A Framework for Diffusion Fiber-based Analysis of T1w/T2w Ratio Maps

by

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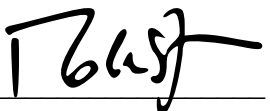
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ABSTRACT

Purpose: To develop, test, evaluate and apply a novel tool for the diffusion fiber-based analysis of T1w/T2w ratio maps quantifying myelin content. **Background**: The cerebral white matter in the human brain develops from a mostly non-myelinated state to a nearly fully mature white matter myelination within the first few years of life. The study of myelination is of interests in a number of brain development studies. High resolution T1w/T2w ratio maps are believed to be effective in quantitatively estimating myelin content on a voxel-wise basis. I propose the use of a fiber-tract-based analysis of such T1w/T2w ratio data, as it allows us to separate fiber bundles that regional analysis imprecisely groups together, and to associate effects to specific tracts rather than large, broad regions. **Methods**: I developed an intuitive tool to facilitate such fiber-based studies of T1w/T2w ratio maps. Via its Graphical User Interface (GUI) the tool is accessible to non-technical users. The framework uses calibrated T1w/T2w ratio maps and a prior fiber atlas as an input to generate profiles of T1w/T2w values using a version of the UNC atlas-based fiber analysis toolkit that I adapted to handle non-diffusion data. The resulting fiber profiles are used in a statistical analysis that performs along-tract functional statistical analysis. We applied this approach to a study of early brain development in neonates. **Results**: I implemented a publicly available tool for the fiber based analysis of T1w/T2w ratio maps and tested it in a study of brain development.

1. INTRODUCTION

The human brain develops from a mostly non-myelinated state to a nearly fully mature white matter myelination within the first few years of life. Quantification of the myelination process in the white matter brain is the goal of a number of brain development studies, especially also of interest with application to neurodevelopmental disabilities (1). The myelination process has been widely analyzed using Diffusion Tensor Imaging (DTI), mainly through the use of DTI property maps Fractional Anisotropy and Radial Diffusivity. However, the measures are also sensitive to several brain maturation or pathological processes, such as fiber organization/wiring, axonal size and fiber density. Thus, more specific measures need to be taken to obtain information specific to myelin maturation via component analysis of T1 and T2 relaxation (2). The ratio of T1w to T2w signal intensity has been employed to show variations in myelin between cortical grey matter in (3) and thus can be used to perform myelin-based analysis of the brain. I believe that the pattern of myelin variation is also of interest in white matter. The directly computed T1w/T2w ratio map can effectively remove the same receive field bias that is consistent between T1w and T2w images. However, the computation does not effectively remove all biases, such as transmit field biases, or receive field biases originating from using T1w and T2w images acquired in different sessions. In order to apply it in quantitative analysis, an additional intensity calibration process is needed to correct raw T1w/T2w ratio image biases in intensity and contrast (see Figure 1).

Several analysis frameworks exist for the study of MRI data. In particular, I will discuss here region of interest (ROI) analysis and quantitative tractography. Region-based analysis uses regional segmentation from structural MRIs of the same subject. The processing of ROIs is relatively simple and robust against imperfect registration. However, ROI-analysis results in non-specific findings as ROIs can contain multiple fiber tracts and multiple fiber situations (single, fanning, crossing fiber situations). Moreover, since ROI methods usually perform segmentation based on lobar regions, each region may not include the full range of a fiber bundle. ROI-analysis thus leads to a limited localization of findings. As shown in figure 2, quantitative tractography performs anatomically informed segmentation on volumetric data to acquire curvilinear regions that are fiber-specific, as discussed in (2). Since myelination is a process that happens along fiber bundles across the brain, a fiber-tract-based analysis via T1w/T2w ratio maps that effectively separates fiber bundles to associate effects with fiber tracts rather than large, broad region is more suited for our goal.
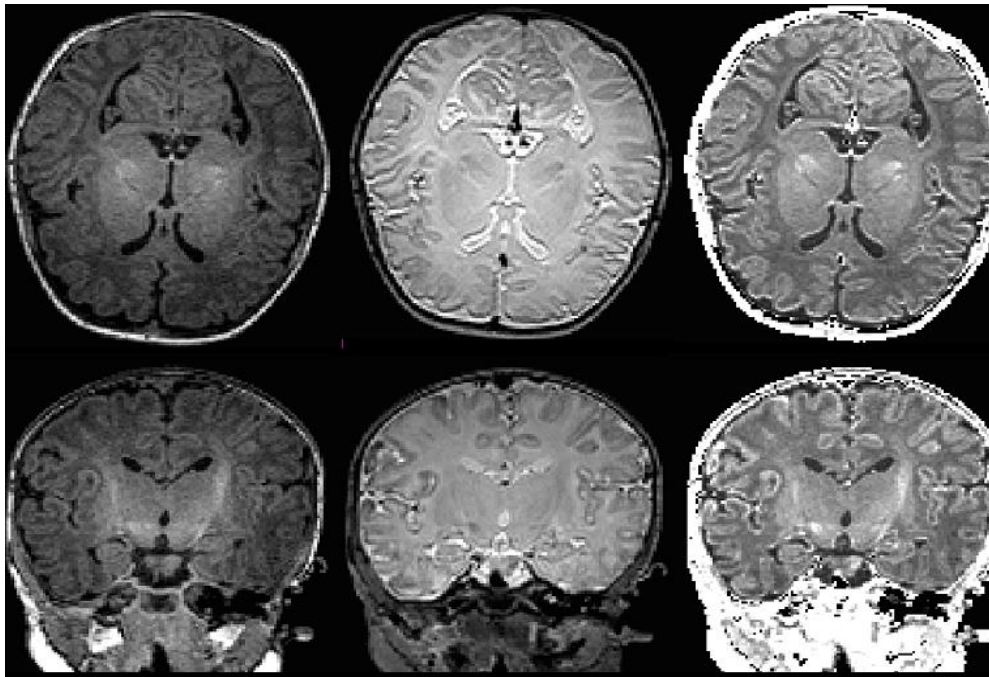

