Over the course of my undergraduate career, I have become fascinated with developing quantitative descriptions for traditionally qualitative observations. In particular, I have been developing methods to draw cortical surfaces and measure axonal fiber orientations in histological tissue samples of the brain. Capturing the human expertise needed to identify these histological features in terms of quantitative descriptions allows hard-earned neuroanatomical domain knowledge to communicate with emerging neuroimaging methods such as diffusion MRI and diffusion tractography to evaluate whether these new technologies can capture anatomical features safely *in vivo*.

The importance of translating qualitative expertise into quantitative measurement has motivated me to pursue graduate study at the intersection of neuroscience and computational science. I envision graduate school will prepare me for a career that allows me to expand scientific understanding by providing an environment where I can access both medical resources – such as brain cutting conferences – and computational resources – such as supercomputing clusters – to develop my training in the identification of features of fiber architecture of the brain as validated by traditional neuroanatomical studies.

I believe my training in translating anatomical expertise to quantitative neuroimaging broadly benefits society through the development of powerful, high-throughput, automated computational tools for quantifying tissue anatomy, which will increase the competitiveness of the United States in the burgeoning field of digital microscopy through increased automation of histological slide analysis, where the current state-of-the-art practices remain manual inspection by histopathology subspecialists.

My future professional goals after graduate school are to pursue a position as an academic researcher, but to do so at the intersection of neuroscience and computational science I will need to increase awareness of how these seemingly disparate fields are complimentary in many problem spaces. My previous work was limited by the lack of established relationships between researchers in the computational sciences and mathematics and researchers in histology and neuroimaging. Receiving a NSF fellowship will give me the flexibility to communicate across departments and develop working relationships among researchers from different fields.

Intellectual Merit. I first became interested in scientific research the summer after my freshman year when I began working with Professor David Van Essen and then graduate student Matt Glasser on a project to better understand fiber trajectories in the brain. For the Human Connectome Project (HCP), fiber trajectories were estimated by diffusion MRI and diffusion tractography, but while these tools have had early success in mapping the long-distance connections of the brain, technical limitations of these methods have become increasingly apparent.

In particular, brain maps built from diffusion MRI tractography have a tendency to terminate fiber trajectories on gyral crowns (ridges on the cortical surface of the brain) versus sulci (grooves surrounding the ridges) at a rate higher than expected from cortical folding-related biases. In addition, small angle fiber orientations are mostly restricted to gyral crowns, indicating that fibers run perpendicular to the surface of the brain, and hence terminate, mostly in these regions. These features were summarized as a gyral bias.

As the gyral bias from diffusion MRI seemed unusual enough to warrant further investigation, I collaborated with Professor Krikor Dikranian to immunostain brain histology in a neuroanatomical study to reveal fiber trajectories in higher resolution than can be seen in diffusion MRI. Here I first encountered the problem of how to translate qualitative observations from histology to evaluate quantitative results from diffusion MRI. I stumbled upon a solution while working at a student newspaper: I realized I could digitize histology as digital microscopy imag-

es, then use the graphics editor available on the photographers' computers to make measurements of fiber orientations.

I found that fiber trajectories take sharp angles when terminating along sulci, and that these sharp angles were not well-represented in diffusion MRI, which contributes to the gyral bias, as few fiber orientations exist to terminate trajectories in the sulci than gyri. This work was awarded a *summa cum laude* merit award (given to the top 5% of trainee abstracts) at the ISMRM 2013 conference [1] and was also published in the 2nd edition of *Diffusion MRI* [2].

These results sparked interest in extending my analysis across the whole brain and I was awarded a Summer Undergraduate Research Fellowship (SURF) to continue my the summer after my sophomore year. I realized that if I were to continue making measurements of fiber orientations and the cortical surface by eye, I could never cover the whole brain, so I developed ways to help automate my analysis by writing spline-drawing algorithms to draw the cortical surface, and on suggestion from then research fellow Stam Sotiopoulos at Oxford Centre for Functional MRI of the Brain (FMRIB), writing structure tensor algorithms to measure fiber orientations with eigenvectors. I presented this work at the Midstates Consortium for Math and Science [3]. Designing a computer algorithm to perform a task that previously required human expertise captured my imagination and led me to take more courses in mathematics to better other possible methods of describing complex visual features quantitatively.

One limitation common to all of my previous works was that the histology samples I was using could only be scanned to make two-dimensional images, which limits the comparisons with the inherently three-dimensional diffusion MRI. The need for three-dimensional histology lead to a collaboration with then graduate student Katherine Holzem and Professor Igor Efimov and we developed a passive clearing variation on the CLARITY protocol to optically clear histology volumes. I then worked with research specialist Dennis Oakley at the Bakewell Neuroimaging Lab to acquire three-dimensional images from two-photon confocal microscopy. With help from programmer Tim Coalson, I co-registered the 3D images from microscopy and diffusion MRI for comparison, which was visualized in Connectome Workbench. This work was submitted as part of my Senior Honors Thesis [4].

