Brain morphometry using diffusion MRI

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Spatial normalization

Subject 1
Subject 2
Subject 3
Population Atlas
Computational Neuroanatomy

With the increasing resolution of anatomical scans of the human brain and the sophistication of image processing techniques there have emerged, recently, a large number of approaches to characterizing differences in the shape and neuroanatomical configuration of different brains. One way to classify these approaches is to broadly divide them into those that deal with differences in brain shape and those that deal with differences in the local composition of brain tissue after macroscopic differences in shape have been discounted. The former use the deformation fields that map any individual brain onto some standard reference as the characterization of neuroanatomy, whereas the latter compare images on a voxel basis after the deformation fields have been used to spatially normalize the images. In short, computational neuroanatomical techniques can either use the deformation fields themselves or use these fields to normalize images that are then entered into an analysis of regionally specific differences. In this way, information about overall shape (deformation fields) and residual anatomic differences inherent in the data (normalized images) can be partitioned.
Jacobian of the transformation is informative of local changes in volume (Tensor-based-morphometry: TBM)

- **ANTS software**
  - (Avants et al. 2008 & 2011)

- **Similarity metric:**
  - cross correlation

- **Transformation model:**
  - Diffeomorphic (symmetric mapping (Syn))

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Single Patient brain or patient template

Control Template

![Log of the Det of the Jacobian of the Transformation](image)

Patient brain registered to the Control template
Applications of TBM based on T1-weighted Images

- Alzheimer disease (Freeborough & Fox 1998)
- Brain development (Thompson et al. 2000)
- Huntington (Kipps et al. 2005)
- Fragile X syndrome (Lee et al. 2007)
- Frontotemporal dementia (Brambati 2007)
- Williams syndrome (Chiang et al. 2007)
- HIV/AIDS (Chiang et al. 2007, Lepore 2008)
- Schizophrenia (Whitford et al. 2007, Hua et al. 2008)
- TBI (Kim et al. 2008)
- Stress (Hanson et al. 2010)
- ...

...
Our Hypothesis:

Diffusion MRI provides clear delineation of anatomical structures that can not be separated in T1- and T2-WI (e.g. individual pathways).

Therefore, tensor-based morphometry (TBM) using DTI-driven registration (DTBM) should be more accurate than T1WI-TBM.
Examples in the literature of TBM with registration driven by diffusion MRI data

Registration based only on FA images
Multiple sclerosis and amyotrophic lateral sclerosis (Pagani et al. 2007)
Alzheimer’s Disease (Oishi et al. 2011)

Registration based on tensor deviatoric

Only one paper with registration based on all tensor elements
Dense feature deformation morphometry: Incorporating DTI data into conventional MRI morphometry Studholme et al., Medical image analysis 12.6 (2008): 742-751.
Investigating white matter fibre density and morphology using fixel-based analysis

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ABSTRACT

Voxel-based analysis of diffusion MRI data is increasingly popular. However, most white matter voxels contain contributions from multiple fibre populations (often referred to as crossing fibres), and therefore voxel-averaged quantitative measures (e.g. fractional anisotropy) are not fibre-specific and have poor interpretability. Using higher-order diffusion models, parameters related to fibre density can be extracted for individual fibre populations within each voxel (‘fixels’), and recent advances in statistics enable the multi-subject analysis of such data. However, investigating within-voxel microscopic fibre density alone does not account for macroscopic differences in the white matter morphology (e.g. the calibre of a fibre bundle). In this work, we introduce a novel method to investigate the latter, which we call fixel-based morphometry (FBM). To obtain a more complete measure related to the total number of white matter axons, information from both within-voxel microscopic fibre density and macroscopic morphology must be combined. We therefore present the FBM method as an integral piece within a comprehensive fixel-based analysis framework to investigate measures of fibre density, fibre-bundle morphology (cross-section), and a combined measure of fibre density and cross-section. We performed simulations to demonstrate the proposed measures using various transformations of a numerical fibre bundle phantom. Finally, we provide an example of such an analysis by comparing a clinical patient group to a healthy...
**Brain morphometry**

From Wikipedia, the free encyclopedia

**Pattern based morphometry**  [edit]

Pattern based morphometry (PBM) is a method of brain morphometry first put forth in PBM.[4] It builds upon DBM and as opposed to typical voxel based approaches which depend on univariate statistical tests at specific voxel locations this is that the inferences are not made locally as in VBM or DBM but globally. This allows the method to detect changes at single voxels. Also the method is more robust to variations in the underlying registration algorithms as compared to.

**Surface-based morphometry**  [edit]

Main article: Surface-based morphometry

Once the brain is segmented, the boundary between different classes of tissue can be reconstructed as a surface and results of such analyses can be projected.

