Qualitative and quantitative analysis of probabilistic and deterministic fiber tracking

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ABSTRACT

Fiber tracking (FT) and quantification algorithms are approximations of reality due to limited spatial resolution, model assumptions, user-defined parameter settings, and physical imaging artifacts resulting from diffusion sequences. Until now, correctness, plausibility, and reliability of both FT and quantification techniques have mainly been verified using histologic knowledge and software or hardware phantoms. Probabilistic FT approaches aim at visualizing the uncertainty present in the data by incorporating models of the acquisition process and noise. The uncertainty is assessed by tracking many possible paths originating from a single seed point, thereby taking the tensor uncertainty into account. Based on the tracked paths, maps of connectivity probabilities can be produced, which may be used to delineate risk structures for presurgical planning. In this paper, we explore the advantages and disadvantages of probabilistic approaches compared to deterministic algorithms and give both qualitative and quantitative comparisons based on clinical data. We focus on two important clinical applications, namely, on the reconstruction of fiber bundles within the proximity of tumors and on the quantitative analysis of diffusion parameters along fiber bundles. Our results show that probabilistic FT is superior and suitable for a better reconstruction at the borders of anatomical structures and is significantly more sensitive than the deterministic approach for quantification purposes. Furthermore, we demonstrate that an alternative tracking approach, called variational noise tracking, is qualitatively comparable with a standard probabilistic method, but is computationally less expensive, thus, enhancing its appeal for clinical applications.

Keywords: uncertainty, diffusion tensor imaging, probabilistic fiber tracking, variational noise fiber tracking

1. INTRODUCTION

Over the last years, diffusion imaging techniques like DTI,[1,2] DSI or Q-Ball[3] received increasing attention, especially in the neuroimaging, neurological, and neurosurgical[4] community. An explicit geometrical reconstruction of major white matter tracts has become available by fiber tracking (FT) based on diffusion-weighted images. The goal of virtually all FT algorithms is to compute results which are analogous to what the physicians or radiologists are expecting and an extensive amount of research has therefore been focussed on this reconstruction.[1–3,5] GPU implementations[6–8] are able to decrease the computation time by an order of magnitude.

In practice, the interesting structures are not individual fibers, which in any case are impossible to reconstruct since the resolution of diffusion-weighted images is much lower than the diameter of the individual fibers. Instead, the interesting structures are anatomical meaningful bundles that fibers form.

The possibility of FT and the quantification of diffusion parameters has established an abundance of new clinically useful applications and research studies that focus on monitoring the progression of diseases such as amyotrophic lateral sclerosis (ALS) or multiple sclerosis (MS),[9] establishing surrogate markers used in assessing the grade of brain tumors,[10] or initiating therapies to ensure the best possible development of children.[11] Several studies have shown that modified values of fractional anisotropy (FA), relative anisotropy, or diffusion strength

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(ADC) are indicators of diseases that affect white matter tissue. MS lesions have been investigated by ROI-based analysis and voxel-wise FA comparisons by which FA changes have been shown to occur in areas containing lesions and in areas of normal-appearing white matter. Moreover, methods for tract-based quantification have been developed for which parameters are computed depending on the local curvature or geodesic distance from a user-defined origin. These methods allow to automatically determine DTI-derived parameters along fiber bundles and have already been used to mirror disease progression and executive function in MS.[12] Probabilistic methods[5] allow for tracking in regions of low anisotropy and are also used to provide a quantitative measure of the probability of the existence of a connection between two regions. These approaches aim at visualizing the uncertainty present in the data by incorporating models of the acquisition process and noise. The uncertainty is assessed by tracking many possible paths originating from a single seed point and by taking the tensor uncertainty into account. Session reproducibility and subject variability of FT algorithms have been examined in.[13] A first comparison of deterministic and probabilistic approaches, both guided solely by the primary eigenvector, in combination with functional localization of brain tumor patients has been given in.[14] However, no qualitative or quantitative tract-based results of a comparison have been given, on which this paper focuses.

