A new volume selective sequence for single-shot diffusion-weighting by the trace of the diffusion tensor

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Introduction

Diffusion-weighted (DW) spectroscopy is a unique tool for exploring the intracellular micro-environment *in vivo* [1]. In living systems, diffusion is generally anisotropic, since biological membranes may exhibit some anisotropic orientation, and signal attenuation generally depends on the orientation of the gradients relative to the cellular orientation, diffusion being characterized by the diffusion tensor **D**. Measuring the trace of the diffusion tensor $D_{av}=1/3\times(D_{xx}+D_{yy}+D_{zz})$ may be particularly interesting. Indeed, since the trace of a tensor is invariant under rotation of the reference frame, D_{av} is independent of cellular orientation within the gradient frame. This might allow the characterization of intrinsic diffusion properties of the intracellular microenvironment without bias induced by the cellular orientation. In this work, a volume selective DW-sequence allowing single-shot measurement of D_{av} is proposed. Cross-terms between diffusion gradients and other gradients (including background gradients) are all cancelled out. In addition, an adiabatic version (similar to the LASER sequence [2], with additional diffusion gradients) is derived, which provides partial immunity to cross-terms. Proof of concept is performed on anisotropic tissues (*ex vivo* chicken muscle), by varying tissue orientation and intra-voxel shim.

Theory

Cancellation of cross-terms: Let's consider the sequence in Fig. 1A, consisting in a non-selective 90° excitation followed by two identical slice selection blocks, each block consisting in a 180° pulse with a slice selection gradient G_{slice}, surrounded by spoilers G_{spoil}. Refocusing is assumed to occur at the center of the pulse. Diffusion-weighting is achieved using two gradient lobes of duration δ and amplitude G_{diff} with opposite polarities, located outside the two slice selection blocks and separated by the delay Δ. A B_0 inhomogeneity gradient G_0 is also considered. As shown graphically in Fig. 1, the particular symmetry of the sequence results in a null integral for $k_{diff}k_{spoil}$, $k_{diff}k_{slice}$ and $k_{diff}k_0$, i.e. cross-terms between diffusion gradients and other gradients cancel out: signal is only weighted by the diagonal term of **D** in the direction of G_{diff}.

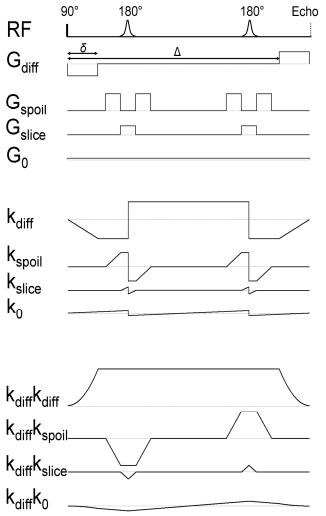

Fig.1: *Measurement of a diagonal term of the diffusion tensor with cancellation of cross-terms using a double slice selective scheme.*

Single-shot D_{av} measurement: Following the above analysis performed for a single diffusion block, it is straightforward to derive a volume selective DW-sequence made of one non-selective 90° pulse followed by three successive orthogonal blocks built by circular permutation of the gradient axes, such as shown on Fig. 2. Because the phase induced by diffusion gradients is refocused ($k_{diff}=0$) at the end of each block, these blocks are temporally isolated from each other and diffusion-weighting arising from the three blocks simply adds up:

$$\log\left(\frac{S(G_{diff})}{S(G_{diff}=0)}\right)=-3\gamma^2 {G_{diff}}^2\delta^2\left(\Delta-\frac{\delta}{3}\right)D_{av}$$

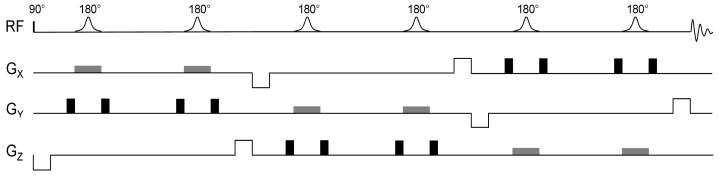

Fig.2: *Volume selective DW-sequence allowing the measurement of D_{av} in a single scan with cancellation of all cross-terms.*

