Research Statement

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As an interdisciplinary scientist with a comprehensive background in the field of biomedical imaging analytics, my research endeavors resonate with both the academic community at the University of Virginia and the wider scientific community. My primary focus lies in advancing our understanding of human systems through non-invasive approaches, employing cutting-edge quantitative imaging techniques. Specifically, my research centers on the development of robust computational tools tailored for extracting meaningful insights from complex imaging data. I also harness statistical methodologies to uncover intricate relationships between these imaging data and other pertinent biomarkers. One distinctive aspect of my research is its commitment to open science principles; in collaboration with fellow researchers, I ensure that all the tools and resources we develop are openly accessible as open-source contributions, thereby enhancing the transparency and reproducibility of our work. Specific contributions are outlined below.

Open-source software development for medical image analysis

The Insight Segmentation and Registration Toolkit

The Insight Segmentation and Registration Toolkit (ITK) is an open-source software library developed primarily by the National Library of Medicine (NLM) at the National Institutes of Health (NIH). Researchers and medical professionals use ITK as a quantitative tool in their work involving medical image analysis, computer-aided diagnosis, and other applications in the field of medical imaging. I currently play a significant role in ITK development and maintenance (and have been for almost two decades where I have been one of the most prolific contributors to the toolkit). This includes refactoring and ongoing maintenance of the image registration framework. My image registration expertise has led to numerous joint research efforts and requests for collaboration. Over the past year alone, this has resulted in multiple external collaborations, e.g., determination of the effects of treatment in brain structures in multiple sclerosis [1], the development of standard image templates to facilitate dementia research in Down syndrome [2], construction of templates from human hand MRI [3], and ongoing work with Yongsoo Kim and Fae Kronman (PSU) involving spatial mapping of mice data. Also see the external funded grant “Methods for integrative analysis of modern data sources to advance understanding of Alzheimer’s Disease” (Kristin Linn, Univ. of Pennsylvania) and external pending grant “Development of Advanced Software Tools for Processing Multimodal Medical Images of Healthy and Diseased Adult Human Hands” (Jay Hegde, University of Augusta) as well as previous and current mentoring opportunities—cf. dissertation committee member for Sebastian Giudice (UVa), Jesse Birchfield (UCLA), and Daniel Brennan (CUNY).

Additionally, I facilitate the integration of my open-source contributions to other packages. For example, I developed an algorithm for removing the low frequency inhomogeneity artifacts common to MR images—commonly referred to in the literature as “N4” or ”Nick’s nonparametric nonuniform intensity normalization (the corresponding journal article continues to be one of the most highly cited publications in the field with currently close to 5000 total citations with an increasing citation rate year-over-year and is also ranked in the top 10, in terms of total number of citations, for articles in IEEE Transactions on Medical Imaging, one of top-tier journals in the field). Such major analytic packages (with sponsoring institution) includes: ANTsX (UPenn/UVa), SimpleITK (National Institutes of Health), Slicer (Harvard), FreeSurfer (Harvard), Nipype (MIT), fMRIPrep (Stanford University), Neuroconductor (Johns Hopkins University), MRtrix3 (The Florey Institute of Neuroscience and Mental Health), QSIPrep (University of Pennsylvania), and volBrain (Universidad Politécnica de Valencia/University of Bordeaux). This particular method has also led to a recent collaborative research projects (e.g, [4]).

The ANTsX Ecosystem

I am one of the co-founders and principal developers of the Advanced Normalization Tools Ecosystem (ANTsX). Since its inception in 2006 with co-founder Brian Avants, ANTsX has empowered imaging scientists and engineers, both in academia and industry, to address contemporary challenges in quantitative biomedical imaging. During my tenure as associate professor, the ANTsX team leveraged development for successful application of two explicitly ANTs-based NIH R01 grants:

> Title: ITK-Lung: A Software Framework for Lung Image Processing and Analysis
> Sponsor: NIH/Univ. of Penn
> Role: Site-PI
> Dating: 6/1/2017-5/31/2021
>
> Title: Advanced Normalization Tools
> Sponsor: NIH/Univ. of Penn
> Role: Site-PI
> Dating: 9/30/2022-6/30/2027

In addition to core algorithmic/methodological innovation, I do significant development for expanding the ANTs framework to other platforms for the purposes of maximizing utility for a diverse research community. This includes the development and maintenance of ANTsR (ANTs in the R Statistical Project) and ANTsPy (ANTs in Python). Additionally, these ANTs-based platforms have facilitated the current research direction of developing and integrating deep learning techniques for biomedical image analysis. Specifically, these have led to the creation of the ANTsRNet and ANTsPyNet libraries for the R and Python platforms which have allowed expansion even further into providing state-of-the-art, high quality measurement tools for scientists.

