A high-resolution large-scale 2D geometric magnetic susceptibility model of white matter microstructure

Introduction Several groups have reported results suggesting that magnetic susceptibility introduces signal changes that relate to white matter tract structure (1,2,3,4). Although macrostructural (bulk) effects may be partly responsible, microstructural compartmentalization of tissue constituents with varying susceptibility have also been implicated. We previously presented a simple, small-scale 3D geometric model to estimate the microscopic field pattern that is driven by of various aspects of underlying tissue microstructure such as orientation to B0, myelin thickness and tissue iron concentration (5). This model can be used to predict susceptibility-based MR contrast such as GRE phase, T2' and BSSFP profile asymmetry. Here, a more robust and flexible 2D geometric model is introduced to allow more physiologically realistic representations of the actual WM microstructure. To validate the 2D model, the corpus callosum microstructure was simulated and the orientation dependence of T2* relaxation to B0 was compared with experiments.

Methods *Model description.* Our white matter model has 3 compartments: axonal, extra-axonal and myelin sheath. The WM fibers (axon+myelin) are first geometrically arranged using a circle-packing algorithm to obtain a densely-packed, random arrangement. The required volume fraction and distribution of fibers are then achieved by calculating and then removing the number of fibers of specific sizes from the existing circle distribution. After placement of the fibers, each fiber is then assigned inner and outer diameters to create myelin and axonal compartments with a specified g-ratio (see Fig 1). The magnetic susceptibility value of each individual compartment is then assigned. Using the analytical solution for the magnetic field perturbation caused by an infinite cylinder (6,8), the magnetic field change caused by each fiber at a single location is calculated. Susceptibility anisotropy effects can also be simulated in each of the compartments. Effect of diffusion is incorporated by performing Monte Carlo simulation on multiple spins at random locations with compartments assumed to be impermeable. *Model parameters*. We simulate a small-FOV "voxel" with 7164x7164 grid points spaced 0.05um apart (FOV 0.35x0.35mm^2). Axonal diameter has a gamma-distribution (9) (α=4.75, β=7) (15), fiber volume fraction is 0.7 and fiber density is 350 000 fibers/mm^2. The fiber orientation is 0 ±10 degrees (i.e. fibers are mostly parallel to one another) and g-ratio is 0.65 ± 0.10. The magnetic susceptibility value of the myelin compartment is -0.061±0.005ppm with respect to the axonal and extra-axonal compartments, which were both set to 0ppm. Magnetic susceptibility anisotropy of myelin was taken to be -0.019ppm (7). The diffusivity of water in the axon, extra-axon and myelin were taken to be 0.001, 0.001 and 0.0001mm^2/s. For T2* simulations, the proton density for the myelin compartment is taken as half that of the proton density in the axonal and extra-axonal compartment and the T2 of axonal, extra-axonal and myelin compartments were 50, 80 and 10 ms respectively. *MRI protocol.* A 2D multi-echo GRE sequence was used to measure the T2* decay in five subjects (TE=4-260ms, ΔTE=2ms ,TR=1.5s, 2×2×2mm, 10 averages, 25 minutes)..The T2* value was estimated with linear fitting to the logarithm of the magnitude images for echoes from 4 to 160ms. DTI data (2×2×2mm, b=1000 s/mm^2, 30 directions) was used to determine the orientation dependence of the T2* of WM fibers relative to B0. An atlas-based ROI of the corpus callosum (CC) was masked with the diffusion orientation to generate perpendicular- and parallel-CC ROIs.

