NeuroImage 81 (2013) 26–48

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Geometrical constraints for robust tractography selection

Rodrigo de Luis-García [a,*], Carl-Fredrik Westin [b], Carlos Alberola-López [a]

[a] Laboratorio de Procesado de Imagen (LPI), ETSI Telecomunicación at Universidad de Valladolid, Campus Miguel Delibes s/n., 47011 Valladolid, Spain
[b] Laboratory of Mathematics in Imaging, 1249 Boylston St, Boston, MA 02215 USA

ARTICLE INFO

Article history:
Accepted 21 April 2013
Available online 22 May 2013

Keywords:
DTI
Tractography selection
White matter analysis

ABSTRACT

Tract-based analysis from DTI has become a widely employed procedure to study the white matter of the brain and its alterations in neurological and neurosurgical pathologies. Automatic tractography selection methods, where a subset of detected tracts corresponding to a specific white matter structure are selected, are a key component of the DTI processing pipeline. Using automatic tractography selection, repeatable results free of intra and inter-expert variability can be obtained rapidly, without the need for cumbersome manual segmentation. Many of the current approaches for automatic tractography selection rely on a previous registration procedure using an atlas; hence, these methods are likely very sensitive to the accuracy of the registration. In this paper we show that the performance of the registration step is critical to the overall result. This effect can in turn affect the calculation of scalar parameters derived subsequently from the selected tracts and often used in clinical practice; we show that such errors may be comparable in magnitude to the subtle differences found in clinical studies to differentiate between healthy and pathological. As an alternative, we propose a tractography selection method based on the use of geometrical constraints specific for each fiber bundle. Our experimental results show that the approach proposed performs with increased robustness and accuracy with respect to other approaches in the literature, particularly in the presence of imperfect registration.

Introduction

Diffusion Magnetic Resonance Imaging (dMRI) is a well-known MRI imaging modality that permits to *in vivo* quantify the diffusivity of water molecules within the tissue, providing information about the organization of the white matter of the brain and the orientation of its fiber tracts. Analysis of the white matter of the brain using dMRI has shown to be relevant in a number of neurological and neurosurgical pathologies, such as brain ischemia, multiple sclerosis or epilepsy, among others (Horsfield and Jones, 2002; Salmenpera et al., 2006; Sotak, 2002; Sundgren et al., 2004).

Whatever the diffusion model, white matter analysis is commonly performed in clinical studies following a volumetric or a tract-based approach. In the former case, a region of interest (ROI) is manually or automatically identified, and then scalar quantities derived from dMRI, such as Fractional Anisotropy (FA) or Mean Diffusivity (MD), can be compared across subjects. With regard to the ROI selection, 2D regions are usually selected when manual delineation is employed (Kubicki et al., 2007). However, automatic approaches have become more commonly employed, usually consisting on the volumetric analysis on images registered to a common template (VBM, Volumetric-Based Morphology) (Wright et al., 1995). Using this technique, each dataset is registered into a standard space and then voxelwise statistics are computed in the whole brain or in certain areas of interest. Even though VBM analysis has been and is very commonly employed for white matter analysis, there has been much debate about its advantage sand drawbacks (Davatzikos, 2004; Melonakos et al., 2011; Smith et al., 2006). The main concern is how can it be guaranteed that the observed changes are a consequence of actual changes in the white matter instead of the effect of an incorrect alignment in the registration process.

In order to address this challenge, tract-based analysis has been proposed. By calculating connectivity information in the dMRI, tractography (Basser et al., 2000; Conturo et al., 1999) is carried out to achieve a representation of the neural pathways. Then, the output of the tractography algorithm needs to be processed in order to select those fibers that belong to a certain fiber bundle. Finally, measures (usually scalar, such as FA, fractional anisotropy) are derived from the selected fibers in order to compare corresponding fiber bundles in different subjects.

Tractography selection is a key step in tract-based analysis in order to obtain meaningful results in tract-based white matter studies. Sometimes, fibers are clustered into fiber-bundles that are homogeneous in shape and location. This process has received considerable attention in the last few years and several algorithms have been developed (Goodlett et al., 2009; O'Donnell and Westin, 2007; Wang et al., 2011). However, the correspondence of these fiber clusters with anatomically meaningful bundles can be challenging, as well as

* Corresponding author.
E-mail addresses: rodlui@tel.uvas.es (R. de Luis-García), westin@bwh.harvard.edu (C.-F. Westin), caralb@tel.uva.es (C. Alberola-López).

1053-8119/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neuroimage.2013.04.096

dealing with spurious or incorrect fibers. Other alternatives have been proposed, such as Tract-Based Spatial Statistics (TBSS), based on the derivation of an alignment-invariant tract representation (Smith et al., 2006), or the use of medial representations for sheet-like fiber bundles or related approaches (Yushkevich et al., 2008; Zhang et al., 2010a). A different option, which constitutes the main focus of this paper, consists in selecting the fibers that correspond to a certain fiber-bundle of interest according to the definition of seed voxels for the tractography to start or some other criteria.

As manual seed placing alone can suffer from reproducibility concerns, the use of multiple regions of interest (MROIs) for tractography selection (Suarez et al., 2012; Wakana et al., 2007; Zhang et al., 2008) has recently received increased attention. Nevertheless, manual delineation of MROIs requires advanced training, is time consuming and may produce expert variability that can negatively affect the fiber selection. Thus, the automation of tractography selection using an MROI approach has been addressed in the literature. In Ku et al. (2010), the authors present a methodology for the selection of 19 major fiber bundles of the brain based on a parcellation of white matter and gray matter structures *via* registration from a brain atlas followed by a hybrid approach with anatomic guidance and similarity clustering. In Zhang et al. (2010b), gray and white matter areas are mapped from a DTI brain atlas (Oishi et al., 2009) using a Large Deformation Diffeomorphic Metric Mapping (LDDMM) (Ceritoglu et al., 2009). Then, the tracts of interest are extracted by selecting those fibers that penetrate the atlas-segmented ROIs associated with them and removing fibers that penetrate other areas of the brain. This type of anatomical guidance was also partially employed in Ku et al. (2010).

