# EFFICIENT AXON DIAMETER DISTRIBUTION RECOVERY WITH LONG DIFFUSION TIME

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TARGET AUDIENCE: Diffusion MRI scientists. Biophysical modelers.

PURPOSE: This work proposes an original method to recover axon diameter distributions (ADD) of white matter (WM) using nuclear magnetic resonance. The technique might be interpreted as an interesting simplification of the AxCaliber framework [1], which leads to a simpler model and an extremely faster acquisition protocol. To test and validate our method, we use the open-source toolkit CAMINO [2] for computing Monte-Carlo simulations of NMR signals. Promising experimental results illustrate the potential of the proposed method.

METHODS: **Tissue model.** As in AxCaliber [1], we consider an area of WM composed of a single fiber path where we model the attenuation E(q) of one single NMR profile perpendicular to the axis of the fibers. Then we can write $E(q)= c\ E_r(q) +(1-c)E_h(q)$, where $E_r$ and $E_h$ are the echo attenuations due to the restricted (intra-axonal) and hindered (extra-axonal) compartments respectively, and c is the intra-axonal water volume fraction. We suppose that the signal is obtained using the PGSE sequence, assuming the short gradient pulse approximation (SGP). The hindered diffusion is modelled as a Gaussian function $E(q)=\exp(-4\pi^2q^2/(\Delta\ D_h))$, where $\Delta$ is the diffusion time and $D_h$ is the apparent diffusion constant of the hindered compartment. The restricted compartment is modelled as an ensemble of parallel cylinder with Gamma distributed radii. Then, the signal attenuation can be written as in [3]:

$$E_r(q) = \int r^2 f(r;\alpha,\beta) E_{cyl}(q,r)dr \Big/ \int r^2 f(r;\alpha,\beta)dr$$

where $f(r;\alpha,\beta) = \beta^\alpha r^{\alpha-1} e^{-\beta r} r\ /\Gamma(\alpha)$ is the Gamma pdf and $E_{cyl}(q,r)$ is the attenuation due to a single cylinder of radius r. In AxCaliber [1], the attenuation from a cylinder is modelled by the expression given in [4] which includes the dependence on the diffusion time $\Delta$ and the bulk diffusivity $D_r$ of the restricted compartment. Here, we model $E_{cyl}$ under the long time diffusion limit regime ($\Delta$ big) as in [3]. Then, we can show that the attenuation is given simply by $E_{cyl}(q,r)=[J_1(2\pi qr)/(\ \pi qr)]^2$, where $J_1$ is the 1th order Bessel function. Substituting the formulas for $E_{cyl}$ and f into $E_r$ and integrating, we obtain the following new a very interesting closed form for the signal attenuation:

$$E_r(q;\alpha,\beta) = {}_3F_2\ (3/2,\ \alpha+1/2,\ \alpha+3/2;\ 2,\ 3;\ -16\pi^2\beta^2q^2) \qquad (1)$$

where ${}_pF_q$ is the Generalized Hypergeometric series using standard notation [5]. This expression is a relatively simple model for the intra-axonal compartment restricted diffusion. It depends only on the $\alpha$ and $\beta$ parameters of the Gamma distribution and not on $D_r$ as in the original AxCaliber formulation. This last issue results from the fact that at long diffusion times, the echo attenuation depends only on the geometry of the medium [7]. Also, as only one (large) value of $\Delta$ is needed, we drastically speed up the acquisition protocol. Indeed this is to be compared to [8] where a recent and optimized AxCaliber protocol is described using 4 different $\Delta$ values. **Monte-Carlo simulations.** To test the method we generate synthetic data using Monte-Carlo simulations on the CAMINO software toolkit [2], following the pipeline described in [6]. The diffusion and the PGSE sequence are simulated on a 3D environment (called substrate) formed by randomly placed cylinders whose radii distribution approximates a Gamma pdf. For the Gamma distribution, we used the parameters given in [6] which were obtained by fitting histology data of ADD. In comparison to [6], we considered a significantly larger number of cylinders ($10^5$) and this gave us a much better approximation of the radii pdf. For the simulations we set $\delta$=1ms, $\Delta$=100ms, and the gradient magnitude was scattered to produce 25 q-values between 0 and 600 $mm^{-1}$. To achieve good convergence of the Monte-Carlo algorithm, $3\times10^6$ particles were launched in each substrate. **Fitting procedure.** A total of four model parameters ($\alpha$, $\beta$, $D_h$, c) must be fitted to the data. The optimization was performed for the 4 parameters simultaneously using the non-linear least squared method included in the native FindFit Mathematica (v9.0, Wolfram Research Inc., Champaign, IL) function. To achieve adequate convergence we needed to indicate a search interval for each one of the parameters.