Results and discussion Figure 2a plots the T2* dependence on orientation to B0 (across all of white matter, with orientation determined from DTI). T2* was found to decrease with increasing orientation to B0, which is in agreement with previous studies (10,11). Our simulated orientation dependence of T2* displays a very similar trend (Fig 2b). The mean T2* measured in our parallel- and perpendicular-CC ROIs was 56.4ms and 47.4ms respectively, giving a difference in R2* of 3.38Hz, comparable to the 2.76Hz simulated from our model. The experimental T2* decay of the white matter tracts was found to show significant deviation from a mono-exponential decay (Fig 3a). Our 2D model also predicted a similar trend (Fig 3b), notably capturing the oscillations of the measured deviation curves that are expected from susceptibility-shifted compartments (12). An important aspect of this model is the incorporation of diffusion, which is important for accuracy, as the high density of the white matter fibers places the system outside the static dephasing regime. A wide range of distributions has been reported in different fiber bundles and this flexible 2D model can easily simulate these different conditions. Some limitations of this 2D model include the lack of blood vessels and 3D structures such as oligodendrocytes. Due to the lack of magnetic susceptibility measurements for our specific compartments, our group has previously relied on measurements of the magnetic susceptibility of closely-related biological molecules in homogeneous solution, which are then combined based on an assumed chemical composition of each compartment. Significant discrepancy exists between experimentally obtained (7,8,13) magnetic susceptibility values of the compartments and estimated values (14). Our model currently uses values (7,8,13) estimated from experiments and is able to predict MRI signal levels in good agreement with literature results. To conclude, we have introduced a physiologically realistic representation of the WM that can be used to study susceptibility-based MR contrast.

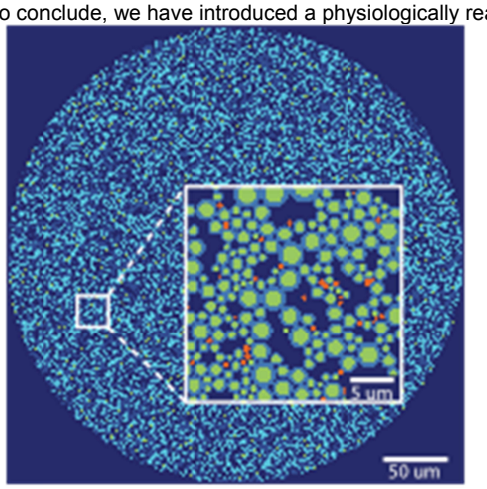

Figure1. Geometric model of white matter microstructural compartments (), each of which is assigned a magnetic susceptibility.

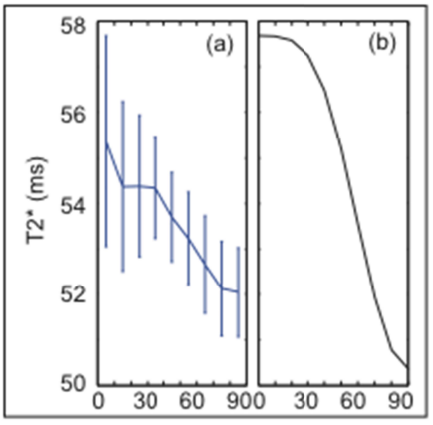

Figure 2. (a) Simulation of T2* dependence to orientation to B0. (b) Plot of experimental T2* against orientation to B0.

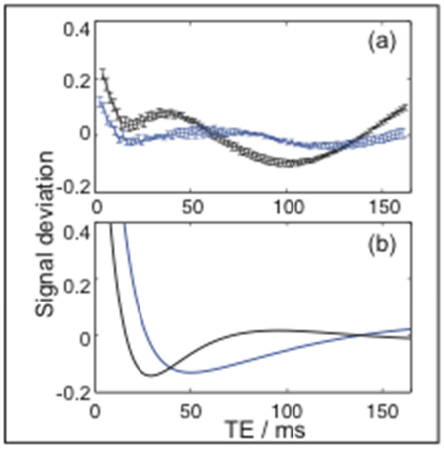

Figure 3. T2* decay minus mono-exponential fit (a) experimental and (b) simulated. Fibres are at 0° (blue) and 90° (black) to B0.

References (1) Duyn PNAS 2007. (2) Li NeuroImage 2006. (3) Miller MRM 2010. (4) Yablonskiy MRM 1997. (5) Chen Proceedings ISMRM 2010. (6) Haacke Wiley 2012. (7) Lee PNAS 2010. (8) Liu NeuroImage 2011. (9) Barazany BRAIN 2009. (10) Bender NMR Biomed 2010. (11) Denk NMR Biomed 2010. (12) Gelderen MRM 2011. (13) Lee NeuroImage 2011. (14) He PNAS 2009. (15) Assaf MRM 2008