**Diffusion-weighted MR-based brain morphometry**  [edit]

Fiber-tracking techniques  [edit]

Nerve fiber-tracking techniques are the latest offspring of this suite of MR-based morphological approaches. They use or diffusion-spectrum imaging (e.g. Douaud et al., 2007 and O'Donnell et al., 2009).

**Diffeomorphometry**  [edit]

*Diffeomorphometry*[^5] is the focus on comparison of shapes and forms with a metric structure based on diffeomorph registration,[^7] introduced in the 90's, is now an important player with existing codes bases organized around ANTS actively used computational codes for constructing correspondences between coordinate systems based on sparse...
Goal:

Achieve a robust and accurate diffusion MRI based registration that could be used to perform TBM-DTI.
Prerequisite: solve the issue of EPI distortions in DWI
Effects of image distortions originating from susceptibility variations and concomitant fields on diffusion MRI tractography results

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**DR-BUDDI** (Diffeomorphic Registration for Blip-Up blip-Down Diffusion Imaging) method for correcting echo planar imaging distortions

M. Okan Irfanoglu a,b,*, Pooja Modi a, Amritha Nayak a,b, Elizabeth B. Hutchinson a,b, Joelle Sarlls c, Carlo Pierpaoli a

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Echo planar imaging
Diffusion tensor imaging
Reversed phase encoding
Diffeomorphic image registration

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**ABSTRACT**

We propose an echo planar imaging (EPI) distortion correction method (**DR-BUDDI**), specialized for diffusion MRI, which uses data acquired twice with reversed phase encoding directions, often referred to as blip-up blip-down acquisitions. **DR-BUDDI** can incorporate information from an undistorted structural MRI and also use diffusion-weighted images (DWI) to guide the registration, improving the quality of the registration in the presence of large deformations and in white matter regions. **DR-BUDDI** does not require the transformations for correcting blip-up and blip-down images to be the exact inverse of each other. Imposing the theoretical “blip-up blip-down distortion symmetry” may not be appropriate in the presence of common clinical scanning artifacts such as motion, ghosting, Gibbs ringing, vibrations, and low signal-to-noise. The performance of **DR-BUDDI** is evaluated with several data sets and compared to other existing blip-up blip-down correction approaches. The proposed method is robust and generally outperforms existing approaches. The inclusion of the DWIs in the correction process proves to be important to obtain a reliable correction of distortions in the brain stem. Methods that do not use DWIs may produce a visually appealing correction of the non-diffusion weighted images, but the directionally encoded color maps computed from the tensor reveal an abnormal anatomy of the white matter pathways.

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**DR-TAMAS: Diffeomorphic Registration for Tensor Accurate Alignment of Anatomical Structures**

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Diffeomorphic image registration  
Fiber tractography

**ABSTRACT**

In this work, we propose DR-TAMAS (Diffeomorphic Registration for Tensor Accurate alignMent of Anatomical Structures), a novel framework for intersubject registration of Diffusion Tensor Imaging (DTI) data sets. This framework is optimized for brain data and its main goal is to achieve an accurate alignment of all brain structures, including white matter (WM), gray matter (GM), and spaces containing cerebrospinal fluid (CSF). Currently most DTI-based spatial normalization algorithms emphasize alignment of anisotropic structures. While some diffusion-derived metrics, such as diffusion anisotropy and tensor eigenvector orientation, are highly informative for proper alignment of WM, other tensor metrics such as the trace or mean diffusivity (MD) are fundamental for a proper alignment of GM and CSF boundaries. Moreover, it is desirable to include information from structural MRI data, e.g., T1-weighted or T2-weighted images, which are usually available together with the diffusion data. The fundamental property of DR-TAMAS is to achieve global anatomical accuracy by incorporating in its cost function the most informative metrics locally. Another important feature of DR-TAMAS is a symmetric time-varying velocity-based transformation model, which enables it to account for potentially large anatomical variability in healthy subjects and patients. The performance of DR-TAMAS is evaluated with several data sets and compared with other widely-used diffeomorphic image registration techniques employing both full tensor information and/or DTI-derived scalar maps. Our results show that the proposed method has excellent overall performance in the entire brain, while being equivalent to the best existing methods in WM.
DR-TAMAS main features

Uses all features of the diffusion tensor to achieve good alignment of white matter, gray matter, and CSF

Large deformation mapping capabilities

Tensor reorientation during optimization

If desired, can use complementary information from anatomical images such as T1W or T2W structural images

Provides robust atlas creation strategies

Can deal with lesion regions (e.g. tumors) or missing tissue.
Native morphology (AC-PC aligned)
Registered using FA (FSL)
Registered using deviatoric tensor (DTI-TK)
RESEARCH ARTICLE

Tensor-based morphometry using scalar and directional information of diffusion tensor MRI data (DTBM): Application to hereditary spastic paraplegia

