Towards Understanding the Anisotropy of Magnetization Transfer Parameters in Human White Matter

André Pampel[1], Henrik Marschner[1], Dirk K. Müller[1], and Harald E. Möller[1]
[1]*Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany*

Introduction and Purpose. Information about myelin can be obtained indirectly from magnetization-transfer (MT) experiments [1-4]. Quantification of MT imaging has been done by many researchers using a two-pool (binary spin-bath) model consisting of a free water pool "a" and a semi-solid, macromolecular pool "b" [2-4]. Integral part of this model is a lineshape describing the absorption probability of the semi-solid pool, which is often assumed to be Super-Lorentzian [5] (SL) [3-5]. It was found that T_{2b} shows an apparent dependence on the orientation of the WM fibers with respect to B_0 [7,8]. This finding was qualitatively related to the partially ordered nature of myelin, but not elucidated completely [7,8]. Here, we attempt to provide a coherent explanation of this effect by introducing a novel absorption lineshape for WM, which permits to predict the experimental outcome.

$$\frac{1}{2}\left|3\cos^2\theta_n - 1\right| = \frac{1}{2}\left|3\cos^2\phi\sin^2\theta - 1\right| \quad (1)$$

$$g_b(\Omega,\theta) = \int_0^{\pi/2} \sqrt{\frac{2}{\pi}}\,\frac{T_{2b}}{\left|3\cos^2\phi\sin^2\theta - 1\right|}\exp\left[-2\left(\frac{\Omega T_{2b}}{\left|3\cos^2\phi\sin^2\theta - 1\right|}\right)^2\right]\mathrm{d}\phi \quad (2)$$

$$g_b(\Omega,\Theta,\sigma) = N^{-1}\int g(\Omega,\theta)\,\frac{1}{\sigma\sqrt{2\pi}}\exp\left[-\left(\frac{(\theta-\Theta)^2}{2\sigma^2}\right)\right]\mathrm{d}\theta \quad (3)$$

MT Background: In the 2-pool model, each pool has independent MR parameters (relative pool sizes M_{0a} and M_{0b}, relaxation times T_{1ab}, T_{2ab}). The compartments exchange magnetization characterized by the pseudo first-order exchange rate constants $R{\cdot}M_{0a}$ and $R{\cdot}M_{0b}$. RF saturation of pool b is described by $R_{rf,b}=\omega_1^2\pi g_b(\Omega)$ and depends on the off-resonance angular frequency Ω, the Rf amplitude ω_1, and the lineshape function $g_b(\Omega)$ [2-4]. Quantitative analysis of adequate MT experiments allows to determine these parameters, but only in terms of "lumped" parameters (Fig. 3), whose entangling requires additional information [2,3,10-11].

Novel Lineshape Model: Since myelin is a lipid bilayer structure enveloping axons, we assume that the assumptions that lead to the SL are valid [6]. However, we cannot assume that θ_n, the angle of the lipid bilayer surface normal with respect to $\mathbf{B}_0$, is evenly distributed. In an idealized cylindrical WM fiber, θ_n of a bilayer wrapped around an axon is a function of the axonal tilt θ and the azimuthal angle ϕ in the axonal frame. Thus the $(3\cos^2\theta_n-1)/2$ term in the SL[5] has to be replaced according to (1). The novel lineshape function $g_b(\Omega,\theta)$ (2) of single WM fiber is derived by integrating over ϕ, which reflects the cylindrical symmetry. A typical imaging voxel cannot be described by a single fiber bundle having one orientation. In this model, we assume that WM consists of a vast number of fibers, each having an orientation θ distributed around the major fiber orientation Θ. The variation is described here by a normal distribution with mean Θ and standard deviation σ. We assume that Θ coincides with the fiber orientation as measured with DTI.

Methods. MRI Scans: Experiments in 8 healthy volunteers were performed at 3T (Magnetom TIM Trio, Siemens) as recently described [6,8]. Measurements comprised multiple MT-prepared gradient echo acquisitions at several TR values, off-resonance frequencies, and MT pulse flip angles, respectively. DTI data were acquired using twice-refocused SE EPI; DW distributed along 60 directions (b=1000 s/mm^2). DTI analysis using FSL was performed to calculate i) the fractional anisotropy (FA) and ii) Θ, which is the angle between the eigenvector of the largest eigenvalue and B_0. MT Data Simulation and Parameter Fitting: Simulation and fitting were performed in Matlab by calculating the time evolution of the magnetization using matrix exponentials [8]. Five parameters (T_{1b}=1s)[9-11] were fitted to the MT data using a trust-region algorithm. For fitting the SL was used. Simulations and fitting were done with identical MR sequence parameters [9].

