# T2* of Myelin Water Edited by Longitudinal Relaxographic Imaging

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Introduction: The interpretation of the initial longitudinal relaxation of water in the human brain at high field (B0 $\geq$ 3 T) is related to an assumption on the exchange rate of water between the confined environment of tight myelin and other spaces: fast exchange is compatible with a magnetization transfer model between semi-solid protons of the myelin membranes and water, whereas slow exchange suggests the distinct observation of mobile water in myelin with a short T_1. Water may directly exchange between the intra-axonal space and the extra cellular matrix (ECM), rich in macromolecules (e.g. glial hyaluronate-binding protein expressed with myelin [1]) through gap-junctions connecting the intra-cellular space of non-compact myelin, e.g. the paranodal loops bordering the Ranvier node. In compact myelin, water needs to either permeate the myelin membranes or diffuse circumferentially in the 20 Å space separating membranes (see Fig. 1). Beside the presence of myelin basic proteins (MBP) and proteolipid proteins (PLP) forming a regular pattern of obstacles to water diffusion, interaction of water with the membrane surface will slow its diffusion, ca. by a factor of ten, as observed when freezing myelin [2]. A slow diffusion of myelin water would be compatible with the observation of a distinct myelin T_1 fraction (shutter speed model). The distinct observation of a T_2 myelin water pool is well established [3]. For comparison with the published T_2 values of myelin water, we investigated the T_2* of the short T_1 peak attributed to myelin water. Further, we employed a computational chemistry approach to investigate the effect of the myelin membrane on the reorientation and translation of water.


Fig. 1

Fig. 2
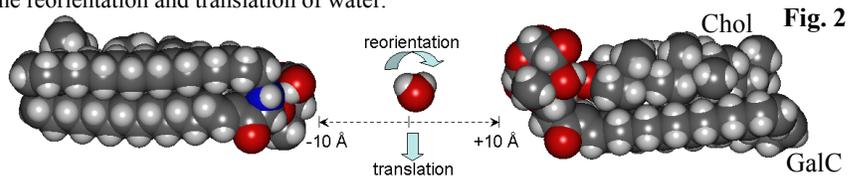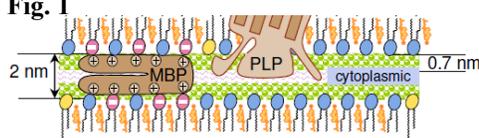
Methods: Pulse sequence and subject – An informed volunteer (w 29y) was scanned at 3 T (Siemens TIM-Trio) with a double-echo PURR sequence: 32 *TI* (17, 43, 69, ..., 8000 ms), 5°-sinc excitation, 1.5×1.5×5 mm^3, *TR* 10 sec, 32 channel array coil, GRAPPA 2, 68 auto-callibration lines. Relaxation data were processed with a cross-regularized inverse Laplace transform [4]. T_2* was estimated by mono-exponential fit of the peak areas observed with forward gradient echoes obtained at *TE* 7 and 19.1 ms [4]. Computational chemistry – A pseudo-myelin arrangement [5] of galactosylcerebroside (GalC) and cholesterol (Chol) was optimized by the semi-empirical self-consistent field AM1 method using the package Firefly 7.1.G [6] and replicated to form a pseudo-myelin opposing head groups along an axis normal to the membrane surface. The two opposite arrangements were separated by 20 Å, a distance representative of the myelin intra-cellular space (see Fig. 2). A water molecule was produced using the package Gabedit 2.4.0 [7], placed on the axis and randomly reoriented (72 reorientations). The heat of formation of the resulting system composed of 417 atoms was estimated with the semi-empirical AM1 method. Additionally, the water molecule was translated perpendicularly to the axis within a radius of 4 Å (72 translations).

Fig. 3

Fig. 4
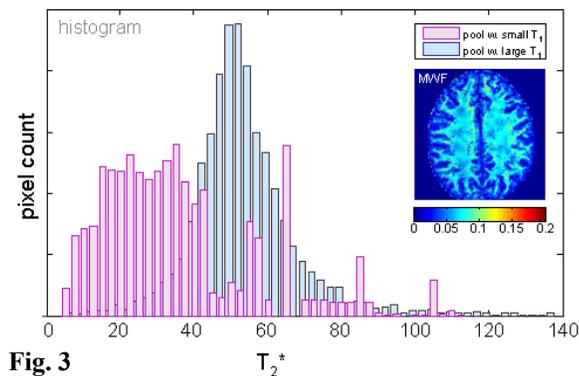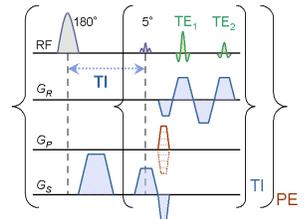
Results & Discussion: In Fig. 3, the T_2* histogram for the pool with long T_1 was unimodal (54.4±15.0 ms). The pool with short T_1 attributed to myelin water showed a mostly unimodal T_2* histogram (29.2±13.4 ms) with minor scattered contributions. The reduced T_2* of the short T_1 pool further confirms the hypothesis of a distinct water pool exchanging slowly and attributed to myelin water. Such slow exchange may be attributed to a reduced mobility of water in a 7 Å thick *hydration layer* [8] where water is subjected to dipole-dipole and van der Waals interactions with the lipids composing the myelin membrane. The upper plot in Fig. 4 displays twice the standard deviation of the heat of formation of the simulated pseudo-myelin as a function of the water position, the bottom plot the minimum of the heat of formation (optimized geometry). The changes for reorientation of water near the pseudo-myelin surface are in the order of 4 Kcal/mol and for translation 3.5 Kcal/mol. These effects become negligible at the center. These results and simulations suggest that water diffusion in myelin is lower than that in other spaces.
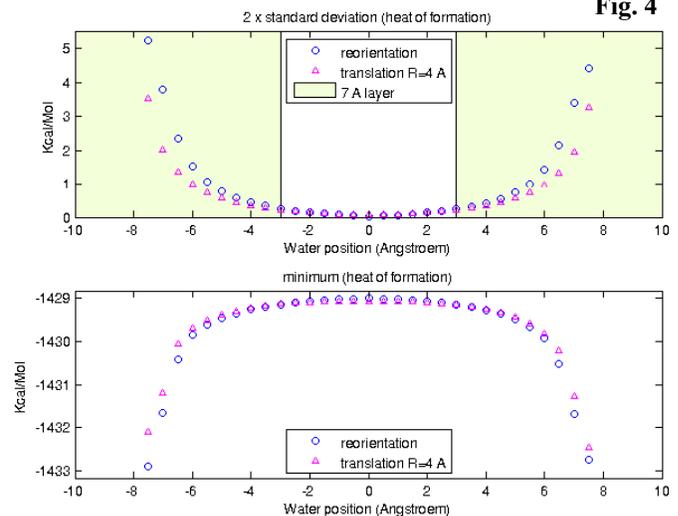
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