1.1 Contributions

The new contributions of this paper can be summarized as follows:

- The uncertainty in diffusion imaging with respect to fiber tracking and quantification results has been evaluated by comparing different probabilistic and deterministic approaches.
- To the best of our knowledge, all proposed algorithms have been implemented for the first time using one software platform. This gives us the full control over all parameters and constitutes the basis for a fair comparison.
- We performed an integrated examination and comparison of the algorithms, namely, both qualitative and quantitative comparisons.
- We examined specific clinical issues such as the behavior of algorithms in the vicinity of tumors or lesions and have examined more than solely whether probabilistic tracking approaches are better in the area of kissing or crossing fibers. Our strong cooperation with clinical partners permits a rigorous evaluation and verification of our results.
- For clinically relevant cases, we have shown that probabilistic tracking is superior and suitable for a better reconstruction at the borders of anatomical structures. For quantification, the probabilistic FT is significantly more sensitive than the deterministic approach.

2. METHODS

To examine the uncertainty associated with FT and tract-based quantification, we focus on two patient groups: glioma patients and MS patients. Whereas tumors can infiltrate or displace white matter fiber tracts, MS lesions do not necessarily influence the localization or structure of axonal fibers. Rather, MS lesions and the corresponding de- and remyelinization may influence the diffusion parameters along the fibers.[12] Thus, for both groups, we perform FT of bundles of interest, i.e., bundles near the tumor or bundles which can be influenced by lesions. In the case of tumor patients, we mainly focused on qualitative comparisons and visually compared the results in order to assess the differences. Furthermore, we determined the volume of a sheath which wraps the fibers in order to estimate the differences. For the MS patients, we also performed a quantification of several DTI parameters along the tracked bundles.

2.1 Image data

For the quantitative analysis, magnetic resonance images of relapsing-remitting MS patients and healthy controls (10 patients, 10 healthy volunteers) were obtained using a 1.5T scanner (Siemens Avanto, Erlangen, Germany). The subjects were supine and a head coil with a circularly polarized array was used with 2D DTI echo planar imaging, 30 diffusion directions and 2 repetitions. The sequence parameters were: repetition time (TR) 8000

msec, echo time (TE) 100 msec, field of view (FOV) 230 mm, voxel size $2.0 \times 2.0 \times 2.7mm^3$, 55 slices, and a scanning time of 8 minutes. Autoshimming and phase correction were activated.

For the qualitative analysis, magnetic resonance images of tumor patients were obtained using a 3T scanner (Siemens Trio, Erlangen, Germany). The subjects were supine and a head coil with a circularly polarized array was used with 2D DTI echo planar imaging, 12 diffusion directions and 5 repetitions. The sequence parameters were: repetition time (TR) 6400 msec, echo time (TE) 91 msec, field of view (FOV) 240 mm, voxel size $2.5 \times 2.5 \times 2.5mm^3$, 50 slices, and scanning time of 8 minutes. Autoshimming and phase correction were activated.

2.2 Probabilistic and deterministic fiber tracking

In the following, we briefly describe the FT algorithms implemented in MeVisLab, our research and development platform.[15]

2.2.1 Probabilistic fiber tracking using a Bayesian approach

Our Bayesian approach[5] is well-studied and has been used by several other authors, such as.[16] Thus, this approach is our first choice for probabilistic FT. The necessary modeling and estimation of fiber orientation and connection can be described at both global and local levels. At the global level, a theoretical foundation for estimating the probability of a connection between two areas in the brain has been given. At the local level, probability density functions of the fiber orientation can be derived in a theoretically justified way via Bayes' theorem. In addition, a theorem has been integrated that facilitates the estimation of parameters in a constrained version of the popular tensor model of water diffusion.

2.2.2 Probabilistic fiber tracking using variational noise

Although we have fully parallelized the Bayesian approach, its high computation time inhibits use in routine clinical tasks. Thus, we propose another novel approach for FT similar to bootstrapping methods,[17,18] but which is faster and does not need several repetitions of the diffusion-weighted images. The new method, which we have named variational noise FT, allows an efficient computation of diffusion-weighted images with user-defined noise while retaining the MRI noise characteristics. The essential idea is to add complex Gaussian noise to the magnitude images[19] and to track the fibers for each artificially computed diffusion-weighted data set.

