# Assessing inter-subject variability of white matter response functions used for constrained spherical deconvolution

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**Purpose**: Spherical deconvolution has become one of the most widely used methods to extract white matter (WM) fiber orientation information from DW-MRI data, overcoming the crossing fiber limitations inherent in the diffusion tensor model [1]. Constrained spherical deconvolution (CSD) is already being routinely used to obtain high quality fiber orientation distribution function (fODF) estimates and fiber tractograms [2] and is increasingly used to extract quantitative parameters such as apparent fiber density (AFD) [3]. A crucial step in the CSD pipeline is that of the definition of the response function. Some authors use a model based response (e.g. tensor model), where the model parameters are set to match those expected in the data set [4]. Others extract the response function directly from the data by selecting voxels with fractional anisotropy (FA) above a predefined threshold, as those voxels are believed to contain only a single coherent fiber population [5]. More recently, a recursive calibration method was proposed that does not rely on FA thresholds but instead recursively excludes voxels containing crossing fibers, converging to a set of voxels that only contain coherently oriented fibers [6]. On the other hand, there is also anecdotal evidence that the WM response function is relatively stable across subjects [7], advocating the use of a canonical WM response, at least for healthy subjects. The aim of this study is to investigate the hypothesis that such a canonical WM response is indeed appropriate, by estimating the response functions from a large collection of DW-MRI data sets from unrelated healthy adult volunteers.

**Methods**: *Data sets*: High-quality high resolution DW-MRI data sets of 100 unrelated adult volunteers were downloaded from the Human Connectome Project (HCP) database (54 females, 46 males, 17 subjects 22-25 yo, 40 subjects 26-30 yo, 42 subjects 31-35 yo and 1 subject > 35 yo) [8,9]. Relevant DW-MRI parameters: 18 b=0 images and b=1000, 2000 and 3000 s/mm$^2$ (90 diffusion directions each); TR/TE=5520/89.5 ms; 1.25mm isotropic resolution. *Pre-processing*: Each DW-MRI data set had already undergone motion and eddy current correction and EPI distortion correction using reversed phase encoded images as part of the HCP processing pipeline [9]. In addition, we corrected spatial intensity inhomogeneity (bias field) using [10] as explained in [3]. *Response function estimation*: Spherical harmonics (SH) coefficients of the response functions were estimated from the data for each b-value independently using the recursive response function calibration tool in MRtrix3 [11], which is similar in spirit to [6]. The maximum SH order of the coefficients estimated for each b-value was: 0, 4, 6 and 8, for b=0, 1000, 2000 and 3000 s/mm$^2$, respectively. Note that, as the response function is assumed to be axially symmetric, all m=0 coefficients are zero and there is only one coefficient to be estimated per even order. Normalization of the intensities across subjects was performed directly on the response functions as follows. First, the average response function of all 100 (unnormalized) response functions was calculated for each b-value. Subsequently, the multi-shell response functions for each individual were scaled with a single scalar to match the average multi-shell response function as close as possible, using a Euclidian norm as a distance measure. After scaling, the average response function was recalculated and the procedure was repeated until convergence. *Assessment of variability*: The mean $m$ and standard deviation $s$ of the SH coefficients were calculated across all 100 subjects (see Table 1). To show the extent of the variability in relation to the mean of the population, we also calculated the relative standard deviation $\mathrm{RSD\%} = (s * 100)/\mathrm{abs}(m)$.

**Results**: As expected, RSD% across the 100 subjects is increasing as a function of both b-value and SH order (see Table 1). RSD% starts at 0.9% for b=0 s/mm$^2$ and order 0, and reaches a maximum value of 11.3% for b=3000 s/mm$^2$ and order 8. Fig. 1 relays the same information by means of polar plots of the mean response functions and their 95% CI. Overall, variations of the response functions across the population are low. Fig. 2 shows the fODFs obtained by constrained spherical deconvolution (CSD) of a single subject both using its own subject-specific response and the most dissimilar subject-specific response found among the 100 subjects. Only very subtle differences can be observed in the fODFs.

