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Assessment of an automatic pipeline for probabilistic tractography in drug-resistant epileptic patients

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Summary. — Diffusion Tensor Imaging is a special technique of Magnetic Resonance Imaging employed for fiber-tracking studies for neurosurgical planning. The aim of this work is to validate the fiber-tracking probabilistic workflow in drug-resistant epileptic patients explored by stereoelectroencephalography (SEEG) at ASST GOM Niguarda Hospital. The method is based on anatomical Regions-Of-Interest (ROI) definition in a common brain template co-registered on each patient's image. The pipeline was developed in Python language using the probtrackx algorithm for fiber-tracking available in FSL platform with ROIs as input (`http://www.fmrib.ox.ac.uk/fsl/`). The accuracy of the method was assessed by automatically comparing reconstructed fibers with pathways previously elaborated during clinical practice, in which ROIs were drawn manually in each patient's images. In 60% of the cases, automatic fibers were found to be anatomically consistent, if compared to anatomical knowledge, while in 36% of the cases, minimal manual corrections enabled appropriate anatomically consistent fibers to be obtained through a fast process. The proposed fibre tracking methodology suggested the feasibility of the process standardization and the achieved results will be further employed for mutual validation of tractographic process and electrophysiological data, which is the reference method for the clinical validation of fiber-tracking preoperative planning.

1. – Introduction

Diffusion Tensor Imaging (DTI) is a peculiar Magnetic Resonance Imaging (MRI) technique suitable for the analysis of tissue micro-structural morphology. Essentially, it provides information about the extent of anisotropic diffusion of water molecules diffusion and its orientation [1, 2]. One application of DTI is Fiber Tracking (FT), which provides a non-invasive means of studying anatomical connectivity of the brain through the reconstruction of fibrous white matter tissue. Several state-of-the-art FT algorithms were developed through the years, and many are based on definitions of "*a priori*" anatomical structures (Regions of Interest, ROIs) identified on anatomical MRI images for tract reconstruction [1]. Although FT is widely used in neurosurgical applications, such as preoperative reconstruction to plan surgical interventions on the patient, there is a lack of reliable validation of the methodology to be used [2]. Fiber Tracking application is a clinical practice widely employed in the field of epilepsy at the "Claudio Munari" Epilepsy Center of ASST GOM Niguarda for preoperative planning to multimodal integration of the stereoelectroencephalography (SEEG) procedures, which is an intracerebral deep electrodes system implanted in patients to study epileptogenic foci. SEEG experimentally evaluates the patient's different brain signals related to different functions (Visual function, Motor function, Thalamocortical Radiations function, etc.) and is the reference method for FT technology validation. The experience gained inside the Munari Center lays the groundwork for mutual assessment of electrophysiological and imaging data. The aim of this work was to standardize the FT technique, which currently suffers from a strong operator-dependence in defining ROIs [1,2]. Therefore, the FT process currently used in the clinical practice was analysed, and possible solutions were evaluated to develop a more robust fiber tracking technique by reducing possible sources of inter- and intra-operator variability. The achieved results will be further validated to implement the developed pipeline in clinical practice.

2. – Materials and methods

2˙1. *ROIs definition.* – ROIs are anatomical structures considered as starting and way points constraints for fiber-tracking [1]. For this work's purpose, it is of a crucial relevance to delineate a robust strategy for ROIs definition in order to evaluate the process operator-dependence and develop an automatic FT pipeline. The outlined strategy is based on the definition of seed and waypoint ROIs, by two Medical Physics Experts (MPE), on the MNI152 standard brain template [3] by employing the FSL platform [4]. The process has to be iterated 5 times during a time frame of the order of days by both operators. ROIs employed for fiber-tracking are provided by the normalized superimposition of the ROIs defined during each session. Final ROIs, defined on MNI space, are then coregistered on each patient's DTI image through the FLIRT registration algorithm available on the FLS platform, which consists of a linear affine transformation with 12 Degrees of Freedom. The coregistration process is automated through a specifically developed Python pipeline.

2˙2. *Fiber tracking.* – MRI datasets of 30 drug-resistant epileptic patients were employed to proceed with fibers reconstruction in both brain's hemisphere. The Thalamo-Cortical tract (THC), related to sensory stimuli elaboration, includes the fibers of interest in this work. THC tracts' importance lays in the fact that its functionality can be evaluated through electrophysiology data, which is the reference method for the clinical validation of fiber-tracking preoperative planning. To this purpose, an automated FT pipeline was developed in Python language by using the probtrackx algorithm for probabilistic fiber-tracking available on the FSL platform [4] with ROIs (sect. **2**˙1) as inputs. Probabilistic tractography methods take into account the probability distribution of estimates of fibre directions within each voxel, and are therefore able to proceed even when the underlying fibre direction is uncertain, by spreading out to trace alternative routes with varying probability, thereby reducing the false negative rate [2].