Adiabatic full passage pulses and cross-terms: The use of pairs of slice selection pulses in the above sequence allows performing refocusing with adiabatic full passage (AFP) pulses, making the sequence a DW-LASER sequence. Indeed in LASER [2], the non-linear phase induced by a single AFP pulse is completely refocused by the second AFP pulse, yielding fully adiabatic volume selection without signal loss. However magnetization cannot be considered to be flipped at the middle of the AFP pulse, spins being instead flipped when the sweeping frequency of the pulse is equal to their Larmor frequency. This breaks the symmetry of the scheme presented on Fig. 1, resulting in non-zero cross-terms between G_{diff} and G_{slice} and G_0 (cross-term between G_{diff} and G_{spoil} remains equal to zero). However, a detailed theoretical analysis shows that cross-terms are proportional to the *R* factor (time-bandwidth product) of the pulse, and should be negligible in practice when R=10 or 20.

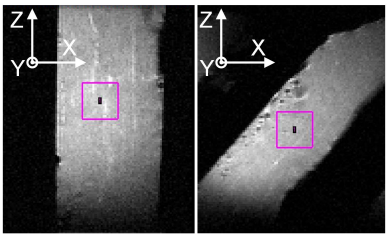

Fig.3: *Position of the 3×3×3 mm³ voxel in the chicken chest muscle ex vivo, with two different orientations of the muscle.*

Methods

The adiabatic version of the sequence (DW-LASER) was implemented on a Bruker 7 T system. A quadrature surface coil was used. The sequence was tested on an *ex vivo* chicken chest muscle by measuring the diffusion coefficient of water in a 3×3×3 mm³ voxel. Two different orientations were investigated (along Z, and rotated by 45° around Y, i.e. along XZ, see Fig. 3) while keeping the sequence gradients unchanged. In addition, two voxel shim conditions (~10 Hz and ~200 Hz) were tested for each orientation. Sequence parameters were TE=48 ms, δ=2 ms, Δ=13.8 ms. 1 ms HS1 pulses (R=10) were used for refocusing. Signal was measured for b=0, 500, 1000, 1500 and 2000 s/mm², and diffusion was evaluated by linear regression of $\log(S/S_0)$. For comparison, a DW-PRESS sequence was implemented, with TE=17.5 ms and similar δ and Δ to yield an identical diffusion time T_D. For the DW-PRESS sequence diffusion, gradients were simultaneously applied on the three axes, yielding similar b values as for the DW-LASER sequence.

Results

The diffusion coefficient measured for water under the various experimental conditions is summarized in Table 1. While the DW-PRESS yields large variations, the coefficient measured by DW-LASER is very stable, demonstrating the ability of our sequence to measure D_{av} in a single scan without significant bias by cross-terms.

	Muscle along X		Muscle along XZ	
	10 Hz shim	200 Hz shim	10 Hz shim	200 Hz shim
DW-LASER	**1.19**	**1.22**	**1.20**	**1.21**
DW-PRESS	1.27	1.40	1.35	1.57

Table 1: *Water diffusion coefficient (in µm²/ms) measured under the various experimental conditions. Values measured with DW-LASER are very stable despite variations in cellular orientation and B_0 homogeneity.*

Discussion and conclusion

Some sequences have been proposed in the past, which allowed the measurement of D_{av} within a single scan [3, 4]. In these sequences, the minimal echo time TE was six times [3] and four times [4] T_D. Besides the shorter minimal TE, the sequence proposed by de Graaf *et al.* [4] was of particular interest since it also provided volume selection. In the present work, we proposed a volume selective DW-sequence allowing the measurement of D_{av} with a minimal TE being only three times T_D. In addition, the sequence can be used with adiabatic pulses, becoming a DW-LASER sequence weighted by trace of the diffusion tensor with only minimal bias. Finally, because it is based on a CPMG pulse train, this sequence provides a substantial increase in T_2 and partial immunity to J-modulation. Therefore, this strategy may be useful for the measurement of metabolite diffusion *in vivo*, as illustrated in the mouse brain in healthy and tumor tissues [Submitted, this symposium].

[1] Nicolay *et al.*, NMR Biomed 2001; [2] Garwood and DelaBarre, J Magn Reson 2001; [3] Mori *et al.*, Magn Reson Med 1995; [4] De Graaf *et al.*, Magn Reson Med 2001.