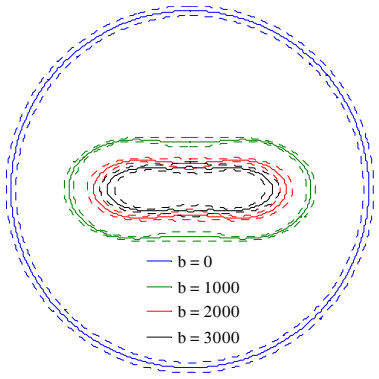


***Fig. 1**: Polar plot of the average response functions (solid lines) and their 95 % CI (dashed lines) for different b-shells*

| order / b s/mm$^2$ | 0 | 2 | 4 | 6 | 8 |
|---|---|---|---|---|---|
| **0** | 999.7 ± 9.2 (0.9%) | | | | |
| **1000** | 498.3 ± 5.3 (1.1%) | -136.7 ± 6.2 (4.5%) | 24.1 ± 1.8 (7.6%) | | |
| **2000** | 336.4 ± 7.9 (2.4%) | -129.0 ± 6.2 (4.8%) | 42.3 ± 3.2 (7.5%) | -9.5 ± 0.9 (9.6%) | |
| **3000** | 267.6 ± 8.4 (3.2%) | -108.6 ± 5.7 (5.3%) | 46.6 ± 3.4 (7.4% ) | -14.9 ± 1.4 (9.7%) | 3.5 ± 0.4 (11.3%) |

***Table 1:** Mean ± standard deviation (RSD%) of the SH coefficients across 100 subjects*

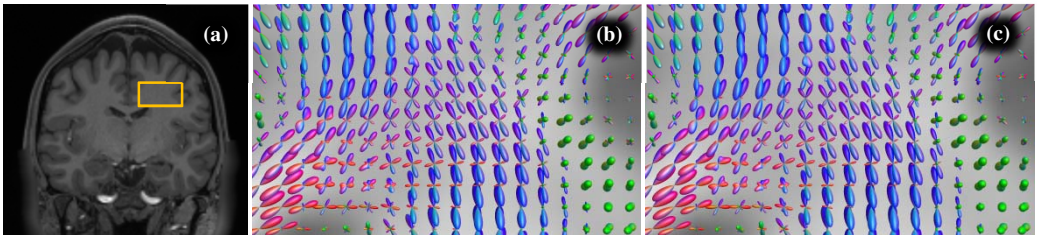


***Fig. 2**: fODFs of a single subject in the region highlighted in (a) using both its own subject-specific response (b) and the most dissimilar subject-specific response found among the 100 subjects.*

**Discussion**: Using a large collection of high quality DW-MRI data sets from unrelated healthy adult volunteers, we have shown that the variability of the WM response across subjects is low, indicating that a canonical response function might indeed be appropriate, at least for healthy subjects. This is true in particular for AFD studies, which use a study-specific response function that is obtained by averaging the response functions from all study participants. In that case, the inter-study variability of the WM response functions would be even smaller than the inter-subject ones reported here.

**References**: [1] Tournier et al., NeuroImage 23:1176-1185, 2004; [2] Farquharson et al., J Neurosurg 118:1367-1377, 2013; [3] Raffelt et al., NeuroImage 59:3976-3994, 2012; [4] Dell'Acqua, IEEE Trans. Biomed. Eng. 54:462-72, 2007; [5] Tournier et al., NeuroImage 35:1459-1472, 2007; [6] Tax et al., NeuroImage 86:67-80, 2014; [7] Tournier et al., NMR Biomed. 26:1775-1786,2013; [8] Van Essen et al., NeuroImage 80:62-79, 2013; [9] Van Essen et al., NeuroImage 80:62-79, 2013 [10] Tustison et al., Insight Journal, 2009. [11] Tournier et al., Int J Imaging Syst Technol 22:53-66, 2012.