Signatures of microstructure in conventional gradient and spin echo signals

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Introduction: Much as non-Gaussian diffusion has long been the hallmark of tissue microstructure, non-monoexponential transverse relaxation is the hallmark of *magnetic structure*.[1-5] Here we focus on the fundamental quantity, the time-dependent transverse relaxation rate $R_2^*(t) = R_2^{\mathrm{molecular}} + R_2^{\mathrm{meso}}(t) + R_2^{\mathrm{macro}}$, and show that its time-dependent *mesoscopic* contribution $R_2^{\mathrm{meso}}(t)$ is related to the structure of magnetic susceptibility variations at the mesoscopic scale, commensurate with the diffusion length. Using a suspension of micron-sized beads, we demonstrate experimentally that the same signatures of magnetic structure are reflected in very different experimental protocols: spin echo (SE), asymmetric spin echo, and the free induction decay (measured using gradient echo). This equivalence allows us to consider which experimental setup is best suited for quantifying magnetic tissue structure on the micron scale.

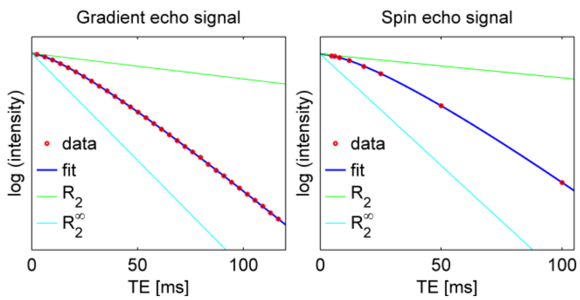

Fig. 1: Signals from multiple gradient echo and single spin echo sequences on a semilog scale from the 20µm bead phantom. The green and cyan lines indicate the asymptotic decay rates R_2 and R_2^∞ for TE → 0 and TE → ∞ respectively.

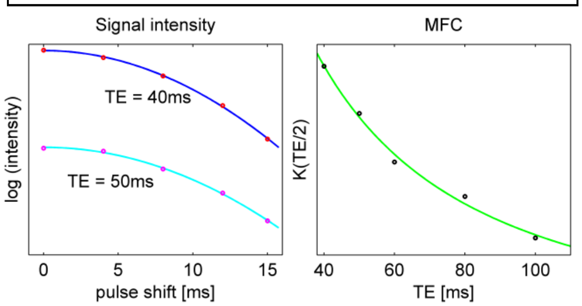

Fig. 2: Signal from the 20µm bead phantom as a function of refocusing pulse shift using the asymmetric spin echo sequence (left) and fitted MFC values as a function of TE (right).

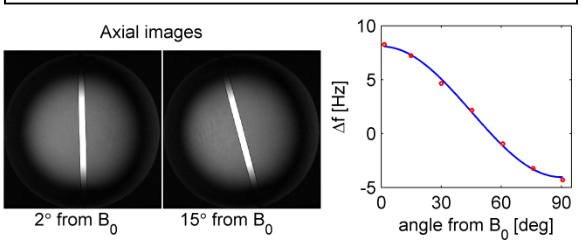

Fig. 3: Images from the orientation experiment used to measure magnetic susceptibility (left) and frequency offset of the lumen as a function of angle with respect to B_0 (right).

	Bead diameter	$\Delta\chi_{SI}$	T_2=1/R_2	T_2^∞=1/ R_2^∞
Gradient echo	15 µm	3.6×10^{-7}	401 ms	48 ms
Spin echo	10 µm	4.6×10^{-7}	622 ms	66 ms
MFC	22 µm	2.5×10^{-7}		
Orientation		3.1×10^{-7}		

Theory: The magnetic field correlation function $K(t) = dR_2^{\mathrm{meso}}(t)/dt$ along the Brownian path over time t defines the time-dependent mesoscopic rate.[2-6] For random media with correlation length l_c, $K(t) = \langle\delta\Omega^2\rangle/(1+t/t_c)^{3/2}$, where $\langle\delta\Omega^2\rangle = \langle[\delta\Omega(\mathbf{r})]^2\rangle$ is the variance in Larmor frequency Ω_0 due to magnetic field inhomogeneities, the correlation time $t_c = l_c^2/D$ is the time for water molecules to diffuse over the correlation length, and D is the diffusion constant. K can be directly measured at $t = \mathrm{TE}/2$ using an asymmetric spin echo (the MFC technique[6]). By measuring K for various TE values, and fitting for t_c and $\langle\delta\Omega^2\rangle$, the radius of the beads can be determined using $R_{\mathrm{sph}} = (6\sqrt{\pi})^{1/3} l_c$, and the susceptibility of the beads relative to the medium can be found from[5,6] $\Delta\chi_{\mathrm{SI}} = \sqrt{(45/4\eta)(\langle\delta\Omega^2\rangle/\Omega_0^2)}$ where η is the volume fraction of the beads.

