Potential effect of varying background B_0 gradients on diffusion measurements: an *in silico* study

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PURPOSE. In diffusion weighted NMR (DW-NMR) imaging and spectroscopy experiments, susceptibility induced internal magnetic field gradients, $\mathbf{G}_{int}$, will interact with external diffusion-sensitizing gradients, $\mathbf{G}_{diff}$, producing cross-terms that may hamper accurate measurements of diffusion-derived phenomena[1]. Numerous methods have been proposed and implemented for counteracting these background gradients effects. Here we investigate two of them: the double polarity stimulated echo (STE)[2] and the magic ratio stimulated echo (MAGSTE)[3] sequences. Although it is well known that the double polarity STE fails in canceling $\mathbf{G}_{int}$ cross-terms whose amplitude varies spatially and temporally[1,2], MAGSTE was designed to compensate for $\mathbf{G}_{int}$ cross-terms whose amplitude varies during the mixing time, but remains piecewise constant during preparation and read interval[3]. However, in living tissues, such as the brain vascular network, basal ganglia and axonal myelin layers induce spatially and temporally varying $\mathbf{G}_{int}$, whose effects on measured diffusion metrics cannot be neglected, especially at high static magnetic fields and long diffusion times. As a consequence, the ability of these sequences to suppress $\mathbf{G}_{int}$ cross-terms in realistic conditions remains an important open issue. The final goal of this work is to investigate by means of numerical simulations whether double polarity STE and MAGSTE can compensate for the effects of white matter (WM) susceptibility induced $\mathbf{G}_{int}$ on DW-NMR signal, in realistic conditions.

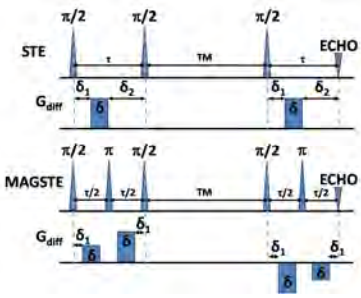

Figure1. *Schematic STE and MAGSTE sequence chronogram.*

METHODS. Towards this goal, model-related numerical simulations of water diffusion within different $\mathbf{G}_{int}$ profiles were performed: *1)* free diffusion (FD) with constant $\mathbf{G}_{int}$= (1,1,0) mT/m; *2)* FD with $\mathbf{G}_{int}$ varying during the mixing time, but piecewise constant during preparation ($\mathbf{G}_{int}$=(1,1,0) mT/m) and read interval ($\mathbf{G}_{int}$=(3,3,0) mT/m); and *3)* restricted diffusion (RD) within the Genu and Splenium of rodent Corpus Callosum (CC). Diffusion without $\mathbf{G}_{int}$ was also considered as reference for each condition. To simulate DW-signal, a Monte-Carlo (MC) simulation was implemented in C++. A total of 10^4 dimensionless spins were randomly placed in a 2D plane of 0.5x0.5 mm^2. A random walk at a rate Δt~2.5x10^{-5} s per step, with bulk diffusivity (D_0) set to 1.4x10^{-3} mm^2/s and particle step size $\Delta x=(4D_0\Delta t)^{1/2}$ was performed in free environment for cases *1)-2)* and between randomly packed axons, for case *3)*. Axonal diameter distribution and density, as derived from[4], were numerically reproduced within the plane. Specifically, the mean axon diameter ± SD and axon density percentage were: 1.0±0.3 µm, and ~50%. Assuming axons as infinitely long coaxial cylinders, with width of ~1 µm and susceptibility difference $\Delta\chi$ = -0.0132 ppm (in SI units) between water and myelin[5] the $\mathbf{G}_{int}$ was computed according to [6] at each particle's position at every MC step, by considering $|\mathbf{B}_0|$=11.7T. STE and MAGSTE sequences, reported in **Figure1**, were simulated to create the DW-signal through spin phase accumulation, taking into account the cross-terms due to magnetic field inhomogeneities. The parameters of the sequences were chosen to be similar to those of experiments we performed and report elsewhere (not shown here): τ=14 ms, δ_1=2 ms, δ_2=10 ms, δ=2 ms and three different TM=100, 500, 1000 ms. The gradient was applied along (1,1,0) and (-1,-1,0) directions, orthogonally to $\mathbf{B}_0$ direction along (0,0,1), with maximum b-value: 2000 s/mm^2 in increments of 40 s/mm^2 by changing the gradient strength. Each numerical experiment was repeated 5 times, and the simulated DW-signals were averaged across the repeated experiments to minimize the deviation from the MC simulation; the relative SD of the simulated DW-signal was ~3x10^{-3}.

