Probing metabolite diffusion at ultra-short diffusion times in the mouse brain using optimized oscillating gradients and a "short" echo time strategy

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Target audience: Those interested in diffusion NMR spectroscopy and diffusion-weighting using oscillating gradients

Introduction: Studying metabolite diffusion over a large range of diffusion times t_d allows us to be sensitive to properties in brain cell structures at various spatial scales. In particular, metabolite ADC at very short t_d (down to the millisecond) may yield information about short-range obstacles and cytosol viscosity, as we have recently proposed [1]. The only practical way to reach such short diffusion times is to use oscillating gradients for diffusion weighting. Since these diffusion times have received little attention so far, it is very important to maximize measurement quality and rule out any kind of bias. In this work we introduce a new kind of oscillating gradients, dubbed "stretched cosine", which allows increasing gradient's moment and consequently b for a given maximal gradient strength G_{max}, while preserving spectral properties of the gradient modulation spectrum. Conversely, this allowed us to reduce gradient duration and hence the echo time. In the mouse brain, this "short TE" strategy led to large SNR, including a large macromolecule (MM) signal which can be used as an internal reference, since macromolecule diffusion is so low that signal attenuation must be negligible at low b values in the absence of motion bias.

Methods: We modified the conventional apodized cosine waveform (as described in [2]) by "stretching" each lobe to increase the area under the gradient. Stretching is parameterized by an exponent α, the exact formula being given below (N being the number of periods, T_p the duration of the whole gradient waveform, and $E(x)$ the integer part of x).

$$G(t) = \begin{cases} G_{max}\cos\left(\frac{\pi}{2}\left(\frac{8Nt}{T_p}-1\right)^{\alpha}\right) & \text{for } 0 \le t < \frac{T_p}{4N} \\ (-1)^{k+1}\, G_{max}\cos\left(\frac{\pi}{2}\left(2\left(\frac{4Nt}{T_p}-k\right)-1\right)^{\alpha}\right) & \text{for } \frac{T_p}{4N} \le t < T_p - \frac{T_p}{4N},\ k = E\left(\frac{4Nt}{T_p}\right) \\ G_{max}\cos\left(\frac{\pi}{2}\left(\frac{8Nt}{T_p}-8N+1\right)\right)^{\alpha}\right) & \text{for } T_p - \frac{T_p}{4N} \le t < T_p \end{cases}$$

The case α=1 corresponds to the conventional apodized cosine gradient as described in [2], while α=infinity would correspond to an oscillating crenel. Comparison between α=1 and α=2 is illustrated in Fig. 1A. Fourier transform of gradient's moment demonstrates that spectral properties of the gradients are preserved by the stretching (Fig. 1B). We also found by numerical calculation that the associated t_d is very close to apodized cosines for a given T_p and N. Stretching yields an increase in b by a factor s(α) given in Fig. 1C. This new gradient shape was inserted in an asymmetric LASER sequence (as described in [1]) on an 11.7 T Bruker scanner with G_{max}=752 mT/m and equipped with a cryoprobe.

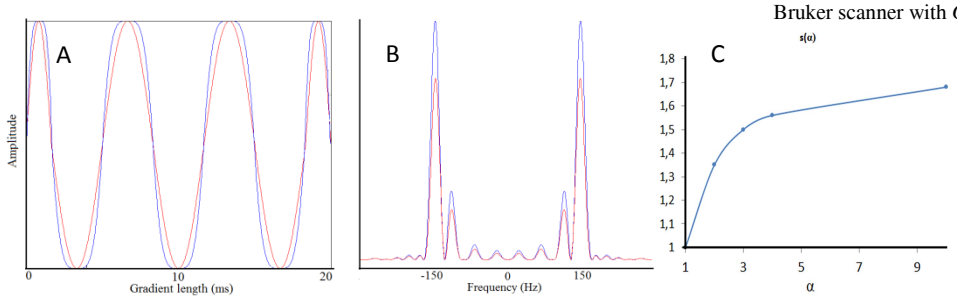
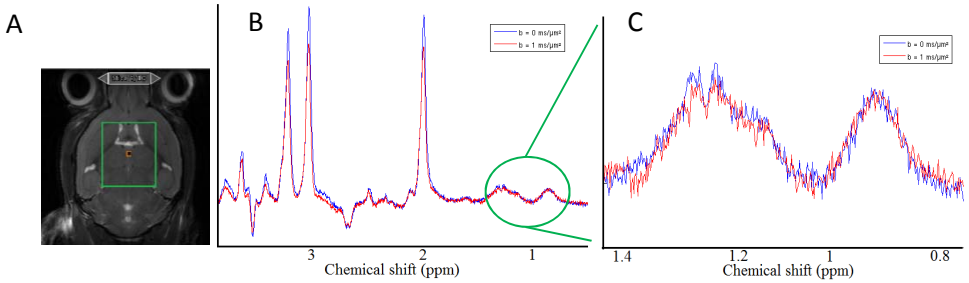


