Quantitative analysis of transverse relaxation due to strongly magnetized micron-sized spheres subjected to unrestricted diffusion in gradient echo and spin echo imaging: Validation of theory with experiments and Monte Carlo simulation

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Introduction- Detailed knowledge and understanding of the mechanisms behind transverse relaxation in the presence of strongly magnetized micron-sized spheres subjected to unrestricted diffusion is of great importance to perform MR-based quantification of paramagnetic particles in biological tissues. This applies to Holmium-loaded microspheres (HoMS) used for internal radiation therapy[1,2], but also to iron-loaded cells[3,4] and microspheres[5]. Several models[8,9,11] have been proposed to describe transverse relaxation of magnetically heterogeneous systems in the presence of diffusion, focusing on the relaxation rate parameters R2*, R2 and