Figure 1:   Raw T1w, T2w images (Left, Middle), calibrated T1w/T2w ratio image (Right).
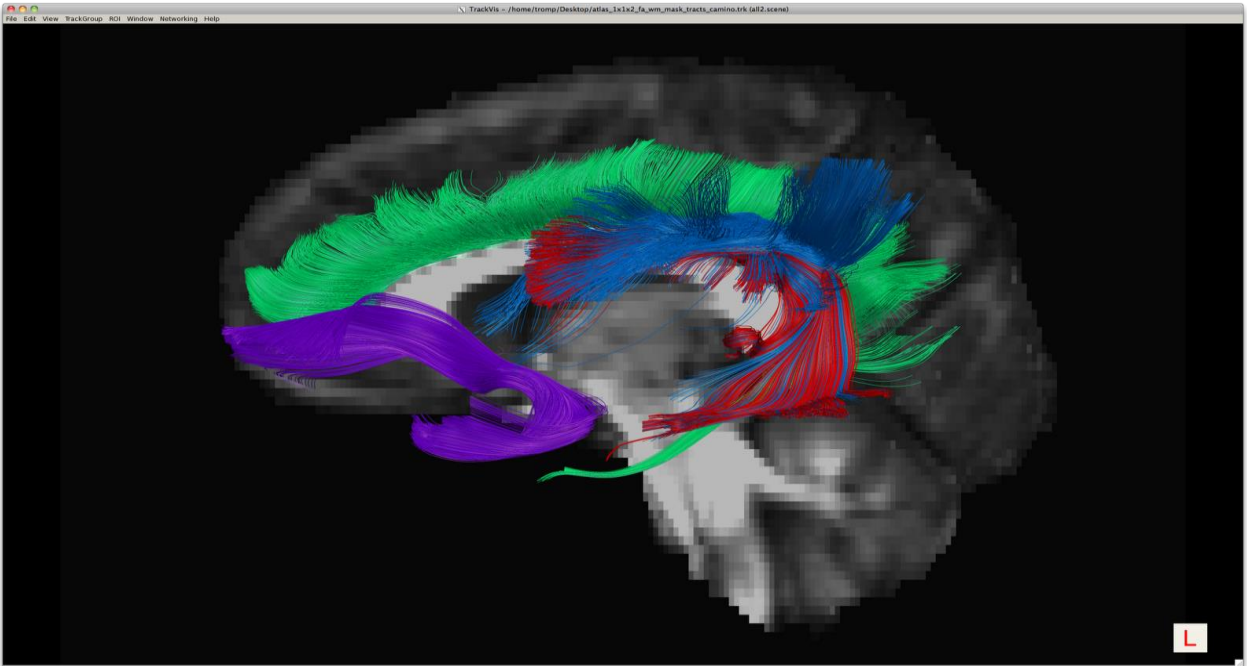Image from (1)

Figure 2. Fiber Tractography of a typically developing cingulum (green), superior longitudinal fasciculus (blue), arcuate fasciculus (red) and unicinate fasciculus (purple) [1]

In a previous study (2), our lab has developed the NA-MIC framework for fiber-tract-based DTI analysis, in which label map tractography has been performed via 3D Slicer (https://www.slicer.org/) to acquire DTI fiber bundles. (2) also shows the building of the DTI atlas and the definition of the major fiber tracts employed in my study. I then use that DTI fiber atlas as the fiber reference, as well as the deformation fields to all subject data (see below) for registering T1w/T2w ratio values.

