On the use of the two-pool model to improve the accuracy of axon calibration

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Target audience This abstract is intended for microstructure modeling community, in particular for axon diameters inference

Purpose We here propose to study the reason for the systematic overestimation of the smaller radius in available axon diameter mapping techniques such as AxCaliber [1] or ActiveAx [2]. In these studies, white matter is decomposed using the CHARMED model relying on the use of two compartments, a restricted compartment corresponding to axons modeled as impermeable cylinders, and an hindered compartment corresponding to the extra-cellular space and glial cells with low residence time modeled using a Gaussian distribution. Recent studies[3] have introduced an alternative model stemming from the assumption of a biphasic behaviour of water molecules in an environment restricted by membranes : water molecules close to the membranes have a slow diffusivity characterized by a high anisotropy while those far from the membranes are characterized by a fast diffusivity and a slower anisotropy, yielding the two-pool model. In [4], we developped the equation of the signal attenuation for a two-pool thick layer cylinder for a PGSE experiment under the Gaussian phase distribution approximation . This model is composed of two pools of water molecules : a layer of molecules with a slow diffusivity (the membrane is in in the middle of this layer) and a cylinder with a fast diffusivity, corresponding to the molecules far from the membranes. This study shows how attenuations for small radii (<=3um) from the two-pool model when varying the thickness of the layer close to axonal membranes can be similar to attenuations from the simple cylinder model with higher radius.

Methods - The echo attenuation under the Gaussian phase distribution approximation for a PGSE experiment using a two-pool cylinder model of the axon is given for the fast part by the echo attenuation in a cylinder introduced by [4]. The slow attenuation, corresponding to the attenuation of the layer around the membranes (the membrane is in the middle of the slow layer) is developed in [5], assuming no exchange between the pools:

$$I = \frac{r_i^6}{\beta_{1m}^2} \times \left(Y_1(\beta_{1m})' \left[\frac{J_2\left(\frac{\beta_{1m} r_o}{r_i}\right) r_o^2}{r_i^2} - J_2(\beta_{1m}) \right] - J_1(\beta_{1m})' \left[\frac{Y_2\left(\frac{\beta_{1m} r_o}{r_i}\right) r_o^2}{r_i^2} - Y_2(\beta_{1m}) \right] \right)^2$$

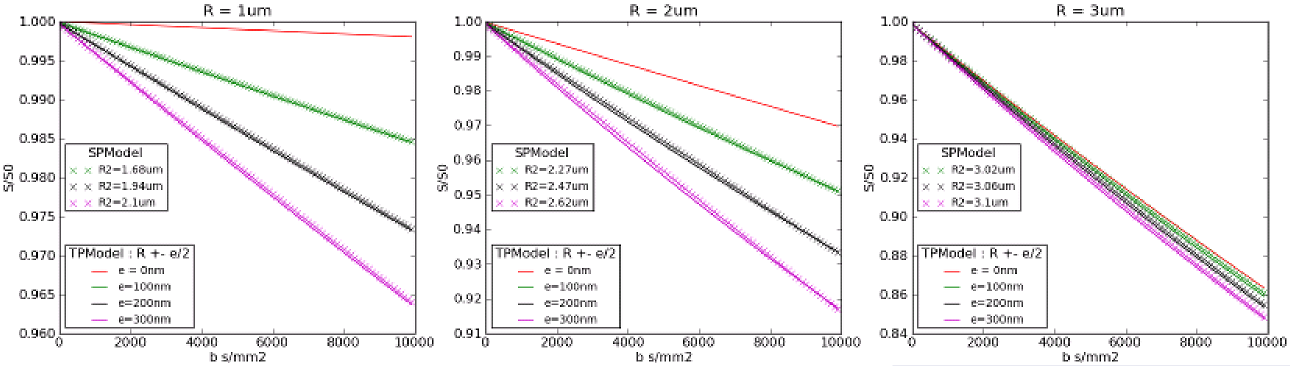
Ji/Yi the bessel functions, Dslow the slow diffusion coefficient, ri = R - thickness/2, ro = R + thickness/2, β_{1m} the eigenvalues for Neuman's conditions, δ, Δ the PGSE parameters.

$$A_{1m}'^{-1} = \frac{r_i^2}{2\beta_{1m}^2} \left[\left(\frac{\beta_{1m}^2 r_o^2}{r_i^2} - 1 \right) \left(J_1\left(\frac{\beta_{1m} r_o}{r_i}\right) Y_1(\beta_{1m})' - Y_1\left(\frac{\beta_{1m} r_o}{r_i}\right) J_1(\beta_{1m})' \right)^2 - (\beta_{1m}^2 - 1)\left(J_1(\beta_{1m})\, Y_1(\beta_{1m})' - Y_1(\beta_{1m})\, J_1(\beta_{1m})'\right)^2 \right]$$

