Diffusion Relaxation Correlation Spectroscopy at Ultra Short Echo Times Reveals Two Major Compartments in Human Cadaver Brain White Matter

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Introduction: MR measurements of water diffusion have been widely used in recent years to identify neurological abnormalities and to characterize white matter fibre tracts. Although diffusion-weighted signal for brain tissue decreases exponentially for low b-values (<2000 s/mm^2), at larger b-factor it is clearly apparent that diffusion is not mono-exponential [1]. This multi-exponential decay may arise from multiple water compartments with slow exchange. However, while efforts continue to correlate fit parameters with physical parameters [2], multi-exponential water diffusion in brain tissue is still poorly understood [3].

The diffusion weighted signal obtained with a Stejskal-Tanner spin echo DWI measurement is T_2 weighted. For a sample with n different water compartments, $S = S_0\sum[P(D_i,T_{2i}).\exp(-TE/T_{2i}).\exp(-bD_i)]$. Therefore, the problem of characterizing water dynamics in brain tissue should be regarded as two-dimensional, requiring a wide range of echo times in order to discriminate the compartments, and the shortest possible diffusion time to allow a short echo time and to reduce inter-compartment exchange. In this study we performed Diffusion Relaxation Correlation Spectroscopy (DRCOSY) measurements with very short diffusion time (Δ = 1.2 ms). This was made feasible in human cadaver brain tissue by the use of an NMR spectrometer with exceptionally powerful gradients.

Method: Figure1 shows the schematic of a DRCOSY sequence, where a Stejskal-Tanner[4] spin-preparation module is followed by a CPMG train without any new excitation.

Five formalin-fixed, excised specimens of human corpus callosum were cut exactly to fit the NMR tube, with fibre orientation in the axial direction. Experiments were performed in a homebuilt Fegris NT 125 MHz NMR spectrometer equipped with gradient of up to 35 T/m in z-direction[5]. The parameters used were: Delta (Δ) = 1.2 ms, gradient pulse duration (δ) = 0.5ms, first echo (TE_1) = 2.4 ms, CPMG echo interval (τ) = 0.5ms. Diffusion gradients were incremented linearly from 0.1 T/m to 28 T/m with intervals of 0.7 T/m (maximum b-value = 11,365 s/mm^2). Eight averages and 6 repetitions were measured. Prior to measurement sample was checked for internal gradients by comparing CPMG attenuation with different echo intervals(τ).

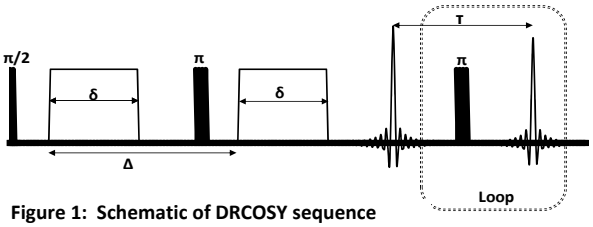

Figure 1: Schematic of DRCOSY sequence

The first-echo diffusion data were first analyzed using a conventional bi-exponential fit and CPMG train from the smallest diffusion coefficient was used for a bi-exponential T_2 fit. The 2D diffusion-relaxation data were analyzed with a 2D inverse Laplace transform [6] with both diffusion coefficients and T_2 values ranging logarithmically from 0.01--4 μm^2/ms and 1 ms--1 s respectively. With the development of efficient 2D inverse Laplace technique [6], adding a second dimension in spin echo measurements has already been applied to study porous materials [7].

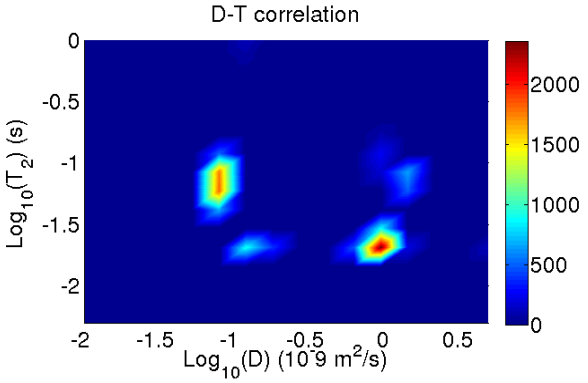

Figure 2: Typical 2D correlation map of diffusion and relaxation values. Two major compartments have diffusion and relaxation components an order of magnitude different from each other. The faster diffusion component shows a shorter T2 relaxation which is opposite of what is normally assumed.

Results: Bi-exponential fitting of the diffusion data resulted in two distinct components D_{fast} ranging from 1.1 μm^2/ms to 0.67 μm^2/ms and D_{slow} (0.1--0.05 μm^2/ms) with relative fractions F_{fast} (0.56--0.42). Biexponential fit of CPMG train also gave a faster relaxing component $T_{2,fast}$ (25.5--18.2 ms), and a slower relaxing component $T_{2,slow}$ (140--95 ms), and fraction of the fast relaxing component ranged from 0.55--0.61.

Two Dimensional Laplace transform also resulted in two distinct peaks, with an order of magnitude difference in both diffusion and T_2 relaxation properties (Figure 2). Surprisingly, the faster component was associated with a faster T_2 relaxation, counter to the common assumption that faster diffusion, characteristic of more mobile water molecules, would be associated with slower T_2 relaxation.

Conclusion: Correlating diffusion and relaxation in a single experimental setup allows us to discriminate multi-compartmental water in the brain tissue without assuming an inherent relation between diffusion and relaxation properties of water in these compartments. Although both diffusion and T_2 relaxation are related to the mobility of water molecules, whereas T_2 relaxation reflects rotational dynamics of the molecule, diffusion is related to the translational motion. We hope that further studies on different brain tissues with this method will allow us to distinctly separate the different water components present and help understand the biophysical basis of diffusion NMR.

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