

**Title:** Pipeline for generating automated fiber bundles extraction applied to raw HARDI data from the TwinsMX data set.

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**Objective:** To develop an automated fiber bundles extraction pipeline that can be applied to raw High Angular Resolution Diffusion Imaging (HARDI) data from the TwinsMX data set using a wide variety of software packages and libraries.

**Methods:** Data acquisition: 3 Tesla MRI was performed using a Philips Achieva TX MRI scanner (Philips Medical Systems, Best, The Netherlands). The protocol was approved by the ethical committee at the Institute of Neurobiology (INB) and the subject provided written informed consent in accordance with the declaration of Helsinki.

Diffusion weighted images (DWI) were acquired with the following parameters:  $b = 1000 \text{ s/mm}^2$  with 33 different directions, echo time / repetition time (TE/TR) = 70 ms/11816 ms, flip angle =  $90^\circ$ , voxel size =  $2.29 \times 2.33 \times 2.30 \text{ mm}^3$ , field of view = 256 mm, and in addition DWI with  $b = 2000 \text{ s/mm}^2$ , with 66 different directions TE/TR = 70 ms / 11723.6 ms, flip angle =  $90^\circ$ , voxel size =  $2.29 \times 2.33 \times 2.30 \text{ mm}^3$ , field of view = 256 mm, a  $b = 0 \text{ s/mm}^2$  was acquired with reverse phase encoding and a T1 anatomical image with TE/TR = 3.8 ms/8.2 ms, flip angle =  $8^\circ$ , voxel size =  $1.00 \times 1.07 \times 1.00 \text{ mm}$ , field of view = 256 mm. Images were reviewed by an expert neuroradiologist to discard brain lesions.

Data processing: The DWI preprocessing employed methods from the software MRtrix3, the FMRIB Software Library v6.0 (FSL), the Advanced Normalization Tools (ANTs) as well as the Diffusion Imaging in Python (Dipy) library. The  $b = 1000 \text{ s/mm}^2$  and  $b = 2000 \text{ s/mm}^2$  images were concatenated into one 4D volume with 99 different direction gradients. Local PCA based denoising<sup>1</sup> and suppression of Gibbs oscillators<sup>2</sup> were performed (Dipy), followed by motion and distortion correction (topup, FSL)<sup>3,4</sup> and brain mask extraction (BET, FSL)<sup>5</sup>. To obtain the response function and the subsequent Fiber Orientation Distributions (FODs) we used multi-shell multi-tissue constrained spherical deconvolution (MSMT CSD)<sup>6,7</sup> (Figure 1).

The T1 anatomical image was registered to the brain extracted and averaged  $b = 0 \text{ s/mm}^2$  image using ANTs<sup>8</sup>. This T1 registered image was used to generate a five-tissue-type segmentation (5tt). Based on this segmentation we used anatomically constrained tractography (ACT)<sup>9</sup> and we seeded 10 million streamlines at the white matter-gray matter interface (WMGM). The resulting streamlines were filtered to 1 million using Spherical-deconvolution Informed Filtering of Tractograms (SIFT)<sup>10</sup>.

Automatic registration and parcellation of fiber bundles was achieved using RecoBundles<sup>11</sup> from Dipy. The resulting recognized subject bundles are produced both in the Montreal Neurological Institute (MNI) space and subject space. (Figure 1 and 2).

**Results/Discussion:** We analyzed HARDI data using MRtrix3, FSL, ANTs, as well as the Dipy library resulting in 79 automated successfully extracted bundles from both cerebral hemispheres in one subject (i.e. left/right corticospinal tract, superior/medial cerebellar peduncle and left/right arcuate fasciculus). However, 11 of the output tracts from RecoBundles (i.e. left/right oculomotor, left/right trochlear and left/right facial cranial nerves) did not contain any streamline. It is noticeable that most of these bundles are bilateral cranial nerves tracts.

Another 4 tracts of the output tracts from RecoBundles contained only one or two streamlines, all of these are unilateral tracts with their contralateral bundle presenting a normal population of streamlines. Future work should focus on optimizing the preprocessing pipeline in order to obtain cranial nerves fiber bundles and brainstem tractography.

