratory system.

    Tustison NJ*, Avants BB, Altes TA, de Lange EE, Mugler III JP, and Gee JC. Ventilation-Based Segmentation of the Lungs Using Hyperpolarized 3He MRI, *J Magn Reson Imaging*, 34(4):831–841, October 2011. Cited 26 times; IF = 3.210; Rank 23 out of 125 radiology, nuclear medicine and medical imaging.

    Tustison NJ, Altes TA, Song G, de Lange EE, Mugler III JP, and Gee JC. Feature Analysis of Hyperpolarized Helium-3 Pulmonary MRI: A Study of Asthmatics versus Non-Asthmatics, *Magn Reson Med*, 63(6):1448–1455, June 2010. Cited 31 times; IF = 3.571; Rank 20 out of 125 radiology, nuclear medicine & medical imaging.

  - Past funding sources:

    Sponsor: NIH-NHLBI
    Title: Simultaneous Xe129 MRI of Regional Lung Ventilation and Gas Uptake in COPD

Role: Co-investigator
Period: 7/1/2011 – 5/31/2016

Sponsor: NIH-NHLBI
Title: Single-session bronchial thermoplasty for severe asthmatics guided by Hxe MRI Role: Principal investigator on UVa subcontract
Period: 9/1/2011 – 1/31/2015

Sponsor: NIH-NHLBI
Title: Regulatory Advancement of HXe as an MRI Contrast Agent
Role: Co-investigator
Period: 9/1/2011 – 1/31/2015

Sponsor: Novartis Pharmaceuticals Corp.
Title: Hyperpolarized noble-gas enhanced imaging of b2-agonist pharmacodynamics and pharmacokinetics in mild to moderate asthma
Role: Co-investigator
Period: 10/15/2010 – 5/31/2014

Sponsor: Vertex Pharmaceuticals, Inc.
Title: A Phase II, Single-Blind, Placebo-Controlled Crossover Study to Evaluate the Effect of VX-770 on Hyperpolarized Helium-3 Magnetic Resonance Imaging in Subjects with Cystic Fibrosis, the G551D Mutation and FEV1 ≥40% Predicted
Role: Physicist
Period: 9/9/2010 – 9/8/2012

- In order to support ongoing software development efforts associated with these collaborations and other external collaborations at the University of Pennsylvania (cf Subsection D. External collaborations), my colleague Dr. James C. Gee and I recently (Oct. 2016) submitted an R01 grant titled *ITK-Lung: A Software Framework for Lung Image Processing and Analysis* (cf Section I D).
- Other current and pending grants:

  Title: Hyperpolarized Xenon-129 MRI: a new multi-dimensional biomarker to determine pulmonary physiologic responses to COPD therapeutics
  Role: Co-investigator
  Period: 5 years

  Sponsor: NIH-NHLBI
  Title: Xe129 MRI of the lung: A new technology to assess treatment for COPD
  Role: Co-investigator
  Period: 7/1/2016 – 6/30/2017

- One of my principal collaborators is James Stone with whom I have been developing quantitative methods for traumatic brain injury although much of our work has been of much more general neuorimaging application.
  - These collaborative efforts have resulted in several publications including the following:

    Stone JR, Wilde EA, Taylor BA, Tate DF, Levin H, Bigler ED, Scheibel RS, Newsome MR, Mayer AR, Abildskov T, Black GM, Lennon MJ, York GE, Agarwal R, DeVillasante J, Ritter JL, Walker PB, Ahlers ST, and Tustison NJ. Supervised learning technique for the automated

identification of white matter hyperintensities in traumatic brain injury, *Brain Inj*, In press. Cited 0 times; IF = 1.822; Rank 187 out of 256 neurosciences and 17 out of 65 rehabilitation.

Wilde EA, Bigler ED, Huff TJ, Wang H, Black GM, Christensen Z, Goodrich-Hunsaker N, Petrie JA, Abildskov T, Taylor BA, Stone JR, Tustison NJ, Newsome MR, Levin HS, Chu ZD, York GE, and Tate DF. Quantitative Structural Neuroimaging of Mild Traumatic Brain Injury in the Chronic Effects of Neurotrauma Consortium (CENC): Comparison of Volumetric Data within and across Scanners, *Brain Inj*, In press. Cited 0 times; IF = 1.822; Rank 187 out of 256 neurosciences and 17 out of 65 rehabilitation.

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.

Tustison NJ, Avants BB, Cook PA, Kim J, Whyte J, Gee JC, and Stone JR. Logical Circularity in voxel-based analysis: normalization strategy may induce statistical bias. *Hum Brain Mapp*, 35:745-759, March 2014. Cited 21 times; IF = 5.969; Rank 2 out of 14 neuroimaging, 27 out of 252 neurosciences, 5 out of 125 radiology, nuclear medicine & medical imaging.