Now with histology data from several experiments, I visited Stam Sotiropoulos at FMRIB on a project to evaluate the performance of a histology-informed generative model of fiber trajectories on our histology and HCP data. This model was presented at ISMRM 2016 [5], and a follow-up paper describing the gyral coordinate system used to describe fiber orientations by their surrounding cortical surface instead of traditional laboratory coordinates has been submitted [6]. From these experiences, I learned the value of accurately describing features with mathematical and statistical methods so clear observations from a qualitative field such as classical histology could inform quantitative models such as in diffusion MRI. I also began to appreciate how machine learning could help in more complicated descriptions, such as using my previous spline-drawing function to train a classifier to recognize the anatomy of cortical surfaces.

As I explored ideas in machine learning, I enrolled in a course on neural computation, where I analyzed the activity of biological neurons with machine learning and statistics, and the performance of artificial neural networks in classification problems. Fascinated by the learning dynamics in biological and artificial neurons, I pursued these ideas further with Assistant Professor Ilya Monosov by recording neurons and behavior in learning during risky decision-making, and the discovery of a spatial gradient-like relationship of neurons and their dynamics, published in *The Journal of Neuroscience* [7] inspired me to create three-dimensional maps of neuronal location and corresponding methods for spatial statistics, which are now a part of the brain map-

ping tools used in the Monosov Lab. Later, I discovered how newly observed signals in the basal forebrain track predictions of reward timing during risky decision-making, which was presented at SfN [8].

Although how neuronal dynamics and behavior map onto brain structures is an incredibly compelling field of research, I felt machine learning and computational methods were best applied to neuroimaging efforts, where the dimensionality of the problems involved give more opportunity for feature discovery. I am currently working with Professor Tammie Benzinger to investigate whether diffusion MRI can also provide accurate measures of cellularity (in addition to the aforementioned measures of fiber orientation) as compared with quantified histology.

Broader Impacts. I am a founding member of Project East St. Louis, the first community service organization at Washington University in St. Louis that works with communities in East St. Louis. The need for such an organization emerged when I noticed among the highly visible community service organizations that claim to serve the Greater St. Louis Metro Area, no organization had a significant presence in Metro East, and thus East St. Louis, a city nationally recognized for its urban blight. Advised by Professor Jack Kirkland, my classmates and I developed a two-pronged approach to addressing these issues: (1) create College Access Mentors, a college mentoring program to work with students in East St. Louis Senior High School who may be interested in further education but lack the resources to pursue the application process or succeed on the ACT exams; and (2) increase awareness of the urban blight in East St. Louis, and how the region is marginalized even within the community of volunteer organizations at Washington University in St. Louis. Project East St. Louis has grown its presence in East St. Louis through the addition of volunteer opportunities at East Side Health District Clinic; at Washington University through an archive of interviews with residents of East St. Louis housed in Olin Library; and between East St. Louis and Washington University through the yearly campus trip, where students in College Access Mentors visit Washington University campus to learn what college might have to offer in terms of their future career goals.

I also work with Einstein Explorers, a student organization that collaborates with Children's Hospitals throughout St. Louis County and allows hospitalized children, oftentimes in intensive care, to perform their own science experiments with common household items. Especially for those in intensive care, this program might be one of few opportunities for children in a hospital setting to interact with someone other than family and staff and actively engage in the steps of experimental design instead of passively watching television.

Finally, my work with diffusion MRI and histology comparisons has generated a slide atlas of high-resolution histology sections that are shared online as educational materials for anatomy courses.

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Motivation. Until recently, systems neuroscience has relied solely on the efforts of researchers to characterize the properties of brain circuitry region by region in hopes of eventually elucidating the properties of the brain as a whole. With the latest diffusion MRI and diffusion tractography algorithms, structural properties of neural fiber pathways spanning the whole brain can now be recovered. Less attention, however, has been dedicated to evaluating these diffusion fiber estimates with fiber architecture observations in microscopy images of tissue samples, which are the gold standard for visualizing neuroanatomical ground truth. Evaluating diffusion imaging with microscopy presents a number of technical challenges: diffusion imaging quantifies three-dimensional fiber orientation estimates across the whole brain, while microscopy itself does not quantify fiber orientations, and is restricted to the two-dimensional plane of the tissue sample. Addressing the inability of histology imaging to provide quantitative results requires developing methods of quantitative measurement comparable to those commonly used in diffusion data. In addition, such methods must reach a comparable level of automation in order to generate quantitative histology measurements for the whole brain. Two methods needed to generate such histology data are: (1) **automated cortical surface reconstruction** [1]; and (2) **automated fiber orientation measurement** [2]. Here I propose approaches to develop both methods.

Aim 1. Develop an automated approach for cortical surface reconstruction. Most assessments of the location of the cortical surface are performed by the trained-eye of a neuroanatomist. However, this approach is neither quantitative nor scalable to large datasets. My previous work focused on developing manual [3] and semi-automated [4] approaches to reconstruct local surfaces through b-splines curves that approximate the convoluted cortical surface, but neither approach can efficiently reconstruct the hundreds of local surfaces needed to span the whole brain. Even preliminary supervised machine learners that learn how to draw these b-spline curves [5] are limited by the small volume of labeled data that can be generated by my previous approaches [3, 4].