Collectively, the ANTs software ecosystem is referred to as ANTsX and is publicly available on GitHub (https://github.com/ANTsX/ANTs) where we address bugs, provide documentation, and otherwise engage with members of the community that use our tools. Related, I participate in tutorials and workshops to provide a hands-on experience for ANTsX users (cf. the Invited Lectures and Symposium of CV). Further discussion of the ANTsX ecosystem detailing functionality and additional evaluation is provided in a recent paper [5] (attached as part of the portfolio).

A sampling of specific workflows that are freely available as part of the ANTsX toolkit include:

- *Cortical thickness*. First reported for cross-sectional data in [6] (with over 600 citations), this framework was extended to longitudinal data in [7] (attached as part of the portfolio). To further enhance accuracy and performance, these pipelines were redesigned using deep learning techniques [5].
- *DeepFLASH*. Collaborator Michael Yassa (Professor at the University of California, Irvine) runs a lab that is broadly interested in learning and memory and we collaborate on quantitative measurements involving the hippocampus [8]. We recently developed a network, *DeepFLASH*, for parcellation of the medial temporal lobe, including the hippocampus and its subfields and extra-hippocampal regions. Current efforts include large-scale processing and evaluation (UK Biobank, ~50,000 subjects [9]) and Parkinson's imaging research (with longtime collaborator, Brian Avants).
- *Cerebellum morphology*. Recent work in Parkinson's disease research with Brian Avants resulted in a cerebellum morphological quantitative pipeline for generating associated image-derived phenotypes (IDPs). Given the unique capabilities of ANTsX, these cerebelluar IDPs comprise both regional

volumes and cortical thickness based on the Schmahmann atlas for cerebellar sub-segmentation. This is ongoing work also involving the UK Biobank [9].

Traumatic brain injury

With UVa collaborators James Stone and Brian Avants, we are engaged in ongoing research investigating chronic neurological changes in individuals repeatedly exposed to low-intensity blasts, most notably in military personnel. We have been particularly engaged in the development of statistical techniques for transforming the large quantities of information associated with image data to interpretable, low-dimensional spaces. Recently, our joint efforts have resulted in a powerful technique called similarity-driven multi-view linear reconstruction (SiMLR) [10]. Recent findings have leveraged SiMLR to characterize the relationship between repetitive low-level blast exposure and behavioral and imaging differences in humans [11]. Related funding includes the following:

Title: Interpretable, subject specific-mapping of neurological health in the performance setting
Sponsor: DOD/ONR
Role: Co-I
Dating: 4/1/2023-3/31/2025

Title: Elucidating the role of increased neuroinflammation and related structural and functional neurological sequelae after exposure to repetitive blast
Sponsor: CDMRP
Role: Co-I
Dating: 9/30/2022-9/29/2026

Our expertise in imaging analytics in the context of traumatic brain injury is well-known which has led to external collaborations (e.g., [12]) and funding opportunities:

Title: Personalized Profiles of Pathology in Pediatric Traumatic Brain Injury
Sponsor: NIH/Univ. of Utah
Role: Co-I
Dating: 1/1/2022-9/30/2026

Title: Advanced Neuroimaging Analyses for LIMBIC-CENC
Sponsor: Veterans Health Admin/Univ. of Utah
Role: Co-I
Dating: 3/22/2023-3/21/2024

Functional lung imaging via hyperpolarized gas

Although most of my application research involves neuroimaging, I have a longer history with the functional lung imaging research group at UVa. Current UVa collaborators include Jaime Mata, John Mugler, and Y. Michael Shim. My role is the development of quantitative techniques for these innovative image techniques and have been working on this for over a decade [13]–[15] and are applied by in our clinical studies (recent studies within the past 2 years include [16]–[20]).

More recently, I have leveraged deep learning techniques for an updated approach to quantification [21], [22]. These approaches have been made publicly available through the ANTsX ecosystem and this work

has led to more wide-scale adoption of these techniques (http://www.xenonanalysis.com). Several ongoing and pending grants include:

Title: Sexual dimorphism in susceptibility to emphysematous tissue injury
Sponsor: NIH
Role: Co-I
Dating: 7/1/2023-6/30/2027

Title: Pilot Study to Determine Health Effects of e-cigarette in Healthy Young Adults
Sponsor: NIH
Role: Co-I
Dating: 8/20/2020-1/30/2024

Title: Developing Hyperpolarized Gas MRI signatures to detect and manage acute cellular rejection
Sponsor: NIH
Role: Co-I
Dating: 4/1/2024-3/1/2029

Title: Multi-omic Characterization of COPD in Females
Sponsor: NIH
Role: Co-I/Penn State Univ.
Dating: 4/1/2024-3/31/2028

Scholarship

Service

- BRATS registration competition

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