Comparison of NOGSE and PGSE sequences for axon diameter estimation

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Target audience. Scientists and clinicians interested in spinal cord diffusion MRI.

Purpose. MRI-based axon diameter estimation has major applications for early diagnosis of neurodegenerative diseases. Most studies have used the Pulsed Gradient Spin Echo (PGSE) sequence, which requires large gradient strength (hundreds of mT/m) to achieve proper sensitivity to small axon diameters (2-5 µm) and which is therefore not well adapted to clinical scanners [1]. By measuring the autocorrelation of spins in restricted compartment, oscillating gradient sequences introduce a novel sensitivity to restricted compartment size. The Non-Uniform Oscillating Gradient Spin Echo (NOGSE) combines two oscillating frequencies to benefit from both low frequency oscillations (equivalent to PGSE) and high frequency oscillations (equivalent to OGSE), providing a theoretically superior sensitivity to axon diameter measurements [2]. While poorly adapted to high gradient strength due to slew rate limitation (~100 mT/m/ms), NOGSE is a promising method to translate the sensitivity of axon diameter on clinical scanners. In this study, we validated NOGSE analytical equations using the Monte Carlo simulator implemented in Camino [3]. A bootstrap procedure was then used to assess accuracy and precision of PGSE and NOGSE sequences at various gradient strengths.

Methods. *Comparison Camino vs. analytical equations.* Camino software was used to simulate the parallel cylinder model and compare it with the analytical equations from the original NOGSE article [2]. The parameters for Camino were: 150,000 walkers, tmax=1000ms, hindered diffusion coefficient Dh=2.0µm^2/ms, diameter d=[4 5 6 8] µm and restricted water fraction *Fr*=0.5. Diffusion weighting period was Tnogse=60ms (TE=120ms), N=12 oscillations, G=40mT/m. The period x of the N-1 CPMG oscillations was linearly varied with 6 data points between 0 and 5ms. The period y of the Hahn oscillation filled the remaining time before the refocusing pulse. *Comparison PGSE vs. NOGSE using bootstrap.* The signal was simulated for both sequences using the analytical equations with the following parameters: G_{max}=[40, 80, 300] mT/m, TE=120ms, axon diameters d=[2 4 6 8] µm, 100 data points, hindered fraction *Fh*=0.5, Dh= 1.2µm^2/ms and Dr= 0.7µm^2/ms (restricted diffusion coefficient). PGSE: Δ=[27 52 93] ms and δ=20ms. NOGSE: N=12 chosen to maximize the signal difference between the diameters. Note that for NOGSE, x_{min} was chosen as the rise time for a corresponding G and slew rate of 100 mT/m/ms. For NOGSE, the distribution of data point was set with a quadratic distribution between the x_{min} and x_{max} (more datapoints towards x_{min}) in order to gain sensitivity to axon diameter estimation. 10% Gaussian noise was added to the data. Fitting was achieved using the Levenberg-Marquardt algorithm by varying *Fh* and *d*. Initialization of the parameters in the fitting was d=7µm and fh=0.2. Bootstrap experiment was done by running the whole procedure 500 times and then calculating mean and standard deviations of the estimated axon diameters.

Results. When compared to Camino, the analytical equation method yielded 2.18, 2.77, 3.07 and 4.62% signal increase in average between the six data points for 4, 5, 6 and 8 µm, respectively. Figure 1 and Table 1 summarize accuracy and robustness for PGSE and NOGSE using bootstrap analysis. At 40 mT/m, both PGSE and NOGSE exhibit poor accuracy, with NOGSE being slightly better: mean square error (MSE) across axon diameter was 1.81 and 1.43 µm for PGSE and NOGSE, respectively. At 80 mT/m, PGSE exhibits a systematic downward bias. MSE_{80} was 1.98 µm for PGSE and 0.53 µm for NOGSE. Note the narrower distribution of axon diameters of 8 µm for NOGSE. At 300 mT/m, both sequences provided much improved results: MSE_{300} was 0.19 µm for PGSE and 0.1 µm for NOGSE. We observed that the fitting of *Fh* presented very accurate and precise results for both PGSE and NOGSE with mean value of 0.49 ± 0.05 (ground truth was *Fh* = 0.5).