In this thesis, I propose a novel framework to register T1w/T2w ratio data along fiber tracts in a straightforward manner. At the heart of this frame-work is a GUI based analysis tool for non-technical users that simplifies interactions to map T1w/T2w ratio map data, deformation data and fiber data to produce T1w/T2w ratio profiles that give meaningful statistically results for studies of white matter. Several steps are handled via integrated modules to perform the registration process and statistical analysis. First, the user selects the subjects of analysis via the GUI. Then, the pipeline calls a module named fiberprocess to sample T1w/T2w ratio values at locations along the selected

fiber tracts. Finally, a module named dtitractstat gathers information from the co-registered fiber tracts and produces the final T1w/T2w ratio profiles. The source code is available at https://github.com/NIRALUser/DTIProcessToolkit. A PowerPoint tutorial is also available at the repository to guide non-technical users to use the GUI. That tutorial has also been appended to this document.

2. METHODS AND MATERIALS

Our framework for the fiber tract based analysis of T1w/T2w ratio maps is composed of four components:

(1) Computation of T1w/T2w Ratio Maps

(2) Diffusion Fiber Atlas Registration

(3) Extraction of T1w/T2w Ratio Profile

(4) Statistical Analysis.

The workflow is visualized in figure 3. All of the tools referenced in the description of our workflow can be utilized as stand-alone command line applications to facilitate scripting. Each component takes certain data subjects as input and produces output for the next step.
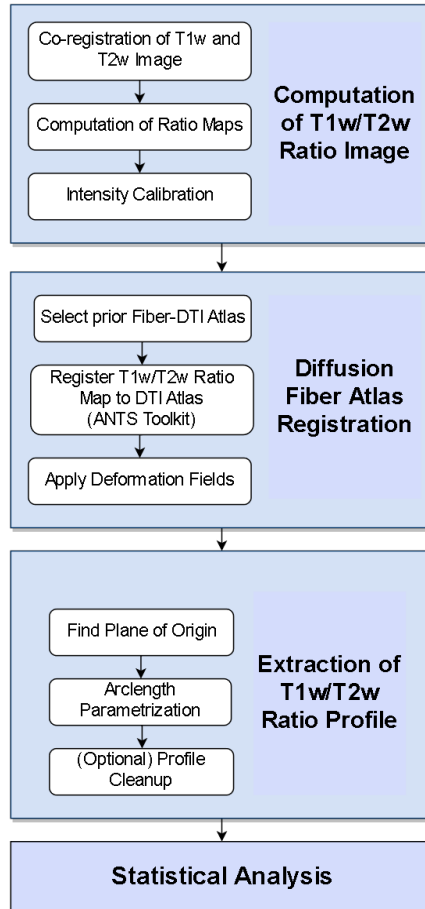
Figure 3. The workflow of our framework

2.1 Subjects and Acquisition

I applied my T1w/T2w-ratio map analysis to neonate datasets acquired on a Siemens Tim Trio 3T scanner at the University of Irvine (UCI). Children were scanned unsedated while asleep, fitted with ear protection and with their heads secured in a vacuum-fixation device. High-resolution T1-weighted images were acquired with a 3D magnetization prepared rapid gradient echo (MP-RAGE TR = 1820 ms, inversion time = 1100 ms, echo time = 4.38 ms, flip angle = 7°, resolution = 1 × 1 × 1 mm3, 6.18 mins). A high-resolution 3D T2-weighted sequence was also acquired at the same Field Of View and resolution as the T1w image (TR = 32000 ms, echo time = 255 ms, 4.18 mins). A total of 73 subjects (40 male, 33 female) were used here, ranging in gestational age at scan from 1 to

10 weeks.

