Probing Internal-Gradient-Distribution-Tensors (IGDT) by Non-Uniform Oscillating-Gradient Spin-Echo (NOGSE) MRI: A New Approach to Map Orientations in Biological Tissues

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Target Audience. Scientists interested in orientation mapping.

Purpose. Mapping fiber orientations by monitoring internal susceptibility-induced gradient distributions without relying on sample reorientations.

Introduction. Orientation mapping plays a central role in functional connectivity studies of the Central-Nervous-System (CNS). Diffusion-Tensor-Imaging (DTI)[1] Susceptibility-Tensor-Imaging (STI)[2] and T_2^* mapping[3] can map orientations of white matter tracts; however, DTI requires that the diffusion path lengths be larger than the assessed pore dimensions, while STI- and T_2^*-based mappings require rotation of the sample with respect to the main magnetic field. The latter methods also inherently rely on non-refocused experiments, giving rise to B_0-associated distortions that may obscure the sought-after microstructural features. A recent study[4] proposed a novel mechanism for probing orientations in heterogeneous media: measuring the width of the internal gradient distribution tensor[4] (herein abbreviated as IGDT). When anisotropic objects are placed in a magnetic field, the ensuing structure originates susceptibility-driven distortions of the magnetic field[4]; in a coherently aligned pack of such objects, an internal gradient distribution ensues. Han et al. have shown that the width of this internal gradient distribution constitutes a symmetric tensor, and that the ensuing IGDT will have minimal principal eigenvalues oriented along the main axis of an anisotropic structure[4]. By applying external gradients at six or more orientations the IGDT can be measured without having to reorient a sample, giving rise to a new approach to map orientations. In their initial measurements Han *et al* focused on water-filled capillaries and monitored their diffusion-driven decoherence under different pulsed-field-gradient conditions;[4] in such instances, multiple sources of decoherence may influence the measurement. Here, we develop and apply a novel approach to detect the IGDT, based on the recently introduced Non-Uniform-Oscillating-Gradient Spin-Echo (NOGSE)[5,6]. A theoretical analysis shows that by suitably exploiting symmetries of the applied gradient waveforms, NOGSE can probe the IGDT in a constant-time fashion that is free from any effects but those arising from the IGDTs being sought. Using this insight it is shown, for the first time, how WM orientations can be mapped without relying on DTI or STI.

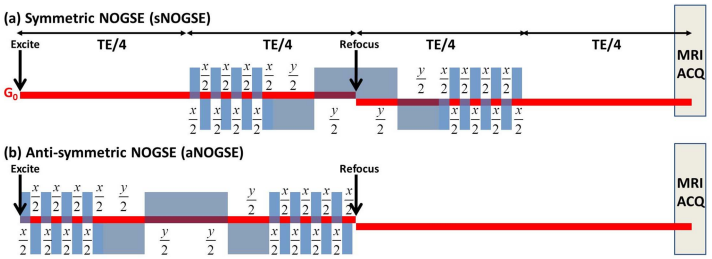

Fig. 1. (a) Symmetric-NOGSE (sNOGSE) and (b) anti-symmetric-NOGSE (aNOGSE). sNOGSE's symmetric waveform vs the central π refocusing pulse makes its cross-term with the internal gradients zero, and hence frees the experiment from IGDTs. By contrast, aNOGSE's waveform will be strongly affected by an IGDT cross-term. By changing *x* and *y* while keeping all other parameters constant the sequence becomes free from gradient/timing imperfections, T_2, T_2*, etc – enabling the characterization of subtle IGDT effects.

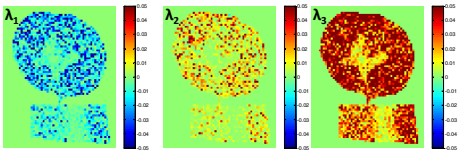

Fig. 2. IGDT eigenvalues in the spinal cord specimen.

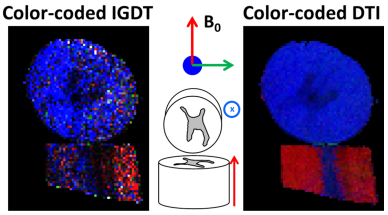

Fig. 3. Color-coded orientation maps (red up-down, blue in-out). IGDT faithfully reconstructs the orientation in these pig spinal cord segments