In this aim, I will instead explore multi-resolution approaches such as Laplacian image pyramids to generate histology images that are not as feature-rich, allowing rudimentary edge detection algorithms to more accurately define the cortical surface. Additionally, I will implement sparsity-based approaches to multi-resolution analysis, which may prove superior to traditional down-sampling approaches that can induce errors into surface mapping [6].

Aim 2. Develop an automated approach for fiber orientation measurement. While my previous work attempted to image three-dimensional histology tissue volumes, the process I used was not able to span the whole brain [7]. In order to solve the problem of image acquisition, I will instead develop an approach using a light-sheet fluorescence microscopy, which acquires images 100 times faster than two-photon confocal microscopy (which was used in my previous studies). Another problem I encountered during my previous studies was a limitation in the number of fiber orientations I could detect. Second-order structure tensor analysis can only capture one orientation; however, in reality fibers can cross in three dimensions. In order to solve the limitation in fiber orientation detection, I will instead explore approaches through higher-order structure tensors [8] as applied to three-dimensional microscopy data.

Institutional resources. Resources at Washington University in St. Louis will be invaluable for progress on this project. The new Center for Cellular Imaging (WUCCI) is a Nikon Center of Excellence and is in the process of acquiring high-end microscopes, including a light-sheet fluorescence microscope. High quality diffusion MRI data is already available from the Human Connectome Project (HCP).

Evaluation. Previous studies using diffusion imaging have found a cortical gyral bias [9], or stronger fiber connections to cortical gyri (ridges on the surface of the brain) than sulci (grooves surrounding the ridges). This feature is interpreted as a product of a specific cortical folding mechanism during brain development across primates and other mammals. My previous work has not found evidence of the gyral bias being an anatomical feature of the brain, but rather a methodological artifact from diffusion imaging. One method to evaluate progress within the alloted time of graduate study (as the above two aims could be improved upon indefinitely) is to use measurements derived from histology to inform generative models of fiber trajectories in diffusion data. Progress is then evaluated on the reduction of gyral bias, which can be quantified, rather than the ability of the above methods to define cortical surfaces and multiple fiber orientations, both of which are subject to subjective measures of quality.

Broader impacts. Both histology imaging (high-throughput microscopy, digital microscopy, and projects like the BigBrain atlas) and MR imaging (the HCP) are facing an explosion of data acquisition. However, histology is lagging behind in quantitative analysis with no widely used methods or standards. My current project proposal focuses on making up this differential when compared to diffusion data, with implications for understanding brain development across primates and other mammalian species. However, the broader impacts extend further, where methodology advancements in my current project can be a "Version 1.0" for processing high-dimensional three-dimensional histology data in scientific research. In addition, this work has the potential to produce high-quality digital microscopy images for educational purposes: already, my previous high-resolution histology images are shared online as educational materials for anatomy courses.

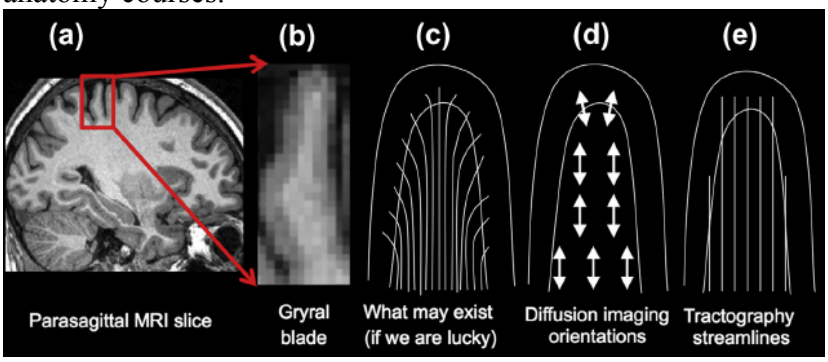

Figure 1. Assumptions of tractography that contribute to gyral bias.

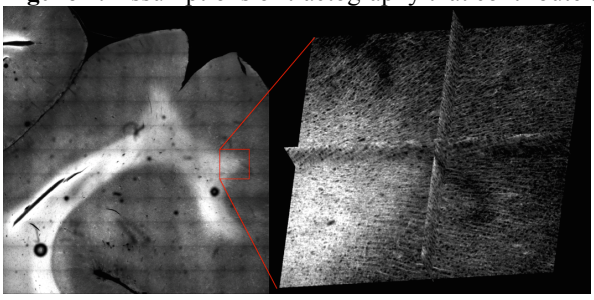

Figure 2. Microscopy image acquisition from histology. Left, an overview image of a gyral blade. Right, a detailed three-dimensional image volume of a gyral crown, where fiber orientations fan out in multiple directions (approximating Subfigure C in Figure 1 closer than Subfigure E).

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