- Past funding sources:

  Sponsor: The Geneva Foundation
  Title: Brain Injury Biomarkers and Behavioral Characterization of mTBI in Soldiers Following Repeated, Low-Level Blast Exposure
  Role: Co-investigator
  Period: 1/1/2013 – 5/31/2015

  Sponsor: Naval Medical Research Center
  Title: Experienced Breacher Study
  Role: Co-investigator – UVa subcontract
  Period: 6/1/2012 – 5/30/2014

- Current and pending funding sources:

  Sponsor: NASA/Medical University of South Carolina
  Title: Human Cerebral Vascular Autoregulation and Venous Outflow In Response to Microgravity-Induced Cephalad Fluid Redistribution
  Role: Co-investigator
  Period: 5/16/2013 – 5/15/2018

  Member Chronic Effects of Neurotrauma Consortium
  Funding period: 2/2016 - 8/2018

- Other successful collaborations with UVa faculty include:
  - Automatic segmentation of brain tumor from multi-modal MRI with collaborators Max Wintermark (now at Stanford) and former radiology fellow Christopher Durst. Our team won the international 2013 Multimodal Brain Tumor Segmentation Challenge (BRATS) which resulted in the following publications:

Tustison NJ, Shrinhidi KL, Wintermark M, Durst CR, Kandel BM, Gee JC, Grossman MC, and Avants BB. Optimal symmetric multimodal templates and concatenated random forests for supervised brain tumor segmentation (simplified) with ANTsR. Neuroinformatics, 13(2):209-225, April 2015. Cited 17 times; IF =2.825; Rank 13 out of 102 computer science, interdisciplinary applications, 124 out of 252 neurosciences.

Menze BH, Jakab A, Bauer S, Kalpathy-Cramer J, Farahani K, Kirby J, Burren Y, Porz N, Slotboom J, Wiest R, Lanczi L, Gerstner E, Weber M-A, Arbel T, Avants BB, Ayache N, Buendia P, Collins DL, Cordier N, Corso JJ, Criminisi A, Das T, Delingete H, Demiralp C, Durst CR, Dojat M, Doyle S, Festa J, Forbes F, Geremia E, Glocker B, Golland P, Guo X, Hamamci A, Iftekharuddin KM, Jena R, John NM, Konukoglu E, Lashkari D, Mariz JA, Meier R, Pereira S, Precup D, Price SJ, Riklin-Raviv T, Reza SMS, Ryan M, Schwartz L, Shin H-C, Shotton J, Silva CA, Sousa N, Subbanna NK, Szekely G, Taylor TJ, Thomas OM, Tustison NJ, Unal G, Vasseur F, Wintermark M, Ye DH, Zhao L, Zhao B, Zikic D, Prastawa M, Reyes M, and Leemput KV. The Multimodal Brain Tumor Image Segmentation Benchmark (BRATS). IEEE Trans Med Imaging, 34(10):1993-2024, October 2015. Cited 131 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.

- ANTs image registration techniques are currently used as part of Mike Salerno's (Cardiac, Radiology & Medical Imaging, and Biomedical Engineering Departments) ongoing development of novel cardiac MRI acquisition techniques. As part of this collaborative work, Mike and I won the best paper award at the Statistical Atlases and Computational Modelling of the Heart (STACOM) motion estimation challenge held in Boston, 2014 as part of the international Medical Image Computing and Computer-Assisted Intervention (MICCAI) conference.
- Recently, Tony Filiano and Jonathon Kipnis of the Neuroscience Department of UVa published a breakthrough paper in Nature concerning the relationship between immunity and social deficits. I was instrumental in that publication in performing the resting state fMRI analysis using some of the software I developed within the ANTsR package:

  Filiano AJ, Xu Y, Tustison NJ, Marsh RL, Baker W, Smirnov I, Overall CC, Gadani SP, Turner SD, Weng Z, Peerzade SN, Chen H, Lee KS, Scott MM, Beenhakker MP, Litvak V, and Kipnis J*. Unexpected role of interferon-γ in regulating neuronal connectivity and social behaviour, Nature, 535(7612):425-9, Jul 2016. Cited 3 times; IF = 38.138; Rank 1 out of 63 multidisciplinary sciences.
- Other current research collaborators include Spencer Payne and Larry Borish (Medicine), Carlos Leiva Salinas (Radiology and Medical Imaging), and Stuart Berr (Radiology & Medical Imaging and Biomedical Engineering).

B. External collaborations

- Jim Gee is an Associate Professor in the Department of Radiology at the University of Pennsylvania and the Director of the Penn Image Computing and Science Laboratory. He was also my post-doc mentor from 2004 – 2010. We continue to work together on multiple projects including the ITK Lung grant previously described. Short-term future plans include a planned ANTs software maintenance R01 grant to be submitted in the February 2017 cycle.

- Mike Yassa is an Associate Professor in the Department of Neurobiology and Behavior and the Director of the Center for the Neurobiology of Learning & Member. He runs the Yassa Translational Neurobiology Lab where I currently have a joint appointment with UC Irvine as a Visiting Assistant Researcher. As a long-time user and promoter of the ANTs software, Mike and I have several shared projects related to Alzheimer's disease and other neurobiological research questions.