Optimized diffusion-weighted LASER sequence for single-shot measurement of metabolite diffusion by the trace of the tensor

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Introduction

Whereas water can diffuse everywhere in tissues, metabolites are specific to the intracellular compartment. DW-spectroscopy is therefore a unique tool to probe intracellular space *in vivo*. The measured apparent diffusion coefficient depends on intracellular properties such as cell shape, intracellular viscosity, and subcellular compartmentation. As cellular organization may be anisotropic, apparent diffusion is anisotropic as well and is better described by the diffusion tensor **D**. In order to characterize **D**, at least 6 acquisitions (plus one reference scan) are required. However, when willing to probe intracellular micro-organization, cellular orientation isn't relevant and it may be more interesting to measure the trace of **D**: D_{av}=Tr(**D**)/3.

In this work, we have developed a new DW-spectroscopy sequence, based on the LASER sequence, which allows the localized measurement of D_{av} within a single scan. The sequence consists in a significant improvement of a previous DW-sequence proposed by Valette *et al.* [1]. Although the previous sequence allows the measurement of D_{av} within a single scan while keeping echo-time short and providing immunity to cross-terms, the diffusion-weighting factor *b* wasn't very strong. In this study, we propose to insert additional diffusion gradients to fill the available time of the original sequence to increase *b* while preserving cross-term suppression. In parallel, effective gradient amplitude is increased by combining diffusion gradients on the three axes simultaneously. We finally show that this strategy, due to its high sensitivity, allows measuring metabolites D_{av} in a small voxel in a deep structure (striatum) of the rat brain.

Theory

The LASER sequence is based on three pairs of 180° pulses, later called "blocks", selecting three orthogonal directions. In the sequence proposed by Valette [1], diffusion-weighting was achieved using two gradients lobes of duration δ and amplitude *G*, of opposite polarities, at the beginning and at the end of each block. Diffusion gradients were applied along X for the first block, Y for the second block, and Z for the third block, ultimately yielding cross-term free diffusion-weighting according to D_{av}. In the compact form of this sequence, $TE=3(\Delta+\delta)$ and $b=(\gamma G\delta)^2(TE-4\delta)$, γ being the gyromagnetic ratio, *TE* the echo time, and Δ the delay between the two gradient lobes.

The **first improvement** consists in inserting diffusion gradients during the delay between the two adiabatic pulses of each block, as shown in Fig. 1. For a compact sequence (no dead time) we get $b=(\gamma G\delta)^2(TE+4\delta)$. With such a scheme, cross-terms with other gradients, including constant background gradients, are suppressed.

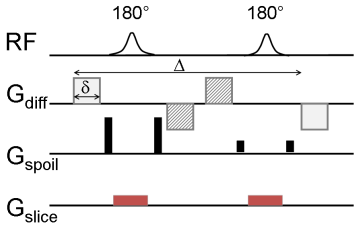

Fig. 1: *Description of a single diffusion block, in the logical frame. The two new diffusion gradient pulses compared to [1] are hatched.*

The **second improvement** consists in optimizing diffusion gradient directions to maximize gradient amplitude. With the proposed sequence consisting in three successive orthogonal blocks built by circular permutation, diffusion gradients have to form an orthogonal basis. In the original DW-LASER sequence, only one gradient was applied at the same time: G_1 (1 0 0), G_2 (0 1 0) and G_3 (0 0 1) as represented in the XYZ frame (green frame in Fig. 2). After optimization on Matlab, we found that the set of orthogonal directions yielding maximal gradient amplitude is G_1 (1 1 -0.5), G_2 (-0.5 1 1) and G_3 (1 -0.5 1) (purple frame in Fig. 2). In that case, gradient strength is increased by $\sqrt{1^2+1^2+0.5^2}$ compared to the initial directions, and *b* is increased by a factor 2.25.

After these two improvements, *b* is increased of a factor $2.25(TE+4\delta)/(TE-4\delta)$ compared to the original sequence, for a given *TE*, *G* and δ.

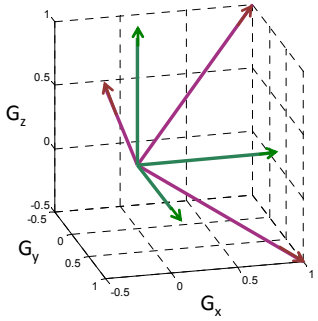

Fig. 2: *The initial gradient frame along X, Y and Z (green), and the new set of directions used for diffusion-weighting (purple).*

Methods

NMR setup:

Experiments were performed on a Varian/Agilent 7 T scanner equipped with a rodent gradient coil reaching 600 mT/m along each axis. RF transmission was performed using a birdcage coil while reception was achieved with a quadrature surface coil.

