How does White Matter Orientation affect Contrast in Gradient-Echo Magnitude and Phase Images? Simulation of a Three Compartment Model

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Introduction: Human white matter (WM) mostly comprises myelinated axons (fibres) connecting brain areas. Since many brain pathologies involve WM microstructure, its characterization is of great interest. Li et al. demonstrated that images obtained using the Gradient-Echo (GRE) sequence at UHF showed considerable inhomogeneity in white matter, especially connected with fibre bundles [1]. Further work has shown that the orientation of fibre bundles relative to the main magnetic field B_0 affects image contrast, both in magnitude [2-4] and phase images [5-8]. The source of this GRE image heterogeneity in WM is still under debate. It has recently been suggested that anisotropic susceptibility effects are responsible for the observed dependence of Larmor frequency on WM fibre bundle orientation [7]. Here we present results of simulations using a microstructural WM model.

Methods: Figure 1 shows (a) an electron-microscope image of a myelinated axon, (b) the model with isotropic susceptibility of myelin and (c) the model with anisotropic susceptibility of myelin. Myelin membranes consist of lipid bilayers, in which the long aliphatic chains of the lipids are aligned perpendicular to the plane of the membrane. Thus the susceptibility of myelin may well change with the direction of the carbon chain axis to the main magnetic field. To first order, this susceptibility variation can be modelled as $\chi = \chi_0\left(1+\delta\cdot\cos^2\varphi\cdot\sin^2\theta\right)$, where δ is the strength of susceptibility anisotropy, φ the in-plane angle of the carbon chain axis to B_0, θ the angle of the fibre axis to B_0 and χ_0 the susceptibility of myelin with fibre orientation parallel to B_0 [9]. In our simulation, the susceptibility values were set to -9.035 ppm (water) for the axonal lumen, the gap between the myelin sheets and the surrounding area of the fibres, and to -9.0938 ppm for the myelin sheets [8]. Since a typical image voxel of WM in MRI contains many myelinated axons, 25 identically modelled fibres were placed in a matrix. The field shift (ΔB) of this susceptibility distribution was then calculated using the fast-forward simulation [10]. The angle of the fibres to the main magnetic field were varied from 0 to 90 degrees in steps of 5 degrees. The complex microscopic MR signal at a field-strength of 7 T can be calculated by $S = \exp(-\mathrm{TE}/T_2^*)\cdot\left[\exp(-i\ \Delta B\cdot 300\mathrm{MHz}\cdot\mathrm{TE}\cdot 2\pi)\right]$ [11]. The T_2* values were set to 25 ms for the axonal lumen, the gap between the myelin sheets and the extracellular water, and to 3 ms for the myelin sheets. The macroscopic MR signal that would be measurable at 7 T and a echo time of 20 ms was then calculated as the vector sum of the microscopic MR signals.

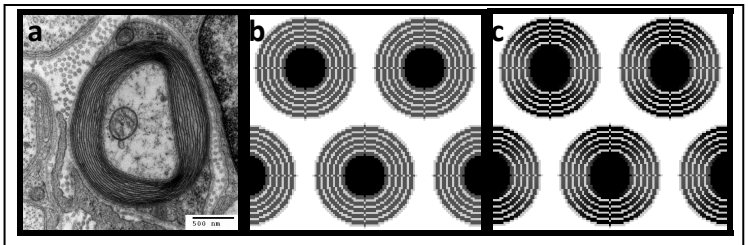

Figure 1: An electron-microscope image of a myelinated axon (a), the model with isotropic susceptibility of myelin, containing axonal lumen (black), myelin sheets (grey) and a gap between the myelin sheets (light grey) (b) and anisotropic susceptibility of myelin displayed as varying grey values (c).

Results and Discussion: Figure 2 clearly shows that both the magnitude and frequency of the MR signal depend on the orientation of the fibres to the main magnetic field, even for isotropic susceptibility of myelin. The orientation dependency of each is stronger if an anisotropic susceptibility is assumed. The change in magnitude and frequency values also depends on the distance of the myelinated fibres. The smaller the distance between the fibres the stronger is the orientation dependency. Furthermore, both magnitude and frequency shifts are smaller for fibres perpendicular to B_0 compared to parallel-oriented fibre bundles. This agrees very well with previous in vivo results [1-6]. In contrast, in a formalin-fixed WM sample, Lee at al. showed a more positive frequency-shift for fibres oriented perpendicular to B_0 [7]. The fixative action of formaldehyde is probably due entirely to its reactions with proteins [12]. Further work will investigate whether the susceptibility of proteins is changed if they are chemically bound to formaldehyde, which may explain the difference between in- and ex-vivo results. If the susceptibility of the myelin sheets after fixation becomes more paramagnetic than water, the frequency-shift in our simulation would be greater for fibres perpendicular to B_0, as compared to parallel, while the magnitude signal would still be lower.

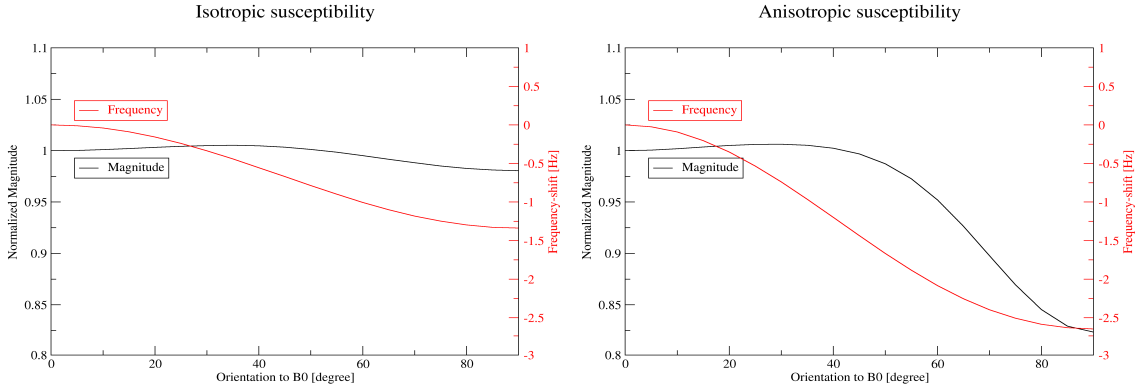

Figure 2: Orientation dependency of the magnitude and frequency assuming a isotropic susceptibility (left) and an anisotropic susceptibility (δ=-0.02) of the myelin sheets (right). The magnitude and frequency-shift were normalized to their values for fibres oriented parallel to B_0. Normalizations were performed by taking the ratio and the difference to the value at zero degrees for magnitude and frequency, respectively.

References: **[1]** Li *et al.* NeuroImage 32 :1032-1040 (2006) ; **[2]** Wiggins *et al.* Proc ISMRM 237 (2008); **[3]** Cherubini *et al.* MRM 61:1066-1072 (2009); **[4]** Bender *et al.* NMR Biomed. 23:1071-1076 (2010); **[5]** Hernández *et al.* Proc ISMRM 953 (2009); **[6]** Schäfer *et al.* Proc ISMRM 956 (2009); **[7]** Lee *et al.* PNAS 107:5130-5135 (2010); **[8]** He *et al.* PNAS 106:13558-13563 (2009); **[9]** Worcester PNAS 75:5475-5477 (1978); **[10]** Marques *et al.* Concepts Magn Reson B 25 :65-78 (2005); **[11]** Kiselev *et al.* MRM 41 :499-509 (1999); **[12]** Helander *et al.* Biotechnic & Histochem 69 :177-179 (1994)