Neda Sadeghi, Filippo Arrigoni, Maria Grazia D'Angelo, Cibu Thomas, M. Okan Irfanoglu, Elizabeth B. Hutchinson, Amritha Nayak, Pooja Modi, Maria Teresa Bassi, Carlo Pierpaoli

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Read the full text  □
Application to Hereditary Spastic Paraplegia

DTBM localizes disease to specific white matter pathways
DTBM results are consistent with selective involvement of long range white matter pathways

- Hereditary Spastic Paraplegia (HSP) is a group of neurodegenerative disorders characterized by lower limb weakness & spasticity.
- The pure form has only motor involvement
- SPG11 is a subtype of HSP with mutation in the SPG11 gene which encodes for a protein involved in the maintenance of axons.
- HSP-SPG11 patients also exhibit other neurological problems in addition to spasticity, for example intellectual disability

- Conventional MRI findings:
  - None in the pure form
  - Thinning of corpus callosum and Enlargement of ventricles in SPG11
T1W-TBM | FA-TBM | DTI-TBM | Control DEC Map

RH | LH | CB | IFOF | CB | gIC | gCC | SS | AF

Tpt | sCC
Figure 6: Fiber tracts located in regions of atrophy in the left hemisphere. AF: arcuate fasciculus; CB: cingulum bundle; CST: corticospinal tract; IFOF: inferior fronto-occipital fasciculus; ILF: inferior longitudinal fasciculus; UF: uncinate fasciculus.
Application to Normal Brain development

DTBM changes generally correlate with FA changes but the regression slope changes in different pathways

Amritha Nayak, Neda Sadeghi, M Okan Irfanoglu, and Carlo Pierpaoli.
Diffusion - Tensor Based Morphometry (DTBM) of Normal Human Brain Development from Infancy to Adulthood. ISMRM 2017
The diffusion tensor imaging (DTI) component of the NIH MRI study of normal brain development (PedsDTI)

Lindsay Walker, Lin-Ching Chang, Amritha Nayak, M. Okan Irfanoglu, Kelly N. Botteron, James McCracken, Robert C. McKinstry, Michael J. Rivkin, Dah-Jyu Wu, Judith Rumsey, Carlo Pierpaoli, the Brain Development Cooperative Group

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0-3 months
6-12 months
18 months
2-4 years
10 years
Developmental trajectories

Fractional Anisotropy (FA)

Age (years)

CC Splenium
CC Genu
Cerebral peduncle
Left and Right
Medial lemniscus
Left and Right
Vermis
Putamen
Left and Right
Volume changes of various brain structures as function of age (relative to volume in adults)
FA changes of various white matter structures as function of age

- **Cortico Spinal Tract**
- **PLIC**
- **Genu of Corpus Callosum**

Age in years
Correlation between FA and Log J

<table>
<thead>
<tr>
<th>ROIs</th>
<th>Slope</th>
<th>R2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CST</td>
<td>5.7377</td>
<td>0.9667</td>
</tr>
<tr>
<td>PLIC</td>
<td>3.827</td>
<td>0.9421</td>
</tr>
<tr>
<td>Genu</td>
<td>7.0699</td>
<td>0.9183</td>
</tr>
<tr>
<td>Thalamus</td>
<td>4.7353</td>
<td>0.892</td>
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</tbody>
</table>
Application to Down Syndrome

Dramatic patients vs controls DTBM differences with no FA differences.

DTBM allows the identification of selective hypoplasia of fronto-pontine-cerebellar connections

Carlo Pierpaoli, Amritha Nayak, Okan Irfanoglu, Neda Sadeghi, and Nancy Raitano-Lee

Brain morphometry using diffusion MRI data (DTBM) reveals abnormalities in Down Syndrome that are not detected by conventional DTI analysis. ISMRM 2018
# Subjects

## Table 1. Demographic characteristics of the sample

<table>
<thead>
<tr>
<th></th>
<th>DS (n=15)</th>
<th></th>
<th></th>
<th>Control (n=29)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>Range</td>
<td>M</td>
<td>SD</td>
<td>Range</td>
</tr>
<tr>
<td>Age</td>
<td>17.02</td>
<td>5.47</td>
<td>6-23</td>
<td>16.17</td>
<td>6.40</td>
<td>5-24</td>
</tr>
<tr>
<td>Nonverbal IQ</td>
<td>59.53</td>
<td>15.19</td>
<td>34-86</td>
<td>113.59</td>
<td>16.27</td>
<td>89-134</td>
</tr>
<tr>
<td>SES (Hollingshead)</td>
<td>35.87</td>
<td>15.62</td>
<td>20-63</td>
<td>39.71</td>
<td>22.24</td>
<td>20-115</td>
</tr>
<tr>
<td>Sex: Female</td>
<td>n</td>
<td>%</td>
<td></td>
<td>n</td>
<td></td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>47</td>
<td></td>
<td>16</td>
<td></td>
<td>55</td>
</tr>
<tr>
<td>Race: White, non-Hispanic</td>
<td>10</td>
<td>67</td>
<td></td>
<td>17</td>
<td></td>
<td>59</td>
</tr>
</tbody>
</table>
MRI Methods