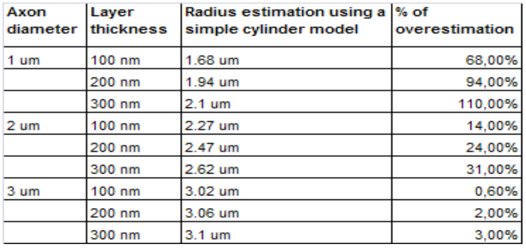
$$< \phi^2 >= 2\gamma^2 g^2 \frac{1}{(r_o^2 - r_i^2)} \sum_{m=1} A_{1m}' I \left[\frac{2D_{slow}\frac{\beta_{1m}^2}{r_i^2}\delta - 2 + 2e^{-\frac{\beta_{1m}^2}{r_i^2}D_{slow}\delta} + 2e^{-\frac{\beta_{1m}^2}{r_i^2}D_{slow}\Delta} - e^{-\frac{\beta_{1m}^2}{r_i^2}D_{slow}(\Delta+\delta)} - e^{-\frac{\beta_{1m}^2}{r_i^2}D_{slow}(\Delta-\delta)}}{D_{slow}^2 \frac{\beta_{1m}^6}{r_i^6}} \right] \quad E_{slow\perp} = \exp\left(- < \phi^2 > /2\right)$$

We used this model to compute the echo attenuation for several small radii from 1µm to 3µm with various thickness of the low-diffusivity layer for a range of b-values from 0 s/mm2 to 10000 s/mm2 with a fixed δ= 29,74ms and Δ= 35,74ms and an increasing gradient strength from 0 to 80mT/m. The echo time is set to TE=65ms.The fast and slow pool diffusivities were set to 10^{-9} m²/s and 10^{-10} m²/s respectively. The echo attenuation computed for each thickness of the layer was used as input of a MCMC algorithm to be fitted using the simple single pool cylinder model, in order to compare the resulting radius obtained using this model to its ground truth.

Results - Figure 1 depicts the echo attenuations obtained for 1 µm, 2 µm, 3 µm axon diameters. Solid lines correspond to the echo attenuations for the two-pool model using different layer thicknesses, and the crosses correspond to the same plot under the assumption of the simple cylinder model using the mean radius stemming from the MCMC fit.This data show that for a small radius (<3um), the echo attenuation for each layer can be misinterpretated as an echo attenuation coming from a one-pool cylinder model characterized by a bigger radius. Table 1 summarizes the results for different layer thicknesses and demonstrates that for small axons of a micrometer diameter, the error on the measurement varies from 68 % to 110 %, giving a putative explanation to the systematic overestimatation of small axon radii using the single pool cylinder. The difference for the radius of 2 µm is lower but still remains significant. We also demonstrate here that for radii greater than 3 µm, the simple pool model becomes a good estimator of the actual axon diameter, since the layer thickness becomes small with respect to the axon diameter, as demonstrated by the computed error not exceeding 3 % for the bigger layer.



Discussion/Conclusion- This work shows that the overestimation observed in the axon calibration studies using CHARMED model for radii smaller than 3um could be possibly explained by the presence of two different pools of water molecules, near and far from the membranes with respectively a slow and fast diffusion coefficient. Indeed, we observed that, for different thickness of the layer, the echo attenuation could also be mathematically well described by the one-pool model used in those studies, but gives overestimated radii for smaller ones. In the future, we will check the adequacy of the two-pool model on real human data, in order to confirm its ability to probe accurately small radii.



Axon diameter	Layer thickness	Radius estimation using a simple cylinder model	% of overestimation
1 um	100 nm	1.68 um	68,00%
	200 nm	1.94 um	94,00%
	300 nm	2.1 um	110,00%
2 um	100 nm	2.27 um	14,00%
	200 nm	2.47 um	24,00%
	300 nm	2.62 um	31,00%
3 um	100 nm	3.02 um	0,60%
	200 nm	3.06 um	2,00%
	300 nm	3.1 um	3,00%

References - [1] Assaf Y et al, Magn.Reson.Med.59(6):1347-54(2008) [2]Alexander DC et al, NeuroImage.52(4):1374-89(2010) [3]Le Bihan et al, Neuroimage. 2012 1;62(1):9-16 [4] Van Gelderen P. et al, J.Magn.Reson B, 103:255-260(1994) [5] Lebois et al, ISMRM Workshop 2013