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Microstructural characterization of demyelinating disease: ActiveAx vs Diffusion Tensor Imaging. A simulation study

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1. Purpose

ActiveAx[1] is a compartimental model of the diffusion processes in white matter. Its output parameters are potentially sensitive to demyelination and axonal loss, two of the pathological processes most often observed in neurodegenerative demyelinating diseases -NDDs. Their implementations could be very potential in the direction of early diagnosis of NDDs but their sensitivity has to be assessed using a clinically feasible acquisition protocol.

The purpose of this study is to compare the sensitivity of ActiveAx model with that one of DTI, in microstructural characterization, using a clinically feasible acquisition protocol. DTI is nowadays the Diffusion Weighted Imaging technique most frequently used in revealing axonal damages. This is a simulation study.

References [1]D.C.Alexander Neuro Image 52 (2010) 1374–1389

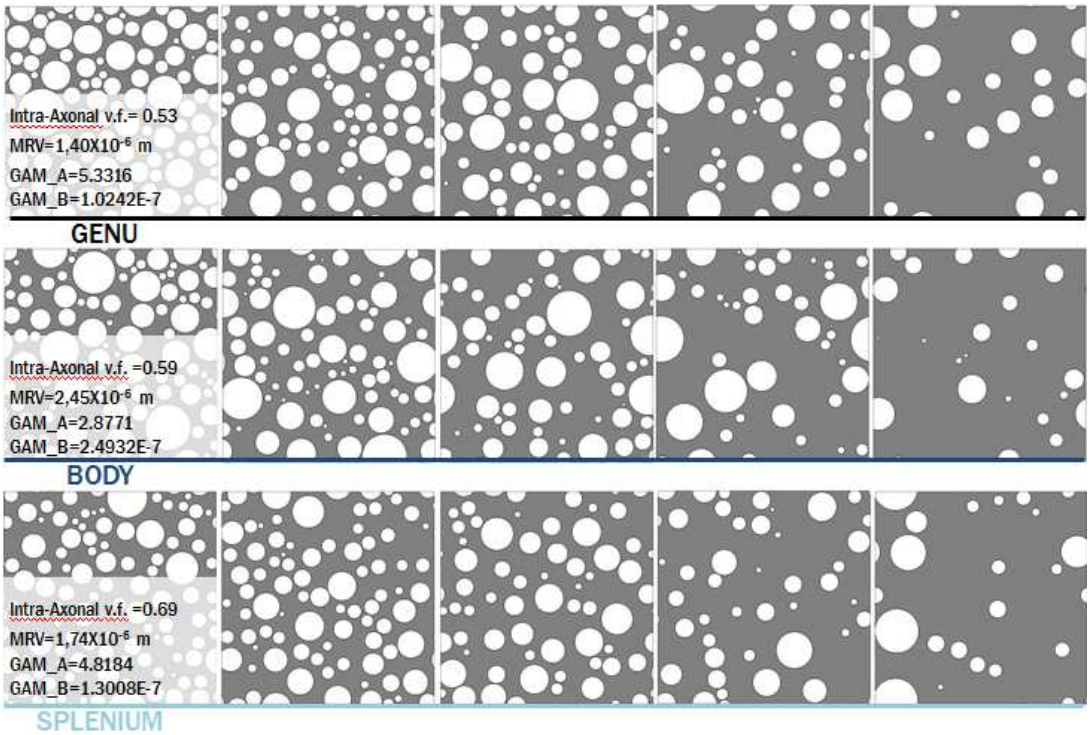
2. Material and Methods

We used Camino[2] diffusion simulation system to provide synthetic RM signals from water molecules in restricted geometries for a certaint acquisition protocol (AP).

A total of 240 substrates have been modeled to simulate three regions of the Corpus Callosum (CC) in 16 different conditions of demyelination (changing axonal membranes permeability[3]) and 5 of axonal loss (axonal density, i.e. intra-axonal volume fraction).

Each region of CC is modeled by a certain number permeable parallel cylinders with the axon radii gamma distribution histologically measured by Aboitiz[4] in CC.

In Figure, the Gamma Function parameters GAM_A and GAM_B and the Mean Radius by Volume (MRV) are presented.



The AP used for ActiveAx is clinically feasible, as per Sneider[5] proposal. It takes 25 minutes (108 acquisitions); the maximum gradient strength is 87mT/m so it is achievable in a common 3T scanner. The AP chosen for DTI is standard in clinical practice and it takes 10 minutes (30 acquisitions) with b = 1000s/mm^2.

References [2] Cook Proc. Intl. Soc. Mag. Reson. Med. 20 (2006), Berlin. [3] http://www.camino.org.uk [3] Nilsson Proc. Intl. Soc. Mag. Reson. Med. 18 (2010). [4] F.Aboitiz Brain Res 1992; 598: 143–153 [5] T.Schneider Proc. Intl. Soc. Mag. Reson. Med.20 (2012).

3. Results

All the output parameters are sensitive to both the pathological processes of demyelination and axonal loss, except Axial Diffusivity (DTI).
Axon Radius Index (ARI) - Activeax - and Fractional Anisotrophy (FA) - DTI - are the most sensitive.
For each output parameter p, a 'sensitivity index' S_p is introduced to quantify the sensitivity of p to changes in permeability - P or axonal density -D:

$$S_p(P/D) = \Delta_p / [\Delta(P/D) \cdot \sigma_p]$$

where Δ_p is the variation of p values corresponding to the variation interval $\Delta(P/D)$ of P or D; σ_p is the mean of the p standard deviations calculated on 10 independent NOISE trials for each substrate conditions setting. For example, in the Splenium, in absence of axonal loss, for a change in permeability of $\Delta(P) = 0.6$ we observed a variation of the output parameter ARI from 0.15×10^{-5} m to 2×10^{-5} m wich corresponds to a $\Delta_{ARI} = 1.85 \times 10^{-5}$ m. The mean of standard deviations is $\sigma_{ARI} = 0.1 \times 10^{-5}$ m, so $S_{ARI}(P) = 30.8$.
The 'sensitivity index' S_p (P) was calculated in healthy condition of Axonal Density (without axonal loss); $S_p(D)$ was calculated with a permeability equal to zero (in absence of demyelination).
In the following list there are the results averaged over the three CC regions.

OUTPUT PARAMETERS	SENSITIVITY INDEX	
	Permeability	Axonal Density
ARI	25,7	8,3
FA	16,8	19,3
MD	12	13,3
RD	19,4	16,7

4. Conclusion

Overall ARI is the most sensitive parameter to demyelination, rather FA is the most sensitive to axonal loss. The difference is that ARI is much more sensitive to demyelination than to axonal loss (so it could be able to distinguish between the two pathological processes), while FA has substantially the same sensitivity and cannot detect any differences between them.
In addition ARI can estimate (considering its error bars) the actual mean axonal radius
(weighted by axonal volume) in the synthetic tissues. In early stages of white matter tissue damage, in NDDs, demyelination appears before axonal loss, so ARI seems to be the most powerful parameter to characterize the lesions. A unique property of ARI parameter is that it can give information about the axonal radii distribution in healthy tissues; nowadays no imaging technique, used in the common clinical practices, succeeds in this.
This simulation study encourages to validate these results in the clinical practice.

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