From this data, I used the following information for the analysis:

1. T1w/T2w Ratio Maps, already calibrated as in (1) and available to this project

2. Prior DTI Atlas Fiber Reference, available to this project

3. Deformation Fields to DTI Fiber Reference, generated during the construction of 2.

2.1.1 T1w/T2w Ratio Maps

High-resolution T1w images and T2w images are acquired in many neuro-science studies from MRI data. The computation of T1w/T2w ratio maps, as the first component of our framework, includes a calibration procedure to prepare the ratio maps for quantitative studies. Following methods proposed by (1), I applied the following steps to compute the T1w/T2w ratio values:

1. Rigid registration of the T1w image into standard MNI space

2. Rigid registration of the T2w image to its aligned T1w image 1

3. Computation of the T1w/T2w ratio maps from 1 and 2

4. Intensity calibration of T1w/T2w maps via atlas based region statistics using deformable atlas registration.

5. Registration of the T1w/T2w maps into the corresponding DTIAtlas space from 2 for fiber trace based analysis via the NA-MIC atlas based fiber tract analysis framework.

The calibrated T1w/T2w ratio images need to be registered and transformed to the fiber bundles of interest, which will be discussed in section 2.2.

2.1.2 DTI Fiber Reference

The fiber atlas is generated via the NA-MIC atlas based fiber analysis toolkit described in (2). First, a deformable, unbiased DTI atlas was created via a tool called DTIAtlasBuilder, which

serves as the global reference space. Then, fiber tract streamline DTI tractography was performed via 3D slicer (http://www.slicer.org) in the DTI atlas space followed by fiber cleaning with FiberViewerLight (www.nitric.org/projects/fwlight). Tractography was performed for major fiber bundles: corpus callosum (genu, rostrum, tapetum, occipital, parietal), Left(L)/Right(R) cingulum, L/R fornix, L/R inferior fronto-occipital fasciculus, L/R inferior longitudinal fasciculus, L/R superior longitudinal fasciculus, L/R uncinate fasciculus, L/R motor, L/R pre-motor, L/R corticofugal parietal and L/R thalamocortical parietal and L/R optic tracts. The resulting fiber inputs are therefore fiber profiles registered in the aforementioned DTI atlas space.

2.1.3 Deformation to DTI Fiber Reference

As part of the deformable atlas generation in the previous step, deformation fields are generated to transform data to/from the DTI atlas and the individual DTI image space. In order to bring the T1w/T2w ratio maps into the atlas space, I need in addition to these DTI atlas deformation fields also deformation transforms that take the individual T1w/T2w ratio maps into the corresponding individual (same subject) DTI image space. These intra-scan DTI to T1w/T2w transforms were computed via symmetric, diffeomorphic image registration with the ANTS toolkit (4). The final deformation fields are computed by combining the corresponding two deformation fields, which transform the individual T1w/T2w ratio maps to the global DTI atlas.

2.2 Fiber Sampling in T1w/T2w Maps

After subjects are selected, the main innovation of this framework is to map T1w/T2w ratio values to the DTI fiber references. Given that fiber tractography has been performed in the DTI atlas space, the registration of T1w/T2w ratio values can be performed by straightforwardly mapping the
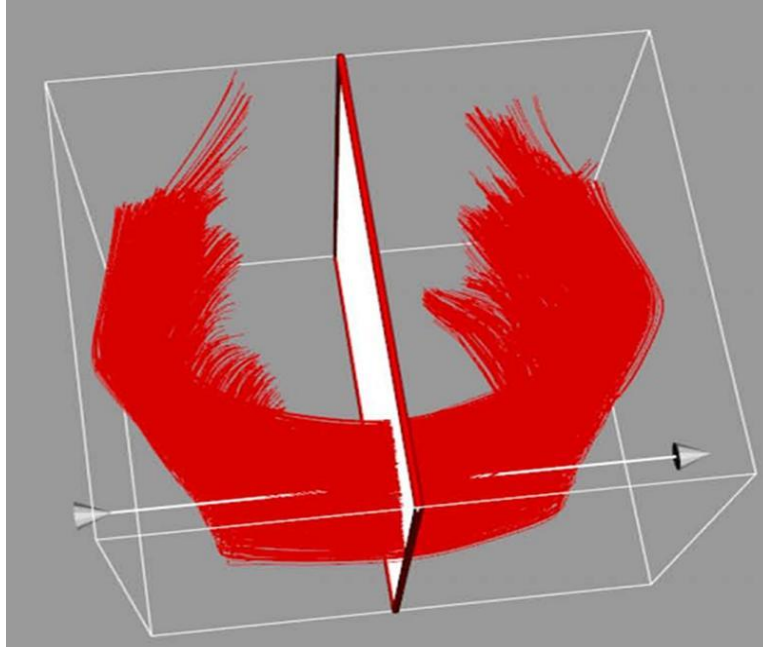
Figure 4. A visualization of the plane function intersecting genus fiber.

