A hierarchy of analytic models for the diffusion MRI signal in brain white matter

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Introduction This study aims to identify the minimum requirements for an accurate model of the diffusion MR signal in brain white matter. We construct a hierarchy of two- and three-compartment models of white matter from combinations of simple models for the intra- and extra-axonal spaces. We also compare the diffusion tensor (DT) [1] and a bitensor model. We create a protocol to examine parallel and perpendicular signals in brain white matter and acquire diffusion-weighted (DW) data with a wide range of imaging parameters to allow evaluation and comparison of all 26 models (DT, bitensor, 6 two- and 18 three-compartment models).

Tissue Models We model white matter with up to three compartments. Each compartment provides a separate normalized MR signal Si, i=1, 2, 3. The signals come from a) intra-axonal (IA) water, b) extra-axonal (EA) water and c) water in other cellular structures. The total diffusion MR signal for a multi-compartment model is the weighted sum of the signals from each compartment, with weights summing to 1. Figure 1 shows the candidate models for each compartment. ***IA:*** We investigate two models: **1.** Behrens' "stick" model [2] which describes diffusion in an idealised cylinder with zero radius and has fibre direction **n** and diffusivity d as parameters. **2.** A "cylinder" model with non-zero radius. We use the Gaussian phase distribution approximation to provide a model for the signal as a function of cylinder radius R, as in [3]. ***EA:*** We investigate three models. Each one is a DT with different constraints: **1.** "Ball" is isotropic as in [2] **2.** "Zeppelin" is a cylindrically symmetric DT as in [4]. **3.** Full tensor [1]. ***Third Compartment:*** We consider three extra compartments intended to capture other cellular structures that can be combined with the two-compartment models from combinations of the IA and EA models. Two of the models assume restriction from isotropically orientated cylinders and one restriction from a spherical boundary. The isotropic orientated cylinders model represents non-parallel axons or dendrites or astrocyte processes. The spherical restriction model represents signal from trapped molecules in smaller cells, e.g. microglia. The models are: **1.** Cylinders with diameter zero and a uniform distribution of orientations. We refer to this model as "astrosticks". **2.** "Astrocylinders" is similar but the cylinders have non-zero radius. **3.** "Dot" is a special case of Murday and Cott's expression [5], assuming particles diffusing inside spherical boundaries with zero radius in which particles do not move so that the signal remains unattenuated, as used in [6]. We use combined terms to refer to specific two- and three-compartment models, for example ``ZeppelinStick" assumes zero radius cylinders for the IA space and cylindrical symmetry for the EA space. The single DT is the same as the EA "tensor" compartment, and the bitensor model is a mixture of two "zeppelin" compartments with the same principle direction.

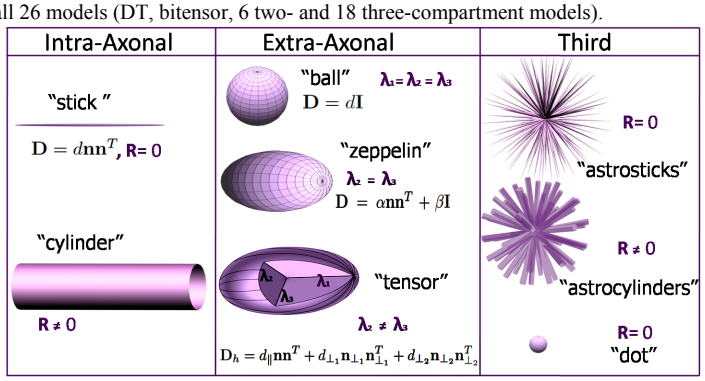

Figure 1. Individual models used for the formulation of the multi-compartment models

MRI Acquisition The experiment acquires DW-MR images of a fixed male rat brain using a 9.4T scanner (Varian) with maximum gradient strength 400mT/m. We use a five direction-encoding scheme: a left-right central direction that corpus callosum (CC) fibres are parallel to, and four evenly spaced directions perpendicular to the central direction. We use the pulse-gradient spin-echo (PGSE) sequence for 67 diffusion weightings: 5 diffusion times Δ=10, 20, 30, 40, 50ms, gradient durations δ=3ms for all Δ and δ=30ms for Δ=40, 50ms and gradient strength G varied from 40 to 400mT/m in ten steps of 40mT/m. We use different echo times (TE) and repetition times (TR) for each combination and correct for T2 dependence by acquiring separate b=0 images for each parameter combination. We also perform a separate diffusion tensor imaging (DTI) acquisition using 42 directions with b value 4.576x10^{9}s/m² and six b=0 measurements. The in-plane field of view is 2cm, the matrix size is 256x256 and the slice thickness is 0.5mm. In total we acquire 450 images in approximately 48 hours.