RESULTS & DISCUSSIONS. **Figure2** shows results for the two FD cases investigated. Despite double polarity STE well compensates for $\mathbf{G}_{int}$ in case *1*, it does not at long TM (>500 ms) and high b-values (>1000 s/mm^2) in case *2* (**Figure2-a** and **b**, respectively). On the contrary, MAGSTE fully compensates for $\mathbf{G}_{int}$ in cases *1* and *2* (**Figure2-a** and **b**). These results show that only MAGSTE is able to fully compensate for magnetic field inhomogeneities varying in time in a piecewise constant manner (case *2*), as expected[3]. Moreover, they demonstrate the high accuracy and stability of our simulations. Considering realistic conditions, such as RD in rodents CC (case *3*), neither double polarity STE nor double polarity MAGSTE can compensate for $\mathbf{G}_{int}$ effects (**Figure2-c**). Indeed, in case of random and uncorrelated $\mathbf{G}_{int}$ variations in space and time, the ADC values measured by these techniques are underestimated respect to the real one, due to uncompensated $\mathbf{G}_{int}$ effects (**Figure2-c**). Specifically, the estimated ADC values are 11% (for TM=100 ms) 34% (for TM=500 ms) and 48% (for TM=1000 ms) lower than the real ones (i.e. calculated with $\mathbf{G}_{int}$=0, leading to constant ADC=0.44 µm^2/ms due to tortuosity, as soon as TM>100 ms), for double polarity STE; and 11% (for TM=100 ms), 25% (for TM=500 ms) and 41% (for TM=1000 ms) lower than the real ones, for the MAGSTE.

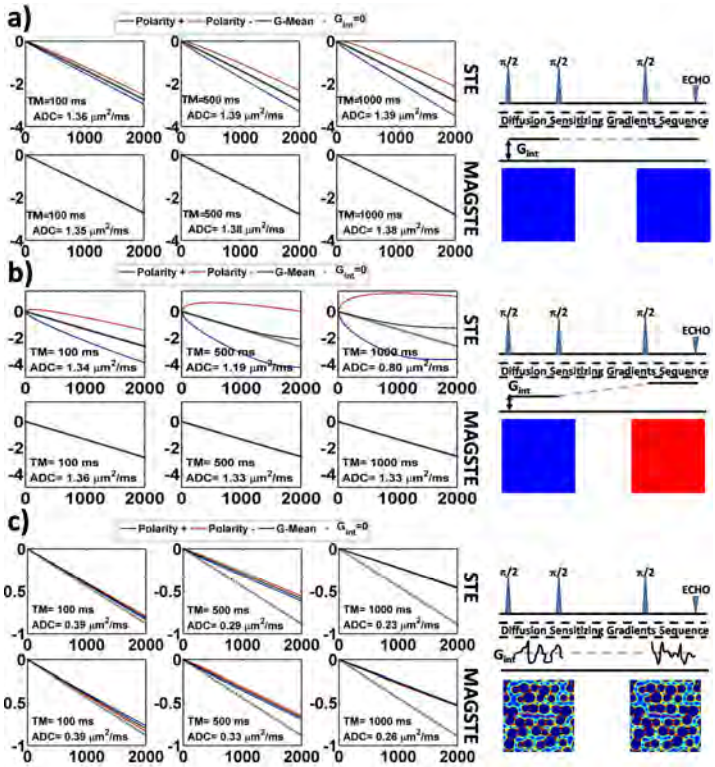

Figure2. *Normalized logarithm of double polarity STE and MAGSTE simulated signal as a function of b-value (in s/mm^2), for the two FD (**a**,**b**) and the RD (**c**) cases investigated (lines), compared to the case G_{int}=0 (points). ADC values obtained from fitting mono-exponential decay to geometric mean of double polarity signals are reported. Reference ADC values are 1.40 µm^2/ms for **a** and **b**, and 0.44 µm^2/ms, for **c** (at tortuosity limit, as soon as TM≥100 ms). Schematic G_{int} profile experienced by a single particle is also reported on the right side.*

CONCLUSION. In this work we demonstrate by using numerical simulations that neither double polarity STE nor MAGSTE can compensate for random and uncorrelated $\mathbf{G}_{int}$ variations in space and time, which is the most common condition in real heterogeneous living tissues. This echoes some experimental results we have obtain in the mouse brain at 11.7 T (not shown here), showing similar signal attenuation measured with STE and MAGSTE. However, further numerical and experimental investigations are required to identify the optimized STE and MAGSTE sequence parameters that may allow a complete or partial suppression of $\mathbf{G}_{int}$ effects *in vivo*. In particular, reducing TE may allow to be closer to the assumption of piecewise constant $\mathbf{G}_{int}$.

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