**Conclusion:** HARDI data preprocessing and subject bundles estimation are long and operator dependent. This pipeline can be of great advantage in large neuroimaging datasets to shorten the time needed for both preprocessing and analysis. In particular, the pipeline will be used to analyze data from TwinsMX, the Mexican Twin Registry, to investigate the genetic and environmental factors associated with white matter integrity and its association with mental health and cognition. Future work is needed to optimize the preprocessing pipeline to obtain cranial nerves fiber bundles.

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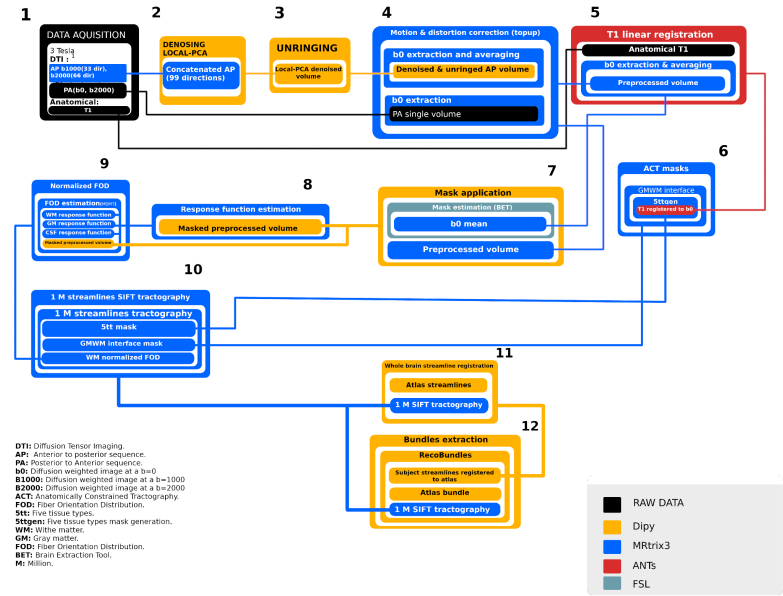


Figure 1. Preprocessing pipeline of the HARDI and T1 MRI data using different software packages.

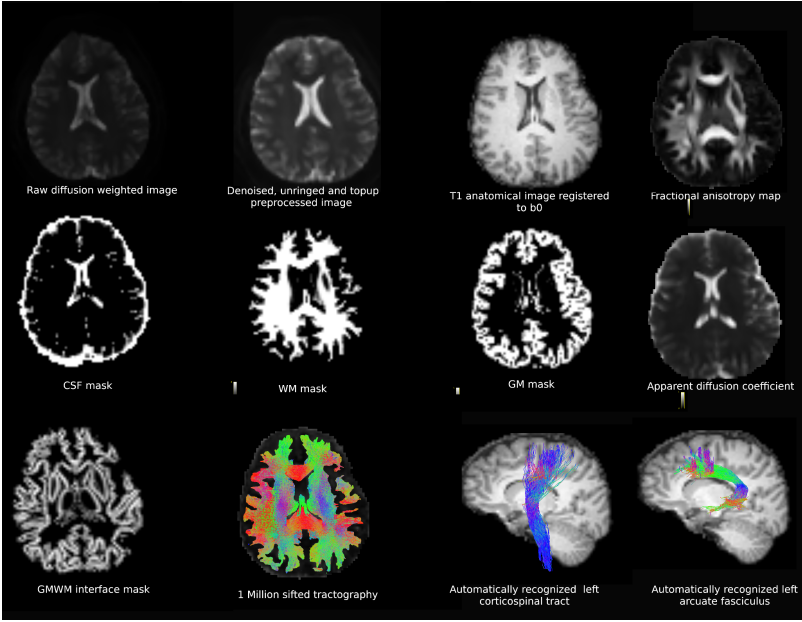


Figure 2. Output images from the preprocessing pipeline Figure 1.

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