On the effects of a varied diffusion time in vivo: Is the diffusion in white matter restricted?

M. Nilsson[1], J. Lätt[1], E. Nordh[1], R. Wirestam[1], F. Ståhlberg[1,2], and S. Brockstedt[1,2]

[1]Dept. of Medical Radiation Physics, Lund University, Lund, Sweden, [2]Dept. of Diagnostic Radiology, Lund University, Lund, Sweden

Introduction. The signal-versus-*b* curve from cerebral white matter (WM) can be modelled by a bi-exponential function, including a fast and a slow diffusion component [1]. Pulsed gradient stimulated echo (PGSTE) NMR experiments with varying the diffusion time (T_d) have indicated that the slow diffusion component perpendicular to WM fibre bundles in excised nerves is restricted [2, 3]. However, the interpretation of such components in the context of *in vivo* MRI remains unclear [4, 5]. In previous MRI studies pulsed gradient spin echo sequences were typically employed, limiting the maximal T_d and the diffusion-measurement direction were, in contrast to NMR experiments, uncorrelated to the actual direction of the nerve fibre bundle (cf. [1]). In this study, measurements perpendicular and parallel to the corticospinal tract (CST) *in vivo* were performed using a PGSTE sequence to investigate whether effects of restricted diffusion could be observed as T_d was prolonged.

Method. Measurements were performed on 7 volunteers using a Siemens 3T Allegra unit. Initially, diffusion tensor (DT) imaging was executed in 12 diffusion encoding directions. A region of interest (ROI) in one slice containing the CST was selected and based on the eigenvectors of the DT in the ROI, new images were acquired with the diffusion encoding direction being either perpendicular ($\mathbf{n}_\perp$) or parallel ($\mathbf{n}_\parallel$) to the CST. Signal-versus-*b* curves were acquired for T_d=64,100,144,196 and 256 ms by varying the mixing time with TR/TE=2500/134 ms and δ=50 ms. For each T_d, 29 *b*-values were sampled with b_{max}=28 000 s/mm^2 along $\mathbf{n}_\perp$ and 30 *b*-values with b_{max}=6 000 s/mm^2 along $\mathbf{n}_\parallel$. In an additional measurement, the signal-versus-*b* curve was sampled using 87 *b*-values up to 86 000 s/mm^2 (T_d=256 ms) in $\mathbf{n}_\perp$. Bi-exponential and mono-exponential functions were fitted to the signal-versus-*b* curves, and were considered acceptable if the index of satisfaction (*IS*) was below 0.001 [1]. Furthermore, two-dimensional Monte Carlo simulations of 5×10^4 molecules placed inside and between a lattice of cylindrical cells (diameter *d*) were performed with sequence parameters as in the perpendicular measurements and with D_{intra}=D_{extra}=1.7 µm^2/ms and an intra-cellular fraction p_{intra} = 80% for *d*=3,7,11 and 15 µm. In each step, the positions were updated with equal probabilities of a positive and a negative step (Δ*x*=0.2 µm). The membrane transition probability was given by $p_0=m/n\cdot\Delta t/\tau_{intra}$, where *m* is the number of possible displacements inside the cylinder and *n* is the number of displacements leading to a possible membrane transition and $\Delta t=\Delta x^2/2D$. For each *d*, five exchange times τ_{intra} were simulated (τ_{intra}=25,100,200,500 and 1000 ms). Violation of the short gradient pulse (SGP) condition implies that expected diameters (d_{exp}) are lower than the simulated *d* (d_{exp} were estimated from Fig. 2 in [6]). Finally, a two-compartment modified Kärger model, similar to the model in [7], was fitted to the data from the perpendicular direction as well as to the simulated signal values.

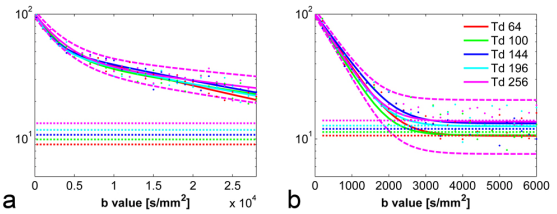

Figure 1. Normalized signal curves from a normal volunteer (a) perpendicular and (b) parallel to the CST. The fitted functions are displayed as solid lines. Dashed lines indicates one standard deviation of the signal for T_d=256 ms. Note that the mean background noise level (dotted lines) appears to increase for increasing T_d due to the normalization of the signal.

Results. The normalized signal perpendicular to the CST did not vary with T_d to any observable extent (Fig. 1), in contrast to the signal from the simulations (Fig. 2), where large effects on the signal-versus-*b* curve were observed for varied T_d. In the measurements perpendicular to the CST, a bi-exponential function was required to fit the data well, but parallel to the tract a mono-exponential model was sufficient. The estimated parameters of the bi-exponential and mono-exponential fit (Table 1) did not change significantly as T_d was varied, but ADC_{fast} and ADC_{slow} decreased and p_{fast} increased for the measurement with higher b_{max}. SNR-values for b_{min} and b_{max} are also displayed in Table 1. The two-compartment model was found to fit well to the simulated signal values. Regarding the estimated parameters (Table 2), the estimated *d* values were in the expected range, except for *d*=3 µm. The estimated τ_{intra} were all in good agreement with the simulated, but in general, p_{intra} was underestimated. Finally, the two-compartment model did not fit well to the *in vivo* signal values and no set of simulated signal versus *b*-curves resembled those obtained *in vivo*.