RESULTS: In Fig. 1 we show the accuracy of the model for the restricted diffusion (eq 1), against the attenuation of the intra-axonal compartment obtained with CAMINO. We stress that no fitting was performed, for a given pair ($\alpha$, $\beta$) we just displayed the simulation results (dots) and the plot of $E_r$ (solid curve). Fig. 1 perfectly illustrates the fact that our model produces the same results than those provided by CAMINO. In Fig. 2 we verify the assumption of being in the long diffusion time regime which is the main simplification with respect to the AxCaliber method. It is clear from Fig. 2 that our model (solid curve) fits better the CAMINO data for large values of $\Delta$. Finally, to evaluate the quality of the parameter recovery method, we selected the value of the first moment <r> and second moment $<r^2>$ of the fitted distributions. These values are simple functions of the recovered parameters $\alpha$ and $\beta$. The comparison against the ground truth is shown in Fig. 3.

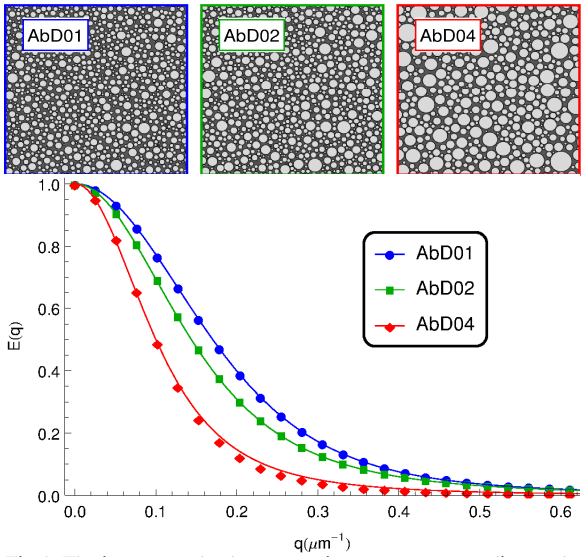


Fig 1. The intra-axonal echo attenuation vs q, corresponding to the substrates displayed on top. The dots are the samples obtained with CAMINO while the solid curve represents $E_r$ (eq. 1).

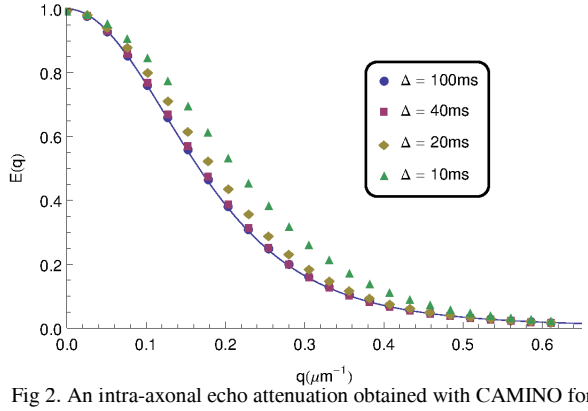


Fig 2. An intra-axonal echo attenuation obtained with CAMINO for different values of $\Delta$ (dots) compared with the model of $E_r$ (eq. 1).

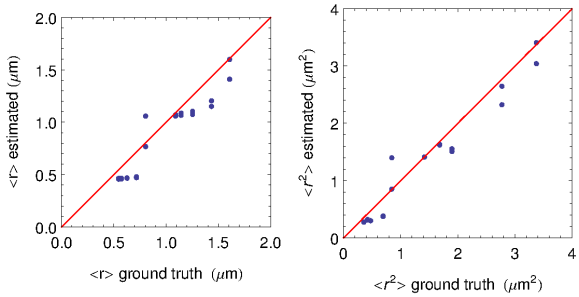


Fig 3. Plot of the measured <r> (left) and $<r^2>$ (right) against their ground truth value.

DISCUSSION AND CONCLUSIONS: We presented a new technique for recovering radii distributions that simplifies the AxCaliber [1] framework in both acquisition time and model complexity. We validated the method and the assumptions by means of CAMINO simulations of WM like environments. The results are promising and further validations on real data are to come.

BIBLIOGRAPHY: [1] Assaf et al. MRM, 59,1347-1354, 2008 [2] Hall et at., IEEE Trans on Med. Imag., 28, 2009 [3] Ozarslan et al. New Journal of Physics 13, 2011 [4] Soderman et al., JMR, 117, 94-97, 1995 [5] Gradshteyn et al., Academic Press, 2007 [6] Alexander et al. Neuroimage 52, 1374-1389, 2010 [7] Price, Cambridge Univ. Press, 2009 [8] Assaf et al. Neuroimage, 80, 273-282, 2013