3D DP-FISP for diffusion measurements in MR microscopy at ultra-high field.

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Target audience. The current work can interest preclinical high-field MR scientists in need of rapid and high-resolution diffusion measurement techniques.

Purpose. MR microscopy is in need of a sequence that allows rapid diffusion measurements with high spatial resolution. The use of EPI for reduced fields of view and voxel sizes leads to severe artifacts related to susceptibility differences, eddy currents and mechanical vibration. A diffusion-prepared fast imaging with steady-state free precession (DP-FISP) sequence has been recently proposed for *in vivo* preclinical imaging[1] (single slice, 0.3x0.3x2 mm^3 resolution). In this work, we aimed to program and test a 3D DP-FISP sequence with suitable timings and resolution for MR microscopy at ultra-high field (UHF). This sequence is intended to be used for diffusion measurements in small biological samples (e.g. isolated cells).

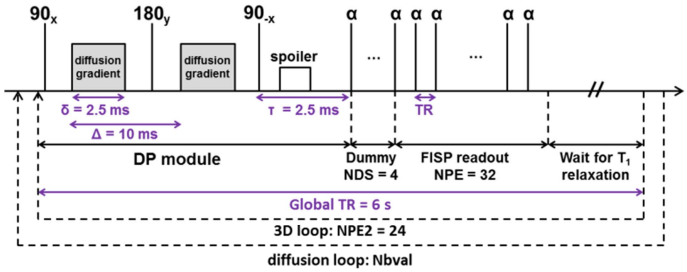

Fig.1. Schematic of the 3D DP-FISP sequence. The encoding is centric on both PE and PE2. Total time between magnetization storing and FISP readout is 23 ms. Total FISP readout time is 166 ms.

Methods. A 3D DP-FISP with centric encoding was implemented on a 17.2 T magnet (Bruker BioSpin). The acquisitions were performed using a homebuilt microcoil (700 µm ID) as RF transceiver. Because the diffusion preparation module is notoriously corrupted by longitudinal relaxation effects, the UHF is highly suited for this technique through prolonged T_1s. Nonetheless, diffusion preparation and FISP read-out timings were kept to a minimum to limit the effects of T_1 relaxation. Fig. 1 shows a schematic of the sequence, with set timings. The sequence was tested against a standard diffusion-weighted spin-echo (DW-SE) sequence, on three different phantoms. The phantoms consisted in 500 µm glass capillaries filled with aqueous solutions of various T_1s. Phantom #1 contained artificial sea water (ASW: mainly NaCl, 1090 mOsm) – with T_1 = 2960±21 ms. Phantoms #2 and #3 contained solutions of NaCl doped with $CuSO_4$ with T_1 = 1315±10 ms and T_1 = 1121±8 ms, respectively. The latter T_1 values are similar to values measured in biological samples at 17.2 T[2]. T_1 relaxation also plays a role in the establishment of steady-state, hence an important choice of the flip angle (FA) during FISP read-out: diffusion measurements with DP-FISP were performed on each phantom for five different FA values: 6/ 10/ 15/ 20/ 25° respectively. Other 3D DP-FISP parameters were as follows: b = 10/ 100/ 200/ 300/ 400/ 500/ 600 s/mm²; TE/TR = 2.6/5.2 ms; matrix 190x32x24; 25 µm isotropic resolution; NA = 4; TA = 9m36s / b-value. 3D DW-SE parameters were chosen to match closely those of the DP-FISP, only differing in the following: 128x32x24 matrix; TE = 18.45 ms; TR = 3 s; NA = 1; TA = 38m24s / b-value. Apparent diffusion coefficients (ADC) were estimated from each data set, with the DW-SE measurement taken as the gold standard. The error in ADC estimation introduced by the use of a DP-FISP sequence was calculated. Signal-to-noise ratio (SNR) was evaluated on b=10 and 600 s/mm² images for both DP-FISP and DW-SE.

Results. Table 1 collects ADC measurements in phantoms. Table 2 collects SNR measurements for DW-SE and DP-FISP (with FA = 20°) for the two extreme b values. The acquisition time of DW-SE is exactly four times that of DP-FISP, therefore an "equivalent SNR" (SNR_{eq}) was also estimated for the DW-SE.