Although they differ in the approach employed in the definition of the fiber bundles in terms of the ROIs they penetrate or do not penetrate, these contributions, however, share one key element: they rely on the accuracy of the registration process that maps the ROIs from an atlas onto the volume under study. Therefore, the success of the fiber selection depends on the registration, even if the anatomical guidance is perfectly defined. An example in which these methods may fail is easy to picture (see Fig. 1).

In this paper we show that tractography selection approaches based on the MROI paradigm are very sensitive to the registration accuracy for ROI location. Accurate DTI registration is extremely challenging, and even small inaccuracies in the registration process may yield significant errors in the tractography selection results, which carry over to the final results of the white matter analysis process. This being the case, clinical findings based on such methods might not be totally conclusive. Consequently, we propose an alternative approach for robust tractography fiber selection based on geometrical constraints and specifically designed to cope with serious inaccuracies in the registration process. Two tensor atlases as well as other DTI volumes (summarized in Table 1) are employed to provide qualitative and quantitative results that demonstrate that the proposed approach can be used for fiber selection with both accuracy and robustness, compared to related methods in the literature.

Materials and methods

DTI data

Three different types of DTI data were employed in this paper (a summary is provided in Table 1):

- First, a single subject DTI white matter atlas was used, the so-called JHU MNI SS atlas. This is a single-subject atlas (a.k.a. *New Eve*) with a comprehensive white matter parcellation developed at Johns Hopkins University (Mori et al., 2005; Wakana et al., 2004). The subject is a 32 year old female, and the volume size is $181 \times 217 \times 181$ with 1 mm resolution. This atlas is B0-distortion corrected by non-linearly warping DTI data to a co-registered T2-weighted anatomical image. The atlas was linearly normalized to ICBM-152 template (MNI space) and the white matter parcellation map was manually segmented based on FA and color (fiber orientation) information.
- Second, the ICBM DTI-81 white matter atlas was employed (Mazziotta et al., 1995; Mori et al., 2008). It is a stereotaxic probabilistic white matter atlas that fuses DTI-based white matter information with an anatomical template (ICBM-152). This atlas is based on tensor maps obtained from 81 subjects acquired under an initiative of the International Consortium of Brain Mapping (ICBM), and a hand-segmented white matter parcellation map was created from this averaged map. The subjects were healthy right-handed adults ranging from 18 to 59 years of age. All studies were obtained on 1.5 T MR units (Siemens).
- Three DTI datasets composed of 12 healthy young subjects, 10 healthy young subjects and 9 aged participants were employed for the development of the proposed tractography selection method, the creation of a set of deformations to be employed in Experiment 2 and the evaluation of the algorithm in a realistic scenario in Experiment 3, respectively. Mean age and standard deviation was 30.6 ± 4.1 for the first group and 27.6 ± 5.4 for the second group. As for the third group, it is composed of three healthy subjects (67.7 ± 10.1 years of age) and six patients diagnosed with dementia due to Alzheimer's disease, according to the National Institute on Aging-Alzheimer's Association Workgroups guidelines. All patients met the criteria for probable Alzheimer's disease dementia. Three of them met the criteria for mild

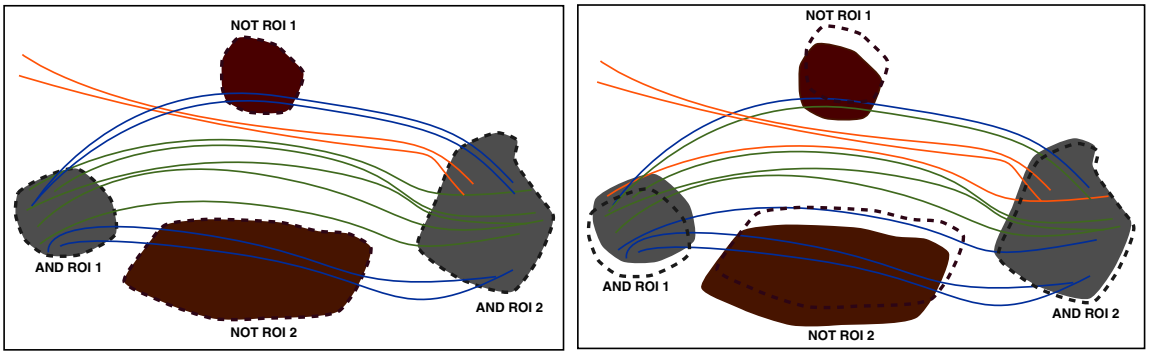

Fig. 1. Graphical description of AND-NOT ROI approaches to tractography selection. Correct fibers are those that penetrate AND ROI 1 and AND ROI 2, but do not penetrate NOR ROI 1 and NOT ROI 2. Fibers that fulfill these criteria are shown in green. Fibers that penetrate any of the NOT ROIs are shown in blue, and fibers that do not penetrate both AND ROIs are shown in orange. Solid objects represent correct locations of ROIs, and dashed-line objects represent ROI locations obtained with registration. (Left) Tractography selection when perfect registration is achieved. (Right) Potential situation when registration errors are present. When ROIs are misplaced, the selected fibers (in green) can differ from those intended.