Introduction. Multiple works have shown that the diffusion attenuation in a voxel significantly deviates from a monoexponential decay, providing evidence that the Gaussian assumption underlying diffusion tensor imaging (DTI) is not appropriate to accurately represent the diffusion-weighted (DW) signal in the voxel. The biophysical mechanisms responsible for this non-monoexponential behavior are numerous and remain under investigation [Yablonskiy2003, Schwarcz2004, Assaf2005, Minati2007, Mulkern2009]. Particularly, it can arise from the presence of multiple fascicles with heterogeneous orientations in voxels (intra-voxel orientation heterogeneity, IVOH) [Minati2007]. Additionally, when using short diffusion pulse duration δ, it may reflect the mixing of unrestricted (free) diffusion, hindered diffusion (arising from water molecules bouncing on the membranes of the cells in the extra-axonal space) and restricted diffusion (arising from the water molecules in the intra-axonal space) for each fascicle [Assaf2005]. However, when imaging with a clinical scanner with long δ, long echo time (TE) and low signal-to-noise ratio, it is not clear that a non-monoexponential decay can be observed for a single fascicle. In this work we hypothesize that, with a clinical scanner, the observed signal arising from a single fascicle may be monoexponential and that the non-monoexponential behavior observed in voxels may reflect predominantly the IVOH and the presence of an additional compartment that is macroscopically isotropic at the measured diffusion scale. We focused on imaging a region containing a single fascicle orientation, the body of the corpus callosum (CC, Fig.1), to eliminate the effect of IVOH. We estimated the parameters of an unrestricted diffusion compartment and investigated the residual diffusion decay when subtracting the contribution of unrestricted diffusion.

Method. Diffusion-weighted magnetic resonance imaging was carried out on a healthy volunteer using a Siemens 3T Trio clinical scanner with a 32 channel head coil (FOV=220mm, matrix=128x128, in-plane resolution=1.7x1.7mm², slice-thickness=2.0mm, TE=126ms, TR=3sec). We first performed an experiment to determine the optimal DWI protocol that ensures uniform SNR across increasing b-values. To this end, we acquired various b-value images between 500 and 5000 in which we measured the SNR. We performed a regression analysis to describe the SNR as a function of the b-value and determined the number of repetitions N_repetition(b) necessary to ensure uniform SNR across all b-values, given by:

\[
N_{\text{repetition}}(b) = \left[ 21/[47.14\exp(-0.0033b) + 32.36 + b^{-0.199}\] \right]^2
\]

We then focused on imaging the body of the corpus callosum (Fig.1). We measured the diffusion attenuation in both the parallel and perpendicular directions with respect to the fascicles (Fig.1a), with various b-values ranging from 500 to 5000 by increments of 250 with constant δ and constant diffusion time separation Δ, by modulation with various diffusion gradient norms. The number of repetition for each b-value was determined by using Eq.1, resulting in up to N_repetition(500)=17 repetitions for b=5000 and a total of 548 DW images. We acquired 15 slices with TR=3sec, long enough to avoid any T1-weighted signal. We also imaged a multi-shell HARDI (Fig.1b) composed of 5 b=0 images, 30 b=1000 images and 15 images at each of b=1500, b=2000, b=2500 and b=3000, leading to a total of 95 images. The gradient orientations were maximally separated across the shells using the electrostatic repulsion model between multiple subsets [Cook2007]. We investigated the diffusion decay in a ROI of the CC (Fig.1c) both in the parallel and perpendicular direction with respect to the fascicles (see Fig.2). The ROI was carefully selected to avoid any partial voluming with CSF. We considered a multi-compartment model with one fascicle represented by a full tensor and an unrestricted compartment modeled by an isotropic tensor. The parameters were estimated using the multi-shell HARDI (Fig.1b). We subtracted the estimated amount of unrestricted diffusion to the original DW signal and investigated the residual attenuation (Fig.3).

Results. Fig.2 shows that when ignoring the unrestricted diffusion, the signal arising from the densely aligned fascicles of the CC significantly deviates from a monoexponential in the perpendicular direction (radial diffusion), even at moderate b-values. In contrast, Fig.3 shows that when subtracting the unrestricted diffusion contribution, the residual radial diffusion decay is well described by a monoexponential decay.

Conclusion. Our results indicate that with a clinical scanner with long δ, when subtracting the contribution of unrestricted diffusion, the remaining radial signal arising from a single fascicle is well described by a monoexponential decay. When modeling the unrestricted diffusion with an isotropic tensor, each single fascicle may be well represented by a diffusion tensor. We speculate that, with long δ as generally utilized to minimize TE and maximize the SNR [Yeh2010], each spin has sufficient time to bounce on the membranes of the cells (hindered diffusion) and to explore a large portion of the space. The spin position tagged by the first diffusion pulse is the mean of all positions over the explored space and that average position is very close to the one untagged by the second pulse very quickly. This may explain the little observable evidence of hindered diffusion at long δ. A limitation of our experiment may be the long TE leading to a relatively low SNR. The parallel attenuation reaches the noise floor very rapidly and additional low b-value measurements may be required for its characterization.