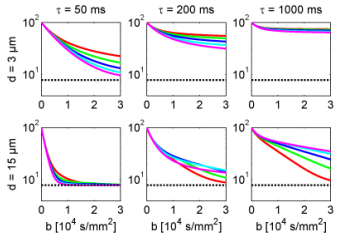

Figure 2. Example of the signal-versus-b curves from the simulations. Dashed lines indicated the noise floor. Colour encoding as in Fig. 1.

Table 1. The parameters of the bi-exponential and mono-exponential fit perpendicular and parallel to the CST, respectively with T_d in ms, ADC:s in µm^2/ms, p_{fast} in percent and SNR-values for b_{min} and b_{max}, respectively. The bottom row (T_d=256 ms) shows parameters from the measurement with higher b_{max}. None of the parameters showed a significant change with T_d in a dependent ANOVA-test with p = 0.30, 0.22 and 0.25 for ADC_{fast}, ADC_{slow} and p_{fast} in the perpendicular direction and p = 0.42 for ADC in the parallel direction (n=7).*

	Perpendicular				*Parallel*	
T_d	ADC_{fast}	ADC_{slow}	p_{fast}	*SNR*	*ADC*	*SNR*
64	0.45 ± 0.13	0.031 ± 0.006	49 ± 4	16/3.8	1.13 ± 0.14	12/1.4
100	0.39 ± 0.06	0.027 ± 0.001	51 ± 3	14/3.7	1.09 ± 0.07	11/1.4
144	0.40 ± 0.07	0.029 ± 0.004	49 ± 3	13/3.4	1.09 ± 0.12	11/1.4
196	0.34 ± 0.10	0.023 ± 0.009	54 ± 7	12/3.1	1.06 ± 0.05	10/1.3
256	0.40 ± 0.09	0.029 ± 0.007	49 ± 6	11/2.9	1.05 ± 0.09	9.2/1.4
256*	0.22 ± 0.06	0.014 ± 0.004	62 ± 5	11/1.6		

Table 2. The simulated parameters along with the parameters estimated by the two-compartment Kärger model. The τ_{intra}:s are averaged over the different diameters (n=5) and the d:s over the different τ_{intra}:s (n=4). The expected d_{exp} was estimated from Fig. 2 in [6]. The p_{intra} was averaged over all simulated settings (n=20).

	τ_{intra} [ms]					*d* / d_{exp} [µm]				p_{intra}
Simulated	50	100	200	500	1000	3 / 0.1	7 / 2.0	11 / 4.6	15 / 8.3	80%
Estimated	45 ± 4.6	89 ± 8.0	180 ± 11	490 ± 4.7	1000 ± 44	1.8 ± 0.75	2.5 ± 0.13	4.6 ± 0.68	7.8 ± 0.68	66 ± 15%

Discussion. In the present study, T_d was varied in approximately the same range as in previous NMR spectrometry studies [2,3], but in contrast to the NMR studies no obvious evidence of restricted diffusion was observed. For example, no increase of the normalized signal value was observed perpendicular to the CST as T_d was prolonged (Fig. 1) and the parameters of the bi-exponential fit did not change as T_d was varied (Table 1). The decrease in ADC_{fast} and ADC_{slow} as b_{max} was increased (Table 1) shows that comparisons of parameters from a bi-exponential fit between measurements with different T_d should only be compared under conditions with identical b_{max}. Since no effects of restricted diffusion perpendicular to the CST was observed *in vivo*, in contrast to similar *ex vivo* NMR studies, we hypothesise that differences between living and excised tissue might account for the observed differences.

The two-compartment exchange model was likely to be able to extract *d* and τ_{intra} in the expected range when the diffusion occurs in cylindrical cells, but since no set of signal-versus-*b* curves from the simulations resembled the signal curves obtained *in vivo*. Furthermore, the model did not fit well to the obtained signal values *in vivo*. Hence, our conclusion is that the diffusion perpendicular to WM tracts *in vivo* should be modelled in another manner than by the two-compartment Kärger model, for example as two slowly exchanging diffusion pools [5].

References. [1] Clark AC, *et al.* MRM 2000;44:852-859 [2] Assaf Y, Cohen Y. MRM 2000;43:191-199 [3] Nossin-Manor *et al.* MRM 2005;54:96-104 [4] Schwarcz A, *et al.* MRM 2004;51:278-285 [5] Le Bihan D. Phys Med Biol 2007;52:R57-R90 [6] Lätt J, *et al.* IEEE Trans Med Imag 2007;26 [7] Pfeuffer J, *et al.* NMR Biomed 1998;11:19-31