For a fair comparison between both probabilistic approaches, the noise of the diffusion-weighted images used for the Bayesian method should match the noise of the images computed by the variational noise technique. In the following, we assume a high SNR so that the noise tends to be Gaussian distributed. If N_{bay} repetitions of each diffusion-weighted image are used to compute one average image for the Bayesian FT, then the variance of this image is σ^2/N_{bay} where σ defines the noise of one single image. Furthermore, if $N_{var} > N_{bay}$ repetitions of each diffusion-weighted image with noise σ are used to compute the image to which variational noise σ_{var} is added, then the variance of an output image of the variational noise technique is $\sigma^2/N_{var} + \sigma_{var}^2$. Consequently, we can compute the noise σ_{var}:

$$\frac{\sigma^2}{N_{bay}} = \frac{\sigma^2}{N_{var}} + \sigma_{var}^2 \Rightarrow \sigma_{var} = \sigma\sqrt{\frac{N_{var} - N_{bay}}{N_{var}N_{bay}}}. \quad (1)$$

2.2.3 Deterministic fiber tracking

The deterministic FT algorithm which we use[20] to compare with both probabilistic approaches is based on the deflection-based approach by Weinstein et al.[21] and makes use of the full diffusion tensor information during tracking. In contrast, commonly employed streamline-based algorithms, such as the FACT (fiber assignment by continuous tracking) method,[1] only consider the largest eigenvector representing the main diffusion direction. In comparison to the method described in,[21] we added a novel moving average estimation of the fiber curvature and anisotropy to the tracking algorithm, which led to more accurate tracking dynamics and more robust termination criteria.

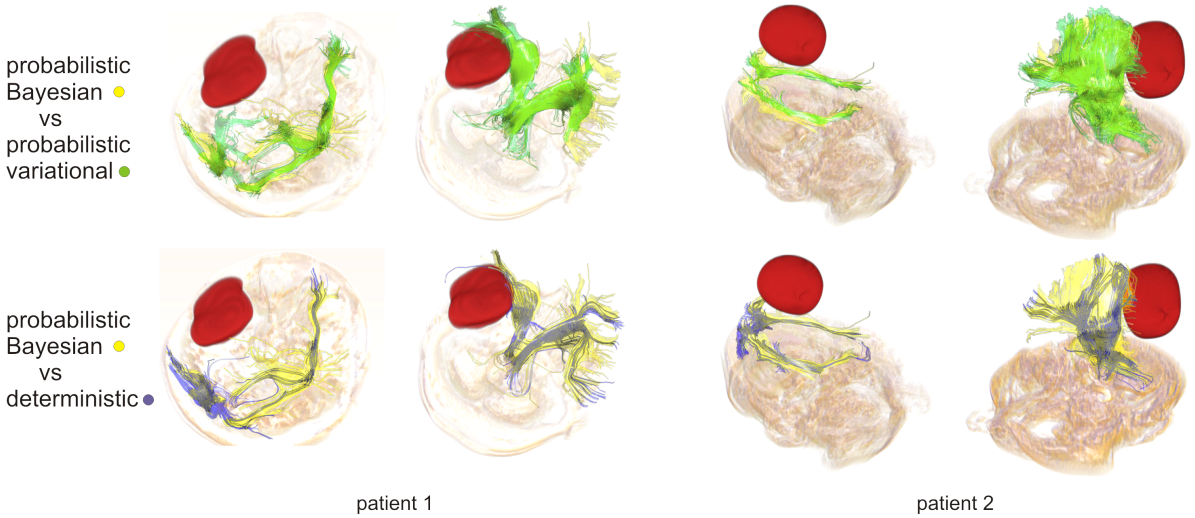

Figure 1. Qualitative comparisons of fiber tracking for two glioma patients. We tracked two important structures, the pyramidal tract and the optical tract. Patient 1: frontotemporal glioma (grade 4), patient 2: progressive astrocytoma (grade 2).

2.3 Qualitative comparisons of fiber tracking (glioma patients)

From a large pool of data sets of glioma patients, we selected some patients for a qualitative comparison. All selected patients have progressive gliomas (grade 4) or progressive astrocytomas (grade 2) next to the pyramidal and the optical tracts. To track the pyramidal tracts, seed regions within the capsula interna were chosen, while for tracking the optical tracts, seed regions in the occipital lobe were used. In all cases, exclusion ROIs (regions of interest) were used to discard unwanted fibers. Moreover, we propose to measure the volume of the sheath that encloses the single fiber tracts. To compute the sheath, we propose a neighboring cells algorithm based on the well-known marching cubes algorithm with which a volume (image) is scanned by discretization into cells. The necessary input volume is determined by voxelizing the 3D fiber tracts.