		Phantom #1		Phantom #2		Phantom #3	
		ADC (10^{-3} mm²/s)	Error (%)	ADC (10^{-3} mm²/s)	Error (%)	ADC (10^{-3} mm²/s)	Error (%)
DW-SE		2.11 ± 0.03		2.21 ± 0.03		2.16 ± 0.02	
DP-FISP	6°	1.86 ± 0.04	-12	2.04 ± 0.10	-8	1.73 ± 0.04	-19
DP-FISP	10°	1.85 ± 0.02	-12	1.94 ± 0.05	-12	1.87 ± 0.03	-13
DP-FISP	15°	1.88 ± 0.02	-11	1.98 ± 0.02	-10	1.87 ± 0.02	-13
DP-FISP	20°	1.91 ± 0.01	-9	1.99 ± 0.03	-10	1.87 ± 0.03	-13
DP-FISP	25°	1.93 ± 0.13	-9	1.99 ± 0.03	-10	1.87 ± 0.02	-13

Table 1. ADC estimates in each of the three phantoms, obtained using DW-SE and DP-FISP with various FA. The uncertainties represent the standard deviations of the ADC fits.

Discussion. Within the range of T_1 values of interest for cellular imaging, the DP-FISP sequence underestimates the ADC by an acceptable amount (9 – 13%), for b values up to 600 s/mm². The choice of FA = 20° appears as the best compromise across phantoms. Two points are worth underlining. On the one hand, ADCs in biological samples are expected to be lower (0.2 – 1.6 x10^{-3} mm²/s, reported by Schoeniger *et al.*[3]), hence a reduced T_1 bias for identical b-values. On the other hand, going to higher b-values with DP-FISP will introduce non-negligible signal recovery from T_1 relaxation, which translates into a deviation from the linear behavior expected in a homogeneous phantom (ln (S/S_0) ≠ -b ADC). This issue has been addressed in a previous study[4], with the final recommendation being to fit ($S = A\, e^{-bD} + B$), where the "B" term will take on T_1 relaxation effects. In our experience, such fits did not prove robust due to the high number of parameters. Therefore, additional work is necessary in order to render this sequence adequate for biexponential fitting. In terms of SNR, the 3D DP-FISP displays very good performance. If time were a critical issue, the current choice of four averages could probably be reduced to one (2m24s / b-value) with SNR~5 at the highest b employed (600 s/mm²). The technique brings considerable improvement compared to sequences used previously for single cell MR imaging[3,5], which only allowed single slice acquisitions at typical resolutions of 20x20x100 µm^3 within the time imparted by cell viability.

		Phantom #1		Phantom #2		Phantom #3	
		SNR	SNR_{eq}	SNR	SNR_{eq}	SNR	SNR_{eq}
b = 10 s/mm²	DW-SE	70	35	98	49	89	45
	DP-FISP 20°	41	41	35	35	29	29
b = 600 s/mm²	DW-SE	21	11	21	11	24	12
	DP-FISP 20°	12	12	11	11	10	10

Table 2. Measured SNR in each of the six experiments: three phantoms and two modalities. SNR_{eq} accounts for acquisition time differences.

Conclusion. We have adapted a rapid diffusion MRI technique for 3D imaging at very high isotropic spatial resolution (25 µm). The technique benefits from use at 17.2 T. The errors introduced in the range of biological T_1s were estimated acceptable and parameters were optimized for error minimization. The sequence is much more time-efficient than standard DW-SE and less prone to artifacts than EPI. It can be used with confidence in the low b-value range for ADC measurements. Measurements in single biological cells using 3D DP-FISP are currently being performed. The use of the sequence in the high b-value range is being explored.

References. [1] Lu L et al. Diffusion-prepared fast imaging with steady-state free precession (DP-FISP): a rapid diffusion MRI technique at 7T. Magn Reson Med. 2012;68(3):868-73. **[2]** Radecki G et al. Toward *in vivo* functional neuroimaging of *Aplysia* using manganese enhanced MRI. ESMRMB 2012, Portugal. **[3]** Schoeniger JS et al. Relaxation-time and diffusion NMR microscopy of single neurons. J of Magn Reson B 1994;103 (3):261-73. **[4]** Coremans J et al. A comparison between different imaging strategies for diffusion measurements with the centric phase-encoded turboFLASH sequence. J Magn Reson. 1997;124(2):323-42. **[5]** Hsu EW, Aiken NR and Blackband SJ. Nuclear magnetic resonance microscopy of single neurons under hypotonic perturbation. Am J Physiol. 1996;271(6 Pt 1): C1895-900.