Fig. 1: Comparison of a cosine (red) and stretched cosine for α=2 (blue) for N=3. (A) waveform (amplitude); (B) gradient modulation spectra; and (C) gain in b as a function of α going from 1 to 10.

A total of 5 mice were repeatedly scanned (body weight 28-30 g). Animals were anesthetized with 1-1.5% isoflurane in a (1:1) mixture of air and oxygen. Water and metabolites spectra (64 repetitions, TE=60 ms, TR=3 s) were acquired at b=0 and for each t_d at b=1 ms/μm^2 at α=2 in a 72 µL voxel (Fig.2A). Scan-to-scan phase correction was performed, and spectra were analyzed with LCModel. ADC was quantified for NAA, total creatine tCr and total choline tCho.

Results and discussion: Stretched cosine gradient has been validated in a water phantom for α = 1, 2, 3, 4. Logarithm of signal attenuation as a function of b is linear and identical for each α ($R^2 > 0.99$), and free diffusion coefficient at 20°C were found to be $ADC_{water} = 2.15 \pm 0.03\ \mu m^2/ms$ which is the expected value. Spectra acquired in mice were of good quality and high SNR (SNR~120 on NAA peak at b = 0 ms/µm², Fig. 2B). MM signal was used as an internal control for each acquisition (Fig. 2C). Spectra showing signal drop for the macromolecule peak were discarded due to possible motion artifact. In the end 3 over 12 acquisitions (3/12) were rejected at N=1 (t_d = 5 ms), 2/9 at N=2 (t_d = 2.5 ms), 6/9 at N=3 (t_d = 1.66 ms), 7/9 at N=4 (t_d = 1.25 ms), 3/12 at N=5 (t_d = 1 ms). Some particular N (3 and 4) with a high rejection rate can be identified, presumably corresponding to some mechanical resonances of the brain for these particular gradient frequencies. Importantly, discarded data did not exhibit stronger scan-to-scan phase variation as associated with a pure translational artifact, and could therefore not be discarded based on this criterion, emphasizing the importance of the internal MM reference. Preliminary results of ADC measurements at different t_d from 5 ms to 1 ms are shown in table 1. ADC seems to increase when t_d decreases, as we have reported previously in the rat brain at lower field, but using longer TE (154 ms) and hence without detectable MM signal to use as an internal reference [1].



t_d (ms)	NAA	tCr	tCho
5	0.15 ± 0.01	0.18 ± 0.01	0.17 ± 0.02
2.5	0.19 ± 0.04	0.21 ± 0.04	0.17 ± 0.02
1.66	0.21 ± 0.01	0.25 ± 0.02	0.23 ± 0.01
1.25	0.19 ± 0.05	0.25 ± 0.03	0.24 ± 0.07
1	0.24 ± 0.04	0.26 ± 0.05	0.27 ± 0.05

Table 1: ADC measured in the mouse brain.

Fig. 2: (A) Voxel localization in the mouse brain; (B) Metabolite spectrum (no filtering) acquired at b=0 (blue) and b=1 ms/µm² (red) at t_d=5 ms (C) Zoom on MM, whose attenuation is indeed negligible as expected in the absence of motion bias.

Conclusion: We successfully implemented stretched cosine gradients and obtained encouraging firsts results on mice at very short diffusion times while keeping TE relatively short. An internal quality control based on MM signal appears to be of great importance to discard spectra corrupted by motion artifacts.

Acknowledgements: This work was funded by the European Research Council (ERC-336331-INCELL).

References: [1] Marchadour et al. *JCBFM* ; **32**(12) ; 2153–2160 [2] Does et al. *MRM* 2003; **49**; 206-215.