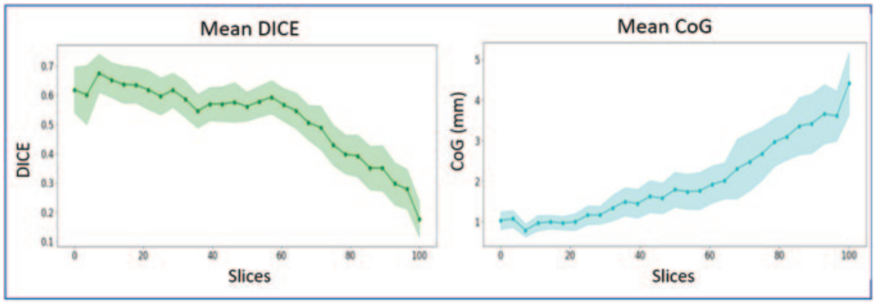

Fig. 1. – DICE and CoG curves with respect to increasing slices. Slices ranges from 0 (seedpoint), to 100 (cortex). Reported values represent a mean with respect to the achieved results for each patient in the database, while uncertainties are calculated as the standard deviation from the mean value.

2˙3. *Inter-operator comparison.* – An inter-operator analysis allows evaluating discrepancies between tracts originated by ROIs defined by the two operators, and the brain areas where the displacement increases. Resulting fibers belonging to the two different sets of ROIs were quantitatively compared by calculating the differences in each slice of their Center of Gravity (CoG) metric and DICE coefficient, which expresses the extent of overlapping between the two volumes under analysis, with values ranging from 0 (no overlapping) to 1 (complete overlapping).

2˙4. *Patient-by-patient validation.* – To assess the validity of the outlined methodology, an MPE is asked to visually and qualitatively assess if tracts automatically obtained for each patient are consistent in terms of anatomical knowledge. Tracts belonging to both operators were rated with an evaluation ranging from 0 (inconsistent tracts) to 1 (consistent tracts) with an intermediate rating of 0.5 if the tract presented a little discrepancy near the cortex if compared to anatomical knowledge. ROIs belonging to incorrect tracts are manually redefined by the operator, and a gold standard tract for each fiber is obtained. The gold standard fiber definition is of crucial relevance to proceed with a final validation of the proposed method with electrophysiology data.

3. – Results

3˙1. *Inter-operator comparison.* – CoG and DICE metrics are firstly calculated between final ROIs identified by the two operators. This step allows assessing if eventual discrepancies between fibres belonging to different operators can be related to ROIs differences. The results of inter-operator comparison showed an average shift in way points ROIs' CoG of 3.55 ± 0.33 mm, while a DICE coefficient equal to 0.67 ± 0.04 showed only partial overlapping between the two structures under analysis. The values obtained represent a mean with respect to the achieved results for each patient in the database, while uncertainties are calculated as the standard deviation from the mean value. Due to THC fiber anatomical displacement, extending from medial brain areas to the cortex following coronal planes direction, it is possible to perform a slice-by-slice evaluation of the selected metrics. This approach allows investigating the trend of the discrepancy between the two set of fibers proceeding towards the cortex. The results obtained for CoG metric and DICE coefficient evaluation are shown in fig. 1.

As shown in fig. 1, a marked discrepancy between different operator's fibers when approaching the cortex is highlighted, reaching DICE values near zero, resulting in

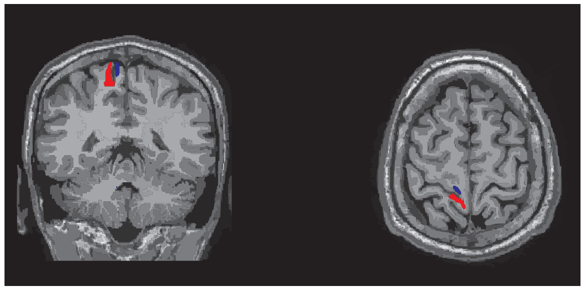

Fig. 2. – The figure outlines an example of a fibre discrepancy between the gold standard tract (red) and a first try of the algorithm providing wrong cortex displacement (blue).

non-overlapping structures, and CoG values up to 5 millimetres, highlighting a strong shift in tracts displacement. The main reason for high discrepancies near the cortex lies in the fact that THC fibers' way point ROIs definition is affected by anatomical variability, since it is located in distal brain sulci, where anatomical variability has to be taken into account. Considering previously highlighted observations, a patient-by-patient evaluation is necessary to identify which of the reconstructed tracts are anatomically consistent.

3˙2. *Patient-by-patient evaluation.* – An estimation of the percentage of automatic tracts belonging to categories defined in sect. **2**˙4 (consistent tracts, cortex discrepancy, inconsistent tracts) is provided:

Consistent tracts	Cortex discrepancy	Inconsistent tracts
60%	36%	4%

By this way, a gold standard tract for each fibre is defined (fig. 2). Tracts classified as anatomically inconsistent, meaning that their volume displacement departs from anatomical knowledge, and fibers which require little modification in their paths near the cortex underwent a new tractography process, after some modifications of correspondent way point ROIs. Since a complete re-definition of ROIs was not necessary, the procedure was not time-consuming and a gold-standard fibre for each tract was achieved.

4. – Conclusion

This study suggests the feasibility of a standardization of the FT process: the process of implementing ROI's and the resulting descriptions of brain fibers in a standardized way is the first step to make a possible systematic work to validate the FT by comparing the results with physioanatomical data obtained by SEEG.

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