Image from (2)

ratio values to that atlas space and transforming the ratio values with the resulting deformation fields. In my framework, this process is done by the fiberprocess module, which accepts as its inputs both the T1w/T2w ratio maps and the computed deformation fields. The outputs of the fiber registration are fiber profiles registered with T1w/T2w ratio values (see Figure 6 in the result section).

2.3 Tract Profile Extraction

Prior to statistical analysis, a final step needs to be performed to extract T1w/T2w ratio properties along the fiber tracts. My method is based on the method to generate diffusion property profiles in (2). For this purpose, a fiber tract parametrization is performed based on fiber arc length. The origins are calculated by intersecting each fiber with an origin plane, as shown in figure 4. Each fiber points will be then parametrized by its signed arc-length distance to the origin plane. This

process is done by the dtitractstat module to analyze scalar data registered along the fiber tracts. While the module could automatically determine an appropriate origin plane, investigators can choose to provide an origin plane for the analysis. The outputs of this step are T1w/T2w parameter profiles stored in csv format. Additional data cleaning can be performed for the profiles for quality control via the DTI statistics tool FADDSter.

2.4 Statistical Analysis

To test how T1w/T2w ratio values relate to other variables of interest, I analyze the obtained profiles via the FADTTS tool developed in (5). FADTTS is a statistics tool specialized for analysis of DTI-based fiber studies. Since T1w/T2w ratio values are essentially scalar values applied on fiber tracts in my study, the tool is easily adaptable for my purpose. It performs several statistics tests including a multi-variate coefficient model, weighted least squares estimation and functional principal component analysis. These tests produce both global and arc-length-based local statistics with confidence bands and the local values are corrected for multiple comparisons with false discovery rate (FDR). FADTTS was applied via the GUI-based tool FADTTSter developed at the NIRAL (see Figure 7 in Results section).

2.5 Open Source Tool

Direct access of the tool to non-technical users is a crucial requirement in software development for neuroscience studies. To facilitate interaction with the framework, I developed a multi-platform GUI software named ScalarFiberAnalyzer (see figure 5) based on Qt (http://www.qt.io/) and CMake (https://cmake.org/). The inputs of the GUI are computed T1w/T2w ratio maps, DTI fiber references and deformation fields. The outputs of the GUI are T1w/T2w fiber profiles as discussed in Section 2.3. Two external modules, fiberprocess and dtitractstat, are also developed to be used by ScalarFiberAnalyzer to execute the pipeline of the framework. To facilitate debugging and re-execution, the GUI generates a python script that runs the entire pipeline of the framework on a prior selection of data. Minimum requirements for these tools are Qt5, CMake 3.2 and Python 2.7. The project can be accessed at https://github.com/NIRALUser/DTIProcessToolkit.

