Classification of axon diameter properties using machine learning

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Introduction: Diffusion MRI opened new horizons in imaging of white matter micro-structure by providing the first *in-vivo* measure of axon diameter through the AxCaliber [1, 2] and ActiveAx [3] frameworks. In AxCaliber, the estimation of the axon diameter distribution (ADD) is done by simultaneous analysis of multiple b-value datasets measured at different diffusion times. Although the bio-physical model of AxCaliber is fairly simple, in many cases the problem is ill-posed and the estimation of its numerous parameters (hindered and restricted diffusivity, their volume fraction and the axon diameter distribution function) usually requires imposing constraints on their range. In this work, we suggest formulating AxCaliber's framework as a classification problem rather than an optimization one. Using statistical learning of predefined ADD functions and their simulated signal decay, we suggest computing probability maps of different ADD distributions.

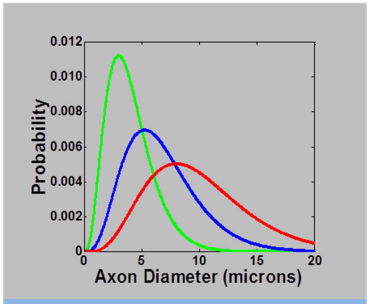

Fig. 1 – The 3 different axon diameter classes: narrow (green), intermediate (blue) and wide (red).

Methods: ***MRI protocol:*** Healthy subjects (n=6) were scanned with a protocol that included a series of DW EPI acquisitions with the following parameters: Four diffusion time (Δ=28, 48, 68 and 88ms), δ =21ms, resolution of 1.5x1.5x3 mm^3, 28 diffusion gradient increments (linearly from 0 to 4G/cm) applied only along the x-direction (perpendicular to the CC).

Statistical learning: We trained a classifier for five different diffusion components: three restricted diffusion components of different axonal diameter composition (narrow, intermediate and wide, Fig. 1) and two hindered diffusion components for diffusion in extra-axonal space ($D=1.5mm^2/s$) and in CSF ($D=4mm^2/s$). The training set included the signal decay for each of the five components generated from the AxCaliber model (Fig. 2). Principal component analysis was applied to the simulated signal decay and the model dimension decreased from 112 to 24 (6 first principal components for each of the 4 Δs). A regularized multinomial logistic regression model was trained and applied to real data. The real data was first fitted with a smooth spline and then projected according to the principal directions. Then the classification model was applied and the probability for each class was calculated.

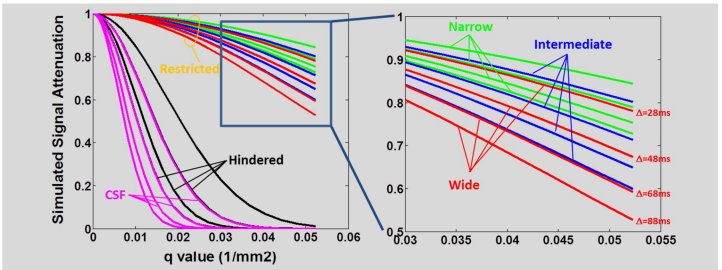

Fig. 2– The training set including the 5 components: diffusion in CSF (magenta), extra-axonal matrix (black) and in axons with narrow (green), intermediate (blue) and wide (red) diameter distributions. On the right, the section in the training set that corresponds to the axonal components is enlarged. Each component has 4 decays at the different diffusion time (noted only for the wide axonal distribution to ease the visualization).

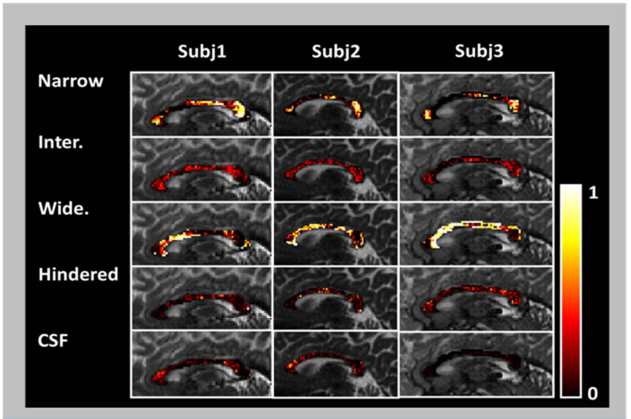

Fig. 3– The model prediction for each of the 5 classes for data acquired from 3 different subjects

Results & Discussion: Figs. 1 and 2 describe the training set. By inspecting the signal decay curves (Fig. 2) for each of the components, it is evident that the signal decays overlaps and obviously mathematical modeling of such differences will require large number of sampling points with high SNR – conditions that are rarely met in a clinical setup. It should be noted that the training set included ten repetitions of the simulated data shown in Fig. 2 with different random Rician noise. Fig. 3 shows the model prediction for real data of three different subjects. The model predicts that the narrow distribution component will have the highest probability in the genu and splenium of the corpus callosum while the wide distribution will have the highest probability in the body. This distribution of the axon diameter distributions is expected from and in agreement with previous histological studies [4]. The intermediate axon diameter distribution is roughly evenly distributed across the corpus callosum as well as the hindered (extra-axonal) component. The CSF component seems to have high contribution at the edges of the corpus callosum.

Conclusions: Diffusion MRI has great potential in revealing the microscopic features of white matter; however the problem might become ill-posed when the model is complex and only a small number of sampling points exist. In this work, we showed that using statistical learning approach we can produce probability maps for predefined, biologically relevant axonal distribution functions. This has great advantage for future research as it allows a more robust means to characterize the axonal diameter properties of different white matter fascicles. Exploring the probability of different axonal populations could be used as a statistical feature to compare between regions or different subject populations.

References: 1. Barazany, D., Basser, P.J. & Assaf, Y. *Brain* **132**, 1210-1220 (2009). 2. Assaf, Y., Blumenfeld-Katzir, T., Yovel, Y. & Basser, P.J. *Magn Reson Med* **59**, 1347-1354 (2008). 3. Alexander, D.C*., et al*. *Neuroimage* **52**, 1374-1389 (2010). 4. Aboitiz, F., Scheibel, A.B., Fisher, R.S. & Zaidel, E. *Brain Res* **598**, 143-153 (1992).