2.4 Quantitative comparisons of fiber tracking (multiple sclerosis patients)

We have tested both the deterministic and the probabilistic FT (Bayesian) to determine whether and how they allow the detection of differences of diffusion-derived parameters between relapsing-remitting MS patients and healthy controls (10 patients, 10 healthy volunteers). For that purpose, we decided to quantify the superior longitudinal fasciculus (SLF) which has already been shown to be a structure for which differences between MS patients and healthy volunteers can be determined very well using deterministic FT.[12] After extracting the right and left SLF, diffusion-derived parameters such as the FA, axial diffusivity, radial diffusivity, and diffusion strength were obtained along the tracts, and average values were computed. Then these values were recoded linearly to better permit statistical examination. For extracting the SLFs, only fiber tracts were considered which were included by two crop ROIs and values were only computed between those two crop ROIs. More precisely, each fiber is resampled so that all fibers consist of n equidistantly distributed fiber points. Using the resampled fibers, an average center line is computed, used to determine n reference planes depending on the local curvature of the center line. Afterwards, a reference plane is used to determine an average diffusion value at a certain position of the bundle by considering one diffusion value per fiber with the nearest distance to that plane.

The number of fibers of the probabilistic tracking has been aligned with the number of fibers of the deterministic tracking. This process occurs before the tracked structure has been cropped to the focus of interest in the SLF to ensure a valid comparison of the parameters after cropping. Furthermore, common parameters such as minimal FA must be adjusted for both algorithms.

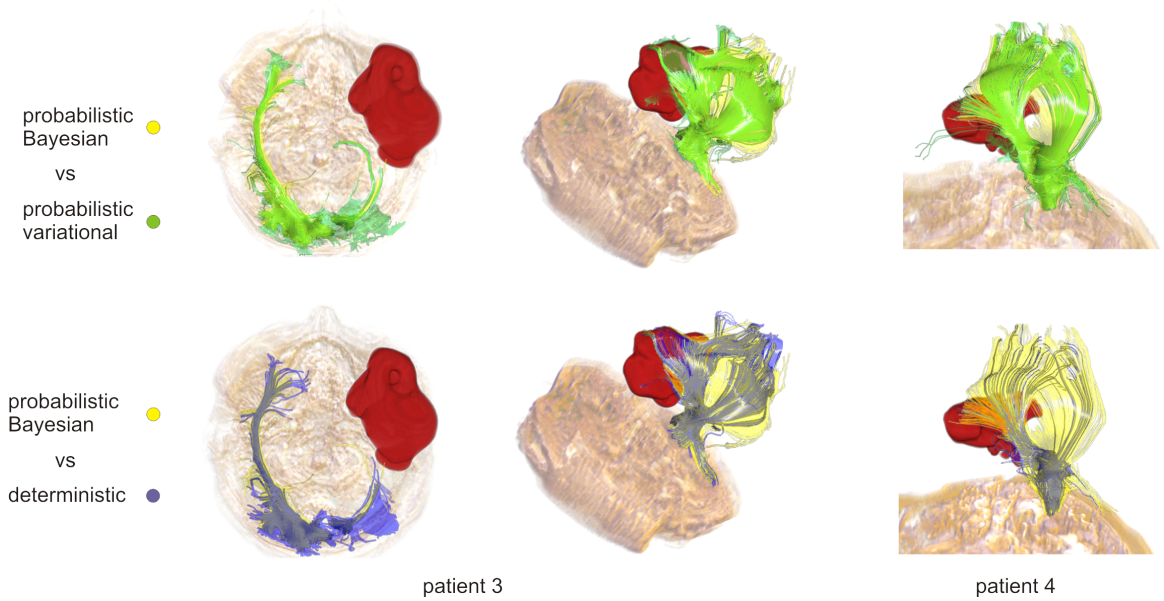

Figure 2. Tracking results of two further glioma patients. The optical tract of patient 4 could not be tracked by any algorithm due to the large tumor. Patient 3: progressive glioma (grade 4), patient 4: glioma (grade 4).