- DTI datasets consisted of 60 volumes with 6 $b=0$, 12 $b=300$, and 42 $b=1100\text{s/mm}^2$. Resolution was 2.5 mm isotropic.
- Control template created using DR TAMAS.
- All subjects individually registered to the control template.
- The log of the determinant of the jacobian was computed from the deformation field maps of each individual subject warped to the control template.
- TBSS and TFCE statistics were computed using FSL randomize program.
- Effect size maps were computed as follows:
  \[
  \frac{\text{mean patients} - \text{mean controls}}{\text{std dev of the population}}
  \]
### Results

**Effect Size of Patients vs. Controls differences**

Cohen’s $d$

Scaled between -3 and 3
Results

Voxelwise Statistical Analyses (TFCE) 
(p < 0.01)
Blue pt lower than ct
Red pt higher than ct
Results

TBSS Statistical Analysys (p < 0.01)
Blue pt lower than ct
Red pt higher than ct
Gray Matter

Ranking of regions from most hypoplastic to least hypoplastic in DS
White Matter

Ranking of regions from most hypoplastic to least hypoplastic in DS

KEY:
- Brainstem/Cerebellar Fibers
- Association Fibers
- Association/Limbic Fibers
- Frontal White Matter
- Projection Fibers
- Commissural Fibers

DS Mean Ln-J: -1.0 -0.8 -0.6 -0.4 -0.2 0.0 0.2 0.4 0.6
Relative Volume: (37%) (44%) (55%) (67%) (82%) (100%) (122%) (149%) (182%)

- Inferior Cerebellar Peduncle
- Transverse Pontine Fibers (ventral)*
- Transverse Pontine Fibers (dorsal)*
- Middle Cerebellar Peduncle*
- Fornix
- Cerebral Peduncle - Lateral*
- Vertical Occipital Fibers*
- Cerebral Peduncle - Medial*
- Inferior Olives*+
- Frontal WM*
- Cingulum
- Medial Lemniscus
- Anterior Limb Internal Capsule
- Uncinate Fasciculus
- Anterior Corona Radiata
- Superior Longitudinal Fasciculus
- Superior Cerebellar Peduncle
- Posterior Thalamic Radiation
- Corpus Callosum
- Cerebral Peduncle - Intermediate*
- Superior Corona Radiata
- External Capsule
- Posterior Limb of Internal Capsule
- Corticospinal Tract/Medulla*
- Splenium
Application to Moebius Syndrome

DTBM identifies atrophy of the Medial Longitudinal Fasciculus as a hallmark feature of Moebius Syndrome

DTBM results allows 100% classification accuracy in differentiating Moebius patients from controls and Congenital Facial Palsy patients

What is Moebius syndrome?

Moebius syndrome is a nonprogressive craniofacial/neurological disorder that involves primarily the facial abducens nerve. Individuals with Moebius syndrome cannot smile or frown, and do not have lateral eye movements. (From http://moebiussyndrome.org)
Figure 4: Left: schematic diagram of muscles and cranial nerves involved in eye movement, SR: superior rectus, IO: inferior rectus, LR: lateral rectus, IR: inferior rectus, SO: superior oblique, MR: medial rectus. Right: schematic diagram of cranial nerves and muscles involved in conjugate horizontal gaze. Motor neurons of CN VI project ipsilaterally to LR to abduct the eye, whereas the interneurons cross the midline via medial longitudinal fasciculus (MLF) and project contralaterally to MR to adduct the eye.
Voxelwise significant differences ($p < 0.01$) on DTBM
(In red on FA map: local Det Jacobian lower in Moebius than in Controls)
High sensitivity and specificity in differentiating Moebius Subjects (MBS) form both Controls and Congenital Facial Weakness (CFW) subjects.
Conclusions

DTBM is a promising tool to complement conventional analysis of diffusion MRI for neurological applications. It has great potential for personalized medicine. It requires “good data” not necessarily “big data”.

Practical consideration

Prospective diffusion MRI studies should be designed with blip-up blip-down acquisitions including also the DWIs.
Special thanks!

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Nancy Reitano Lee Drexel U
Irini Manoli NHGRI
T1 average study template  DEC map  Trace (D) map

Effect Size log J map T1  Effect size log J map DTI  Effect size log J map FA
T1 average study template  DEC map  Trace (D) map

Effect Size log J map T1  Effect size log J map DTI  Effect size log J map FA
Mean FA skeleton

Controls significantly higher than patients at $p<0.01$

Patients significantly higher than controls fat $p<0.01$

Log J: Log of the determinant of the jacobian