DW-spectroscopy sequence:

Optimized DW-LASER sequence (Fig. 3) was implemented with TR/TE=2000/40 ms, δ=1 ms, Δ=12.3 ms. 2-ms HS4 (*R*=20) pulses were used for refocusing.

Experiments:

Experiments were performed on a healthy Sprague-Dawley rat. Spectra were acquired in a small voxel (40 µL) localized in the striatum (Fig. 4). All experiments consisted in acquiring both reference spectra (1 average) and metabolite spectra (192 averages) at *b*=0 and at *b*=2000 s/mm². Reference spectra were used to correct for eddy currents on metabolite spectra. Spectra were quantified using LCModel [2]. D_{av} was calculated as $-1/b.\ln(S/S_0)$.

Results and discussion

Due to the use of short TE combined with the fact that T_2 is increased and J-modulation is minimized during CPMG refocusing pulse trains such as the LASER sequence, signal quantification and ADC estimation could be achieved for 6 metabolites with a good precision (criterion was LCModel's Cramér-Rao lower bound <10%): for N-acetylaspartate (NAA D_{av}=0.14 µm²/ms), inositol (Ins D_{av}=0.12 µm²/ms), total creatine (tCr D_{av}=0.17 µm²/ms), glutamate (Glu D_{av}=0.18 µm²/ms), total choline (tCho D_{av}=0.12 µm²/ms) and taurine (Tau D_{av}=0.32 µm²/ms). These results are consistent with literature data (e.g. [3-5]), although D_{av} for taurine is relatively high.

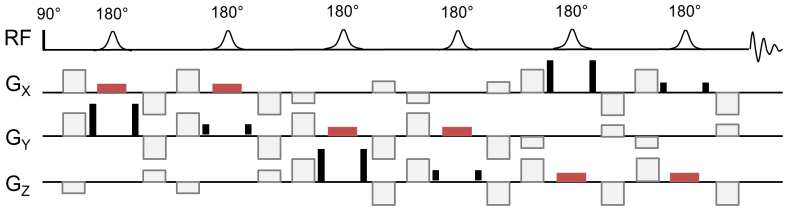

Fig. 3: *Optimized DW-LASER sequence represented in the physical frame (slice selection gradients in red, spoilers in black, diffusion gradients in light grey).*

Our sequence offers the same advantages as the sequence proposed by Valette *et al.* [1], while providing stronger diffusion-weighting. Considering identical sequence timing (*TE*=40 ms, δ=1 ms), *b* is 2.75 times higher with the present sequence. Symmetrically, this sequence allows decreasing *TE* while keeping *b* unchanged. As a consequence, the optimized DW-LASER sequence is useful to maximize measurement accuracy on a high number of metabolites (including J-modulated metabolites), which may be of great importance when investigating intracellular diffusion in challenging conditions. For example, measuring metabolite ADC in small voxels localized in deep brain structures (such as the striatum in models of Huntington's disease) may lead to new biomarkers of neurodegeneration.

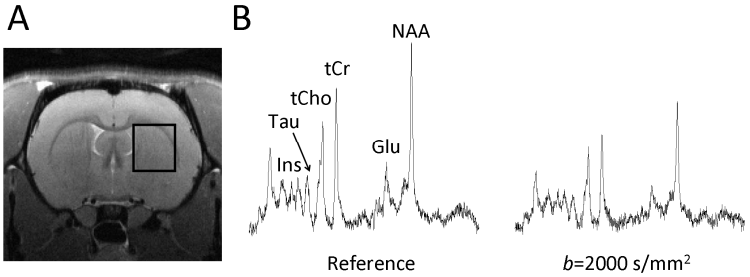

Fig. 4: *A) Position of the 40 µL voxel in the rat brain. B) Spectra acquired in the rat brain at b=0 and b=2000 s/mm² (192 averages).*

[1] Valette *Proc ISMRM* 2010; [2] Provencher *MRM* 1993; [3] Dijkhuizen *JCBFM* 1999; [4] Pfeuffer *JCBFM* 2000; [5] Dreher *MRM* 2001.