3. RESULTS

3.1 Qualitative results

Some of the qualitative results can be found in Fig. 1 and Fig. 2. In nearly all cases, both probabilistic approaches are superior to the deterministic algorithm. In particular, fibers at the marginal regions of the white matter are more precisely tracked if the probabilistic algorithms are used (patient 1, 2, and 4). Consequently, the sheath volumes differ substantially for the different algorithms (probabilistic results are about 30% higher on average). The differences between the variational noise tracking approach and the Bayesian approach are very small for all patients. There is only one outlier, namely, the pyramidal tract of patient 1, where the Bayesian FT is able to track fibers more lateral which could probably be prevented by adapting the two slightly different stopping techniques.

3.2 Quantitative results

The quantitative results can be found in Tab. 1 and Tab. 2 (appendix). In two of the MS cases, fiber tracts could not be determined between both crop ROIs by the deterministic approach. Thus, these two cases were discarded. We used analysis of variance (ANOVA) through GLM (general linear model) for repeated measurements to analyze the sensitivity of the deterministic and the probabilistic method for pathological alterations in the MS patients. The FA and ADC values of the SLF left and the SLF right were used as dependent variables. The patient versus healthy control status is used as independent variable (between-subject factor), the hemisphere and the type of algorithm (deterministic/probabilistic) as within-subject factors. For the ADC values, there is a main effect for the cerebral hemisphere [F(1,16): 11.027, $p < 0.01$], a main effect for the algorithm used (deterministic vs. probabilistic) [F(1,16): 4.444, $p = 0.05$] and a significant interaction between algorithm used and patient groups [F(1,16): 4.444, p = 0.05]. Moreover, the independent group factor is also significant [F(1,17): 12.085, $p < 0.01$].

Patients had higher ADC values than healthy controls (3.625 vs. 2.25), right hemisphere ADC values are higher than left hemisphere ADC values (3.194 vs. 2.681), in healthy controls the ADC values did not differ between deterministic and probabilistic algorithm (2.25 vs. 2.25), but in patients the probabilistic model yielded higher values than the deterministic algorithm (3.75 vs. 3.5) (compare Fig. 3). Note that these values are not the empiric data itself, but estimated marginal means, thus error-corrected values based on our empiric data.

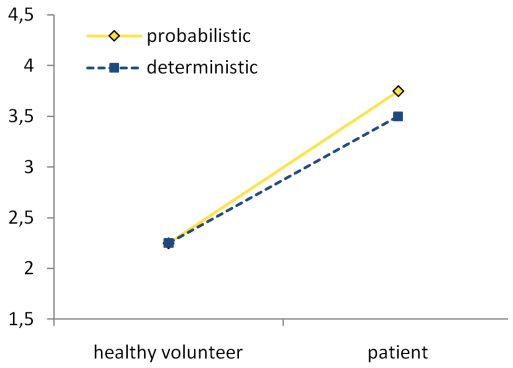

Figure 3. Estimated marginal means (ADC values).

For the FA values, the only significant effect is a main effect for the cerebral hemisphere [F(1,16): 5.47, p = 0.03].

The number of fibers after the cropping varies widely not only between different persons, but also between hemispheres of the same brain. Statistics show that the probabilistic algorithm tracks an average of 254 fibers (SD=199), whereas the deterministic algorithm tracks an average of 188 fibers (SD=167). The standard deviation is high, that it seems impossible to interpret these results at first glance. However, the correlation between the probabilistically and deterministically gained numbers of fibers, found by Pearson test to be 0.89, shows that the trend between the algorithms is congruent. This indicates that the variance of the number of fibers is not due to the type of algorithm or chance, but primarily due to the underlying image data. Additionally, this highly variant but congruent trend indicates a high sensibility towards inter-individual differences in image data and demonstrates reliable algorithms.

4. CONCLUSIONS AND FUTURE WORK

Our qualitative results have shown that both probabilistic approaches are superior for tracking fibers near tumors or MS lesions with respect to completeness, quality and coverage of anatomical structures at their borders. Under the condition that all approaches are parameterized so that they track the same initial number of fibers, the probabilistic approaches are able to compute more fibers that pass two distant crop ROIs, indicating that fewer fibers were aborted during the fiber tracking process. The variational noise fiber tracking produces qualitatively very similar results compared to the Bayesian approach, but is computationally less expensive, thus, enhancing its appeal for clinical applications.