Model fitting We fit each model to the data by minimising the sum of squared errors using a Levenberg-Marquardt algorithm and synthesise DW data from the fitted models. We choose the best fit parameters after 1000 perturbations of the starting point to avoid local minimum.

Experiments & Results We choose a region of interest (ROI) that has principal fibre direction in alignment with the central direction. We manually segment the CC on a fractional anisotropy (FA) map from the DTI acquisition and threshold for voxels in which the principal direction of the DT is parallel to the central gradient direction, within 2º. We average the data contained within all 21 voxels of the resulting ROI. The Bayesian information criterion (BIC) evaluates the models accounting for varying complexity. Figure 2 compares data synthesised from the DT, the bitensor and the best two- and three-compartment models by plotting the normalised signal S at certain values of Δ and δ as a function of the gradient strength for the parallel and perpendicular directions. The symbols show the scan data and the lines correspond to measurements predicted by each model.

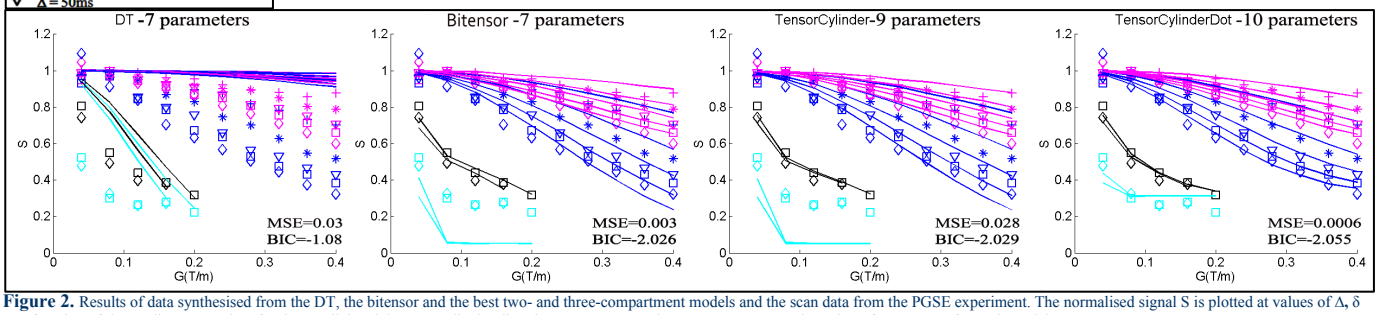

Figure 2. Results of data synthesised from the DT, the bitensor and the best two- and three-compartment models and the scan data from the PGSE experiment. The normalised signal S is plotted at values of Δ, δ as a function of the gradient strength G for the parallel and the perpendicular directions. Mean-squared error (MSE), BIC and number of parameters for each model.

Discussion & Conclusions The DT model shows significant departure from the scan data and confirms expectations that the model is poor for high b value data. The bitensor model improves the fit in both directions. There is no clear qualitative improvement of the "TensorCylinder" model over the bitensor model, however the MSE and BIC are lower for the "TensorCylinder", revealing that in fact the "cylinder" model explains the data better and provides a sensible estimate for the mean radius weighted by axon volume at 2μm [4]. In all two-compartment models we observe restriction in the parallel direction for δ=30ms that is not captured by the models, in agreement with previous studies [7]. The third compartments capture this departure improving the overall fit. However, the simplest third compartment, the "dot" model performs much better than the "astrosticks" and "astrocylinders", and the "TensorCylinderDot" model minimizes the BIC.

References & Acknowledgements [1] Basser et al, Biophys J, (1994), [2] Behrens et al, MRM, (2003), [3]Stepisnik , Physica B (1993) [4] Alexander, MRM, (2008), [5] Murday and Cotts, JChemPhys, (1984), [6] Alexander et al, NeuroImage, (2010), [7] Panagiotaki et al, MICCAI, (2009). **This work is funded by the EPSRC grant EP/E056938/1**