Theory. The method proposed herein exploits timing symmetries of novel sequences incorporating non-uniform oscillatory gradient (NOGSE) waveforms.[5,6] Two sequences are run and compared in such a way that the distributions of internal gradients can be selectively probed, whilst all other sources of decoherence –including those arising from water diffusivity, T_2, T_2* and pulse/gradient/timing imperfections– are factored out. The principles of the methodology are shown in Figure 1, and its key aspect is a reliance on two different NOGSE sequences. One of these, which we term symmetric NOGSE (sNOGSE), comprises a waveform that is mirrored with respect to a central refocusing pulse; the second is an anti-symmetric NOGSE (aNOGSE), where the gradient waveform is placed entirely on one half of the sequence. For both sNOGSE and aNOGSE, the spin-signal will decay due to diffusion processes occurring while the gradients are oscillated. These can be described by an exponential $exp(-\beta(TE))$, where the attenuating exponent is an overlap between the diffusion spectrum $D(\omega)$ and a filter function $F(\omega,TE)$ given by the Fourier transform of the total gradient modulations $G_{tot}(t) = G_{NOGSE}(t) + G_0(t)$; i.e. $\beta(t) \propto \int D(\omega)/\omega^2 |F(\omega,TE)|^2 \, d\omega$ (see Refs. 5-7). Involved in this expression is the applied NOGSE gradient waveform G_{NOGSE}, and the internal gradient G_0 that is being sought. It follows from this that the attenuation factor will comprise of three terms: $\beta(t) = \beta_{G_{NOGSE}^2} + \beta_{G_0^2} + \beta_{G_{NOGSE}*G_0}$, where the first term is given by the applied external gradient, the second term arises purely from the internal gradient, and the last term is a cross-term reflecting the interference between G_0 and G_{NOGSE}. Notice that the first two terms will be independent of the time symmetry of the sequence. By contrast, the product in the latter term will be an odd or an even function of time with respect to the center of the sequence, for sNOGSE and aNOGSE respectively. It follows that the $\beta_{G_{NOGSE}*G_0}$ term will be identically zero in sNOGSE, but will be proportional to the internal gradients (i.e., non-zero) in aNOGSE. Since all other possible sources of decoherence (T_1, T_2*, T_2, diffusion) remain identical in both sNOGSE and aNOGSE[5,6], one can selectively probe the internal gradients while removing all other sources of decoherence. It can also be shown that in the presence of internal gradient distributions, the variance of the internal gradient strengths can be determined using the comparison of sNOGSE and aNOGSE measurements. Hence this approach allows one to measure, and in combinations with MRI map, the anisotropy-imposed IGDTs.

Methods. MRI experiments were performed on a 9.4 T vertical bore Bruker AVANCE III equipped with gradients capable of producing 291 G/cm in all directions. sNOGSE and aNOGSE experiments were performed on two fixed pig spinal cord sections that were stacked one on top of the other – one parallel to B_0 and one perpendicular to it. NOGSE measurements in general involve measuring an amplitude modulation ΔM_{NOGSE} as a function of *x, y* (cf. Fig. 1);[6] in this case two images – one with x<<y and one with x=y– were recorded. These sNOGSE and aNOGSE's amplitude modulations were measured for 6 non-collinear directions {[1 1 0] [-1 1 0] [0 1 -1] [0 -1 -1] [1 0 -1] [-1 0 -1]}. The images arising from these experiments were subtracted and normalized; the ensuing six maps represent the projections of the IGDT along six non-collinear directions. IGDT's eigenvalues and eigenvectors were then obtained as described in Ref. 4. The orientation mapping scheme employed here involved the conventional DTI RGB color-mapping scheme (red: up-down, blue in-out, green: left-right). Notice that when relying on IGDTs, the minimum eigenvalue determines the principal axis of the orientation[4]. Parameters for the NOGSE MRI measurements were: TR/TE = 4000/50 ms, resolution = 156x156x1000 (μm)^3, NA = 4, G_{NOGSE} = 35 G/cm, the total number of NOGSE oscillations was 10 and the total NOGSE gradient modulation time was 20 ms.

Results and Discussion. Figure 2 shows IGDT eigenvalue maps obtained in this fashion, clearly demonstrating an anisotropy in the internal gradients. Notice that the third eigenvalue represents the maximum distribution of gradients and that, as could be expected from the variation of magnetic fields in packed cylinders, it is much larger than the other two eigenvalues[4]. Figure 3 shows fiber orientation maps arising from these IGDT characterization; clearly, the WM of the lower spinal cord segment points parallel to B_0 (red in our RGB scheme), whereas the upper spinal cord section points perpendicular to the main field (blue in our RGB scheme). Interestingly, one can also use the sNOGSE data measurements to extract the diffusion tensor. Excellent agreement between the IGDT and the diffusion tensor orientations was evidenced. The diffusion tensor shows stronger contrast to noise, likely due to the relatively small susceptibility-induced internal gradients in WM.

Conclusions. The approach reported here provides a new means for mapping orientation by probing IGDTs. As opposed to STI and T_2^* mapping, this approach benefits from a fully refocused nature that provides robustness towards global B_0 distortions, while requiring no rotation of the sample in the magnet. This approach could be of importance in those scenarios where DTI is tenuous, *i.e.*, when diffusion path lengths are not sufficiently long to fully probe the pore boundaries. Examples of such instances will be presented.

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