Via the GUI, the T1w/T2w ratio map and deformation field inputs are located according to the input csv files that specify the path to the data. The GUI will automatically match the T1w/T2w ratio maps with deformation fields by case id. After the matching, fiber tracts of interest can be selected upon which T1w/T2w ratio map analysis is performed. The user also needs to specify configurations for paths to external modules being used by the pipeline script, namely the executable path of python, fiberprocess and dtitractstat. The GUI utilizes a QtGUI framework, developed by a group of students at UNC, such that users can save and load their specified parameters and configurations. Once configuration and selection are complete, the entire pipeline can be executed by hitting a single run button. Outputs of the GUI are stored as extracted fiber profiles in csv format, which can be further analyzed statistically.
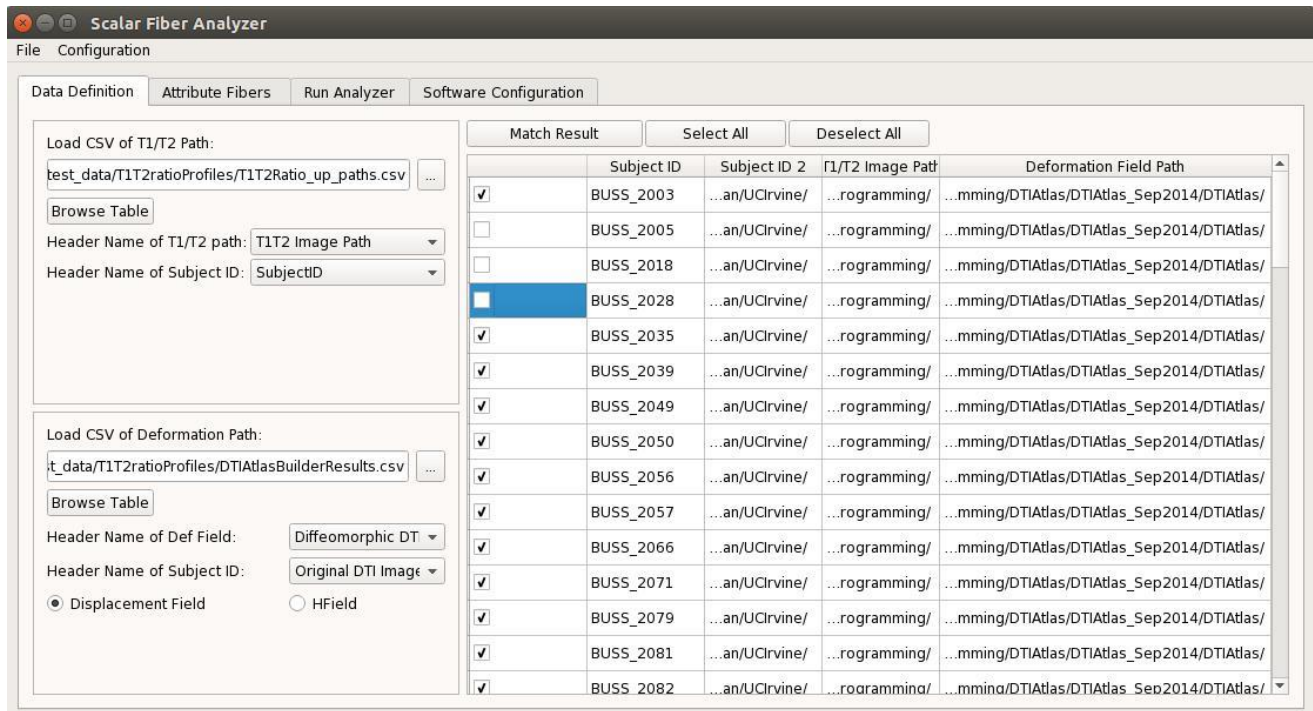
Figure 5. A Snapshot of ScalarFiberAnalyzer, displaying the opening screen on the data definition tab. There are additional tabs for the specification of parameters associated with the T1w/T2w attribution process and the specification of the paths to the modules necessary for the execution of the processing.

3. RESULTS

For testing our proposed framework, I conduct an example study using data of 73 neonate subjects from UC Irvine. The T1w/T2w ratio maps and diffusion fiber data are processed by the GUI I developed to generate parameter profiles that parametrizes T1w/T2w ratio maps of every subject along every fiber bundle from our data. Figure 6 shows an example fiber (Cortico Fugal Left Parietal Bundle) sampled for a representative neonate subject with the diffusion property FA as well as the T1w/T2w ratio measurement. While a clear correlation between the two measures is visible along the tract, there are also tract regions that show differences, such as in the inferior tract parts where FA is low despite high myelin content due to crossing fiber situations.

The resulting T1w/T2w ratio profiles are analyzed via FADTTSter, an improved FADTTS tool developed at NIRAL (see https://github.com/jeantm/FADTTS), to test covariation between the ratio values and several factors: gestational age (by week), postnatal age (by week) and gender. The tool provides plots of the covariate beta values which capture the association of the covariate (e.g. postnatal age) with the T1w/T2w ratio measurements as seen in Figure 7. The plot highlights significant tract regions for each covariate with an additional dot on the plot curve. Positive beta values indicate a positive association between the covariate and the T1w/T2w ratio measures at the corresponding arc-length. In Figure 7, it can be seen that for most of the tract, both postnatal age at scan as well as gestational age at birth are positively associated with T1w/T2w ratio, though a significant interaction is observable only for the inferior sections (those with lower arc-length locations) and the postnatal age at scan.