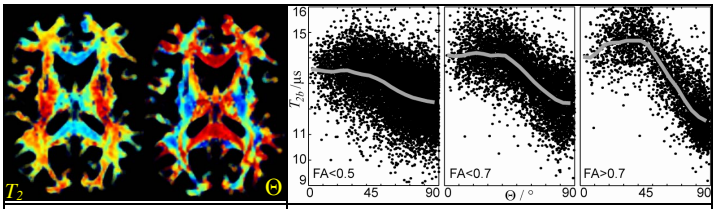

Fig.1 T_{2b} map [9µs-16µs] and WM fiber orientation map Θ [0°-90°]. Slice orientation axial.

Fig.2 T_{2b} vs. Θ of all volunteers subdivided into subsets with increasing FA. Data overlaid with the moving average.

Results and Discussion. T_{2b} data and the corresponding Θ map from one volunteer are shown in Fig.1. Fiber tracts with major head-foot direction are parallel to $\mathbf{B}_0$. The variation of T_{2b} with the fiber orientation closely resembles the contrast in the Θ map, which is affirmed by the scatter plot of the data from all volunteers in Fig. 2. To validate the reliability of the novel lineshape, MT data were simulated using this lineshape assuming T_{2b}=13.5 µs. In particular, it was assumed that θ is normally distributed (σ=19°), where the mean orientation is identified with Θ. Other MT parameters used in the simulation match the MT parameters obtained *in vivo* and none of these parameters was provided with an explicit dependency on Θ. The resulting data were analyzed by least-squares fitting assuming the SL, as it was done with *in-vivo* data as input. The results of fitting the simulated data together with the MT parameters obtained from *in-vivo* data (voxels with FA>0.7) are shown in Fig.3. The orientation dependent T_{2b} variation found in the simulated data matches the orientation dependency $T_{2b}(\Theta)$ that is found in the experimental data (FA>0.7) reasonably well. Furthermore, there is a dependency on Θ—albeit with varying peculiarity—of all *in-vivo* MT parameters. Although this dependency was not included in the calculation of the simulated data, it immediately arises from parameter fitting utilizing the SL.

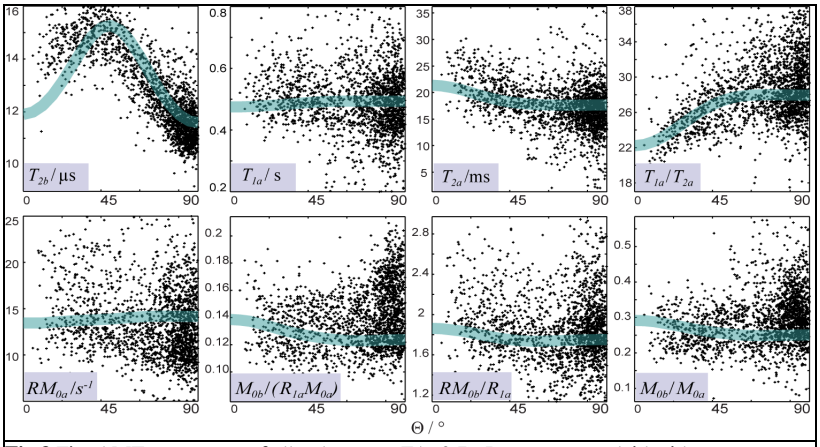

Fig.3 Fitted MT parameters of all volunteers (FA>0.7). Data were overlaid with parameters as obtained by parameter fitting of the data simulated using the novel lineshape.

Conclusion. A good agreement between the $T_{2b}(\Theta)$ dependency as obtained from *in-vivo* data and those predicted using the orientation-dependent lineshape is found. In addition, the orientation dependency of other parameters as obtained *in vivo* could be reproduced for WM voxels FA>0.7. For highly ordered WM, the simple model seems to be justified. For WM with lower FA, the orientations dependency gets more and more buried (see Fig.2), which can be reproduced also in the simulations by increasing σ. The results suggest that the dependency of MT parameters should be generally taken into account.

References. 1. Laule et al. *Neurotherapeutics* 4(3),p.460; 2007. 2. Henkelman et al. MRM 29(6),p.759;1993. 3. Morrison et al. *MRM* 33(4),p.475;1995. 4. Morrison et al. *JMR(B)* 108(2),p.103;1995. 5. Wennerström, *Chem.Phys.Lett.* 18(1),p.41;1973. 6. Wilhelm et al. *PNAS* 109(24), p.9605;2012. 7. Müller et al. *ISMRM 2010*#2996; 8. Yarnykh, *MRM* 68(1),p.166;2012. 9. Müller et al. *JMR* 230, p.88;2013. 10. Sled et al, *MRM* 46(5),p.923;2001. 11. Ramani et al. *MRI* 20(10),p.721;2002.

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