Increasing the sensitivity of temporal diffusion spectroscopy with circularly polarized oscillating gradient spin echo

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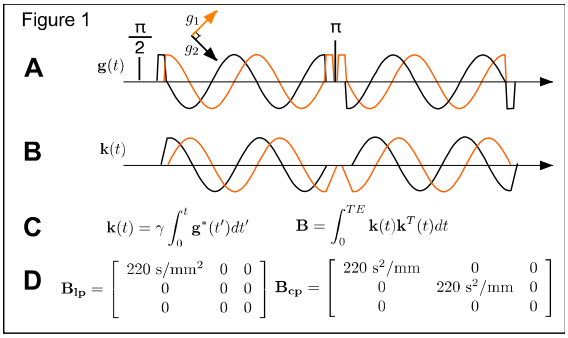
INTRODUCTION: Variations in microstructural restrictions can be investigated at short diffusion times with temporal diffusion spectroscopy using oscillating gradient spin echo (OGSE) [1]. The rate of increase in diffusivity varies in different restricted geometries with increasing oscillation frequency (i.e. decreasing effective diffusion time). This technique, in combination with diffusion tensor imaging, provides a new contrast in brain regions with densely packed cells like in the hippocampus and in the cerebellum [2]. Unfortunately, the *b*-factor decreases rapidly at high frequencies with a $1/f^2$ dependence making acquisitions on clinical scanners and other systems with moderate gradient performance hard.

Aim: To increase the diffusion weighting and thus the contrast to noise (CNR) in OGSE acquisitions we introduce the use of circularly polarized OGSE (CP-OGSE) gradients. We show that in addition to rendering the same microstructural information as conventional linearly polarized OGSE CP-OGSE improves data quality.

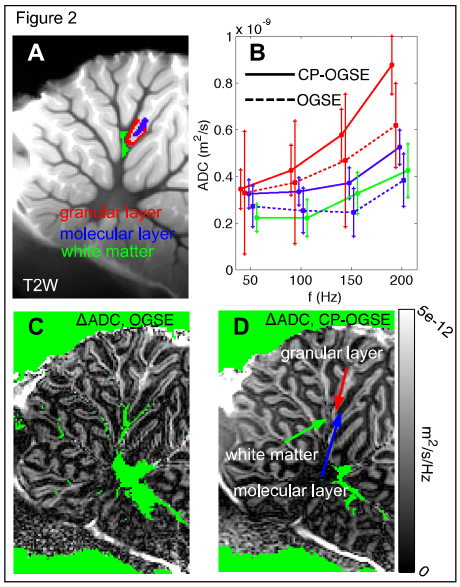
Figure 1



CP-OGSE: Figure 1A shows a CP-OGSE design with two independent orthogonally oriented gradients $\mathbf{g}_1$ and $\mathbf{g}_2$ out of phase creating a circular trajectory in phase space ($\mathbf{k}(t)$ in figure 1B). A conventional OGSE experiment corresponds to only one of these two gradients. We can use the conventional diffusion tensor formalism [3] and calculate the **B**-matrix of the CP-OGSE gradients (figure 1C). CP-OGSE creates diffusion weighting in a plane rather than along a direction and the corresponding B-matrix has two nonzero eigenvalues. $\mathbf{B}_{cp}$ in figure 1D is the **B**-matrix for one CP-OGSE trajectory in the xy-plane and has a *b*-factor (trace(**B**)) twice as large as the $\mathbf{B}_{lp}$ of a OGSE with the same frequency and gradient strength, here applied along the x-axis. Similar to OGSE and PGSE data, the diffusion tensor can be fitted to a normalized dataset with a minimum of 6 non-coplanar CP-OGSE trajectories. In this study we show that the CP-OGSE renders the same microstructural information as the OGSE and improves data quality due to the increased diffusion weighting.