A more thorough analysis of results for all tracts is necessary to understand the interplay between T1w/T2w ratio and diffusion property values, as well as to characterize the association of the T1w/T2w ratio with gender and age at scan in early infancy. Such an analysis is not part of this thesis, but the aim of our future work.
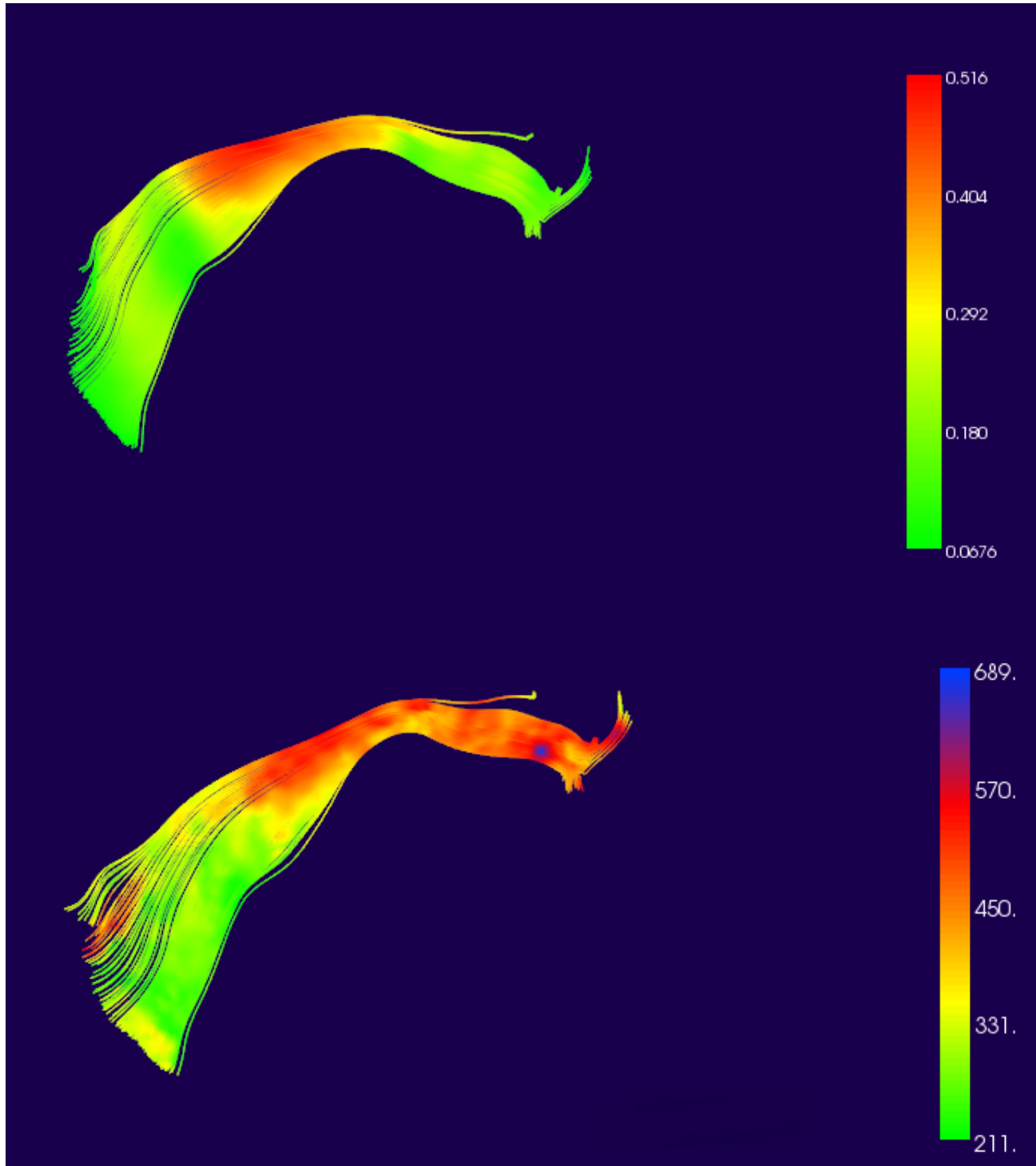
Figure 6: ShapePopulationViewer visualizations of Cortico Fugal Left Parietal Bundle for a representative subject. Top: Fractional Anisotropy map. Bottom: T1w/T2w ratio map. While there is a clear correlation visible between the measurements, also inferior regions (to the right side of the visualization) show high myelination content and relatively low FA due to crossing fibers situations.
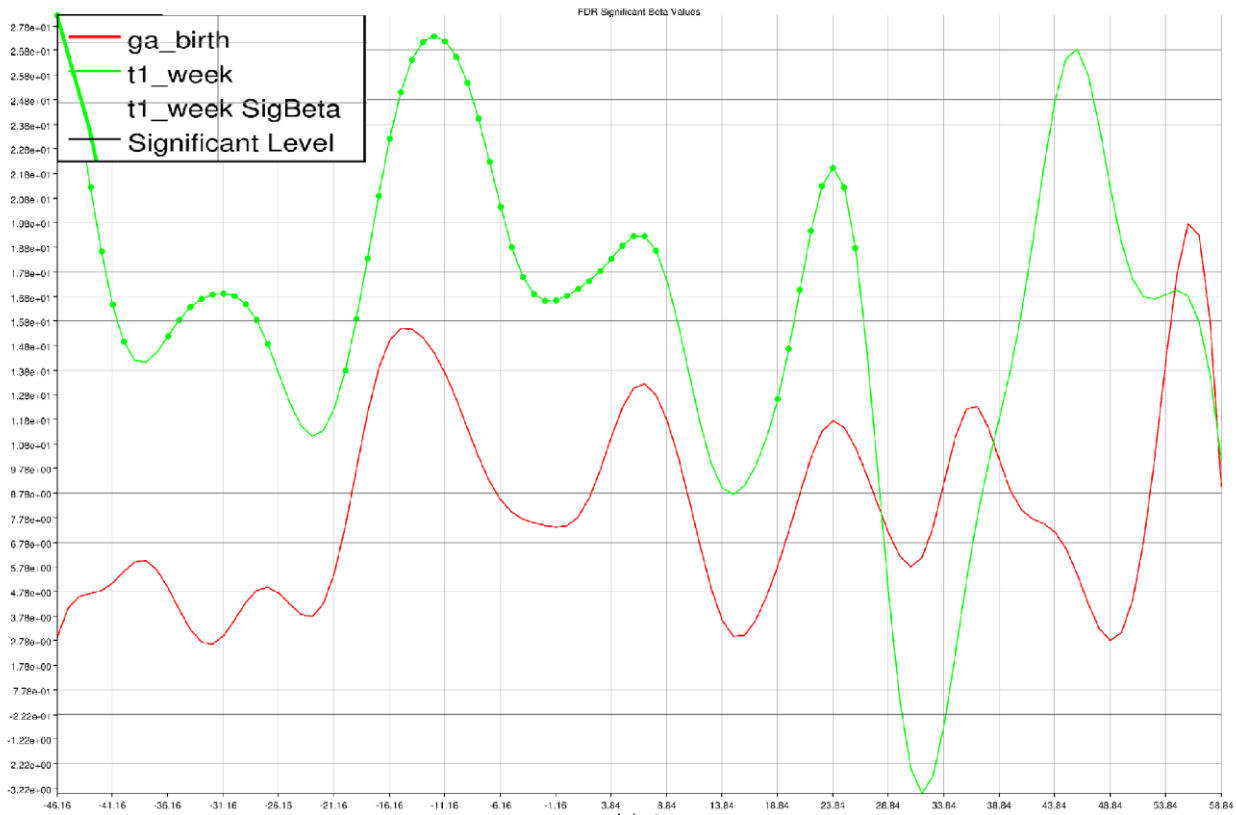
Figure 7: Multi-variate coefficient plot from FADTTSter of the corticofugal left premotor bundle with arc-length as the x-axis and T1w/T2w ratio value as the y-axis. The dotted portion of the curves shows that correlation is statistically significant at that arclength. The results in this example tract shows that all association of the T1w/T2w ratio with gestational age at birth are positive but not significant along the tract. In contrast, the association of the T1w/T2w ratio with postnatal age is positive and significant ($p <$ 0.05, corrected) for a large inferior section of the tract. This observation is not surprising and fits well with our hypothesis of positive association of the subject's age with the myelin content in early myelinating

4. DISCUSSION AND CONCLUSION

This thesis discussed a framework for diffusion fiber-based analysis of T1w/T2w ratio maps to study myelination in white matter. Our main contribution in this thesis project is the development of the software tool that implements pipeline functionality for our proposed framework. With our implementation, statistical analysis can be performed on T1w/T2w ratio distribution on individual fiber bundles to gain insight into how myelination in white matter may be correlated with different factors. We tested this analysis framework on a study of neonate brain development with preliminary results shown. As mentioned before, a more in-depth analysis and interpretation of those results will be one of our next steps.

While our framework provides a straight-forward and efficient way of analyzing T1w/T2w ratio values along fiber tracts, it requires prior data from DTI study and preprocessing of T1w/T2w ratio maps. Since neuroscience researcher may wish to directly start from T1w images and T2w images or to perform analysis without the acquisition of DTI data of the subjects, improvements can be made to our framework to include computation and calibration of T1w/T2w ratio image and registration of deformation fields in our software pipeline.

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