We predict that this same information can be extracted from conventional gradient and spin echo signals, as they originate fundamentally from the same underlying quantity $K(t)$. It can be shown that these signals depend on microstructure through

$$\ln(S_{\mathrm{GRE}}/S_0) = -R_2 t - 2\alpha^2 \left[t/t_c - 2\sqrt{1+t/t_c} + 2\right]$$

$$\ln(S_{\mathrm{SE}}/S_0) = -R_2 t - 2\alpha^2 \left[t/t_c + 6 + 2\sqrt{1+t/t_c} - 8\sqrt{1+t/2t_c}\right]$$

where $t = \mathrm{TE}$, $\alpha^2 = \langle\delta\Omega^2\rangle t_c^2$ is the dephasing strength (with α being a typical phase acquired over time t_c), and we require that $\alpha^2 \ll 1$ to ensure validity of the theory (the same condition as for $K(t)$). By fitting α^2 and t_c we can determine the radius of the beads and their susceptibility difference from the surrounding medium using the earlier equations. Note that for short echo times the decay rate for both gradient echo and single spin echo signals approaches the molecular relaxation rate R_2, while for $t \gg t_c$ it approaches the limit $R_2^\infty = R_2 + 2\alpha^2/t_c$.

Methods: Polystyrene beads of uniform 20µm diameter were purchased from Microbeads AS (Norway). Since the beads were slightly denser than water and had a magnetic susceptibility very similar to that of water, they were mixed with a solution of 3% gelatin doped with 0.1% gadobutrol (Bayer Healthcare). The mixture was injected into a 25mL pipette (28cm long, 1.4cm inner diameter) and rotated frequently as the gelatin set to prevent the beads from settling. A second phantom containing doped gelatin without beads was prepared as a control. The phantoms were imaged at 3T (Tim Trio, Siemens) in a wrist coil using conventional multiple gradient echo (MGRE) and single spin echo (SE) sequences, as well as an asymmetric spin echo sequence to measure MFC. Imaging parameters were as follows. MGRE: 3D, 0.7mm isotropic, 32 monopolar echoes, TE = 2.46 – 116.54 ms; SE: 2D, 4mm thickness, 0.8mm x 0.8mm in-plane, repeated 8 times with TE = 4.7, 6, 8, 12, 18, 25, 50, 100 ms; MFC: 2D, 1.4mm thickness, 1.4mm x 1.4mm in-plane, refocusing pulse shifts 0, 4, 8, 12, 15 ms, TE = 40, 50, 60, 80, 100 ms, EPI factor 3. To determine the susceptibility of the beads relative to the doped gelatin, each phantom was imaged in a circular water bath at 7 orientations between 0° and 90° using a 3D MGRE sequence with 1mm isotropic resolution and 6 monopolar echoes (TE = 2.41 – 17.21 ms). The frequency difference between the tube lumen and the water bath was measured for each orientation and fitted to the equation $\Delta f = f_0 \Delta\chi_{\mathrm{SI}} (\cos^2\theta - 1/3)/2$ to determine the susceptibility difference in SI units between the lumen of the tube and the surrounding water, where f_0 is the Larmor frequency in Hz. The susceptibility difference between the beads and doped gelatin is then $\Delta\chi_{b-g} = (\Delta\chi_{m-w} - \Delta\chi_{g-w})/\eta$ where *b*, *g*, *w* and *m* denote beads, gelatin, water and bead-gelatin mixture respectively, and $\eta = 0.2$ is the volume fraction of the beads in the mixture.

Results: On a semilog scale, the signals from the bead phantom for the multiple gradient echo and single spin echo sequences decreased nonlinearly as a function of TE, in agreement with theory (Fig 1). Fits to the model functions produced estimates of the bead diameter and magnetic susceptibility that were in rough agreement with the nominal bead size and the result from the orientation experiment respectively (see table). The fitted values for the molecular relaxation time T_2, however, were longer than expected. The MFC results also provided reasonable estimates of the bead diameter and magnetic susceptibility difference.

Discussion: Conventional gradient and spin echo signals from a well-shimmed sample are generally assumed to decay monoexponentially with time scales T_2^* and T_2 respectively. We have demonstrated that these signals are more complex than typically assumed, and contain information about microstructure on a cellular scale. This has important implications for the interpretation of gradient and spin echo signals. It also suggests that simple, fast and readily available sequences such as 3D gradient echo may hold promise for extracting microstructural parameters in addition to relaxation rates in a single acquisition.

References: [1] Yablonskiy, Haacke, MRM 32:749 (1994) [2] Kiselev, Posse, PRL 81, 5696 [3] Jensen, Chandra, MRM 44:144 (2000) [4] Kiselev, Novikov, PRL 89:278101(2002) [5] Sukstanskii et al, JMR 103:236 (2003), JMR 167:56 (2004) [6] Jensen JH, MRM 55:1350 (2006). Supported by NIH NS039135 and P41 EB017183