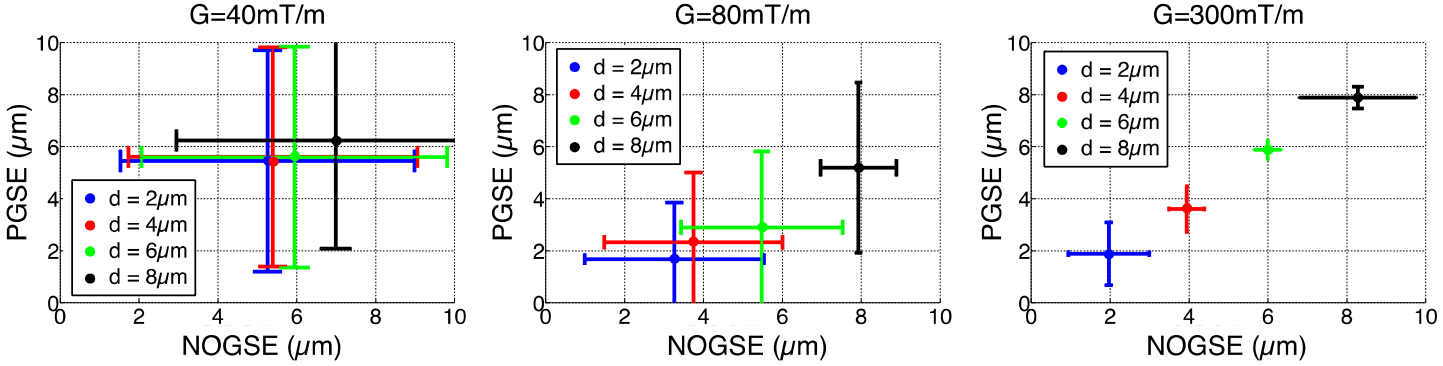

Fig. 1. Bootstraps results showing the estimated diameters for PGSE and NOGSE, with TE=120ms, SNR=10. From left to right, G=40, 80 and 300 mT/m

Diameter µm	2	4	6	8
G=40 mT/m (PGSE / NOGSE)	5.45 / 5.25	5.61 / 5.39	5.60 / 5.94	6.23 / 6.99
G=80 mT/m (PGSE / NOGSE)	1.67 / 3.26	2.33 / 3.74	2.90 / 5.48	5.19 / 7.93
G=300 mT/m (PGSE / NOGSE)	1.88 / 1.96	3.60 / 3.94	5.88 / 5.99	7.88 / 8.27

Table 1. Mean values of fitted diameter for PGSE and NOGSE at different gradient strengths.

Discussion and Conclusion. The goal of this study was to evaluate PGSE and NOGSE sequences for quantifying axon diameter at various gradient strengths. Firstly, we showed that Camino and the analytical equations of NOGSE [2] yielded similar simulation results (maximum 5% difference). Secondly, the comparative results of PGSE vs. NOGSE suggest that (*i*) the precision of axon diameter estimation increases with gradient strength for both techniques and that (*ii*) accuracy was higher for the NOGSE technique. Bias toward smaller diameter estimated in PGSE could be explained by the higher sensitivity for larger axons, giving smaller probability to overestimate than underestimate diameters. The bias toward larger axon diameter estimated at 40mT/m could be due to the high sensitivity of the gradient descent optimization to initial parameters. Another bias stems from the fact that the distribution of fitted diameters is not symmetrical for both sequences. With the current trends for stronger gradients on clinical product lines (up to 80 mT/m per channel are now available), the NOGSE technique seems a good candidate for quantifying axon microstructure. While the present study was done assuming single axon diameter distribution, further work is required to validate the accuracy of both techniques for multiple diameter distributions.

References. [**1**] Gore J, et al., NMR in Biomedecine, 2009;23:743-756. [**2**] Shemesh N, et al., Journal of Magnetic Resonance, 2013;237:49-62. [**3**] Hall MG and Alexander DC. IEEE Transactions on Medical Imaging, 2009;28:1354-1364.

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