The quantitative results in combination with the qualitative results have shown that the probabilistic fiber tracking is more sensitive than the deterministic approach, especially if measuring the ADC values. The statistically significant interaction effect for ADC values between the algorithm used (probabilistic/deterministic) and the health status can be seen in Fig. 3. This interaction effect results from the fact that on one level of the between-subjects factor (healthy volunteers) the algorithm used has no influence on the ADC scores, on the other level (patients) it influences the values. One can interpret this effect as a brain anatomy related effect of the algorithms used to generate the ADC values. The normal or more ideal brain anatomy of healthy volunteers allows less differentiation between the methods than does the pathological brain anatomy of patients. For quantification, we concentrated on one important fiber structure, the SLF, however, samples of other structures have shown similar results.

It is advisable to combine the quantitative and qualitative results to obtain an overall picture. For example, some MS patients could not be added to the quantitative analysis because only the probabilistic algorithm is able to produce processable results. This indicates that in clinical cases with brain lesions or neuronal diseases, the probabilistic algorithm is the method of choice. Although first papers have already proposed to implement probabilistic approaches on the GPU,[6] this field of research should be examined in the future as probabilistic approaches are still an order of magnitude slower than deterministic solutions.

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APPENDIX A. SPSS SOURCE CODE

We used analysis of variance (ANOVA) through GLM for repeated measurements to analyze the sensitivity of the deterministic and the probabilistic method for pathological alterations in the MS patients. For this purpose, we utilized the statistical analysis software SPSS. The source code for our analysis can be found below. There, adcPro_r defines the mean ADC value which has been measured in MS patients in the right hemisphere using the probabilistic approach. The substring _l defines the left hemisphere and the substring Det denotes the deterministic approach.

```
GLM adcPro_r adcDet_r adcPro_l adcDet_l BY patient
    /WSFACTOR=hemi 2 Polynomial method 2 Polynomial
    /METHOD=SSTYPE(3)
    /PLOT=PROFILE(patient*method patient*hemi)
    /CRITERIA=ALPHA(.05)
    /WSDESIGN=hemi method hemi*method
    /DESIGN=patient.
```

APPENDIX B. MEASUREMENT VALUES

	FA (prob.)	**FA (det.)**	**RD (prob.)**	**RD (det.)**	**ADC (prob.)**	**ADC (det.)**	**AD (prob.)**	**AD (det.)**
mean (right)	0.4130	0.4120	0.000544	0.000545	0.000716	0.000717	0.00106	0.00106
stddev (right)	0.0285	0.0311	$3.48 \cdot 10^{-5}$	$3.26 \cdot 10^{-5}$	$2.84 \cdot 10^{-5}$	$2.58 \cdot 10^{-5}$	$3.40 \cdot 10^{-5}$	$3.78 \cdot 10^{-5}$
mean (left)	0.4190	0.4170	0.000528	0.000529	0.000692	0.000692	0.00102	0.00102
stddev (left)	0.0300	0.0352	$3.05 \cdot 10^{-5}$	$3.14 \cdot 10^{-5}$	$2.89 \cdot 10^{-5}$	$2.69 \cdot 10^{-5}$	$4.30 \cdot 10^{-5}$	$4.65 \cdot 10^{-5}$

Table 1. Control group. FA: fractional anisotropy, RD: radial diffusivity, ADC: diffusion strength, AD: axial diffusivity.

	FA (prob.)	**FA (det.)**	**RD (prob.)**	**RD (det.)**	**ADC (prob.)**	**ADC (det.)**	**AD (prob.)**	**AD (det.)**
mean (right)	0.3680	0.3740	0.000645	0.000643	0.000810	0.000809	0.00114	0.00114
stddev (right)	0.0405	0.0390	$7.50 \cdot 10^{-5}$	$7.80 \cdot 10^{-5}$	$7.36 \cdot 10^{-5}$	$7.74 \cdot 10^{-5}$	$8.46 \cdot 10^{-5}$	$8.80 \cdot 10^{-5}$
mean (left)	0.3900	0.3910	0.000603	0.000600	0.000771	0.000767	0.00111	0.00110
stddev (left)	0.0403	0.0416	$7.90 \cdot 10^{-5}$	$7.60 \cdot 10^{-5}$	$7.53 \cdot 10^{-5}$	$7.33 \cdot 10^{-5}$	$6.87 \cdot 10^{-5}$	$7.14 \cdot 10^{-5}$

Table 2. MS patients. FA: fractional anisotropy, RD: radial diffusivity, ADC: diffusion strength, AD: axial diffusivity.