METHODS: ***Gradient waveform design:*** Apodized cosine modulated gradients were used [1]. The circular trajectory was started and ended with trapezoidal pulses at G = .5 T/m (see figure 1A) to approach a cosine and a sine wave in $\mathbf{k}(t)$ (figure 1B). Maximum gradient amplitude G = 0.5 T/m was used for the highest frequency set to f = 200 Hz giving b = 220/440 s/mm2 for the OGSE and CP-OGSE respectively with a total gradient train length of 42 ms. The gradient strengths of the lower frequencies f = [50, 100, 150] Hz were adjusted to G = [.14 .26 .38] T/m to match the same *b*-values. An OGSE experiment, gradient g_2 only, was repeated along 20 uniformly distributed directions and the CP-OGSE gradients were oriented in planes with normal vectors along the same 20 directions. ***Brain tissue sample:*** An excised cerebellum from a perfusion fixed Vervet monkey was used and prepared following an optimized procedure for post mortem DWI [4]. All procedures for handling of experimental animals were approved be the relevant authorities. ***Simulation:*** White matter was modeled as parallel impermeable hexagonally packed cylinders with diameter d = 6 µm with 0.05 µm spacing and the free diffusion coefficient D = 2e-9 mm/s^2. We implemented the tissue model in the Camino software with 10000 walkers, a time step of 4.2 µs and simulated both the OGSE and the CP-OGSE in all 20 orientations [5]. ***Imaging:*** Data was acquired on an Varian 4.7 T preclinical scanner with .6 T/m gradients. Both OGSE protocols were acquired with TR/TE = 2500/68 ms, .16x.16 mm^2 in plane resolution and 2 mm slice thickness. The image plane was centered sagittally over vermis of the cerebellum. The same scan time and number of excitations were used for the OGSE and CP-OGSE protocols respectively and the protocols were interleaved with T2W b = 0 references every 5th acquisition. Total scan time was 27 hours for 2 protocols × 20 orientations × 4 frequencies + 40 T2W = 200 images. ***Data analysis:*** Image data was registered and resliced in plane to one T2W reference and normalized to the mean of all T2W images. The B-matrices were calculated by numerical integration of the gradient time vectors. Diffusion tensors were calculated using linear least square fitting and the linear increase in diffusivity as a function of f, ΔADC was calculated.

Figure 2



Tabel 1	50 Hz	200 Hz
OGSE	$[2.142, 0.160, 0.152] \cdot 10^{-9}\mathrm{m}^2/\mathrm{s}$	$[2.223, 0.654, 0.623] \cdot 10^{-9}\mathrm{m}^2/\mathrm{s}$
CP-OGSE	$[2.148, 0.164, 0.135] \cdot 10^{-9}\mathrm{m}^2/\mathrm{s}$	$[2.213, 0.654, 0.617] \cdot 10^{-9}\mathrm{m}^2/\mathrm{s}$
	D eigenvalues $[\lambda_1, \lambda_2, \lambda_3]$	

RESULTS & DISCUSSION: ***Simulated results*** for diffusion tensor eigenvalues for f = 50 and 200 Hz are presented in table 1. We found similar eigenvalues from CP-OGSE and OGSE in noise free conditions. The two minor eigenvalues were similar and incresed at high frequency due to decreased restrictions at short length scales. It should be noted that the CP-OGSE resembles the double pulsed field gradient experiment with orthogonal pulses and short mixing time. However, interaction between the two directions will only be apparent with non-Gaussian diffusion components that mainly appear at long diffusion times. The experiment is otherwise equivalent to the measurements in the individual gradient directions and the CP-OGSE is therefore a valid substitute for the OGSE at high frequencies with short effective diffusion time [6]. ***Imaging results*** are shown in figure 2. Figure 2A shows a T2W reference image with three ROIs drawn in white matter (green), in the inner granular layer of the cerebellar cortex (red) and in the outer molecular layer (blue). Differentiation between the three regions increased at higher oscillation frequency with the largest ADC increases in the densely packed granular layer (figure 2B, the colors correspond to the colors of the ROIs in 2A). The ADC was measured more consistently and with smaller variance with the new CP-OGSE approach compared to the conventional OGSE (solid vs. dashed lines). Due to low CNR, ADC could only be reconstructed in white matter using the CP-OGSE. ΔADC-maps, shown in figure 2C and 2B for OGSE and CP-OGSE respectively, had large contrast between the granular and molecular layers not visible in T2W or PGSE ADC images. Voxels with negative eigenvalues, i.e. insufficient contrast to noise, were excluded from the analysis and are colored green in figures 2C and 2D. The overall visual appearances of CP-OGSE results were similar to OGSE but less noisy.

CONCLUSION: CP-OGSE provides twice the diffusion weighting compared to conventional OGSE which is a large experimental benefit. In addition, robustness was improved on perfusion fixed brain tissue. CP-OGSE can be a significant contribution for making OGSE and temporal diffusion spectroscopy possible with higher frequencies with potential for studies of the human brain *in vivo* on clinical systems with moderate gradient strengths.

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REFERENCES: [1] Gore et al, NMR Biomed, 23, 2010.,[2] Aggarwal et al, MRM, 67, 2010, [3], Basser et al, JMR., 103 1994, [4] Dyrby et al, HBM, 32, 1994, [5] Hall et al, IEEE Trans. Med. Imag., 28, 2009. [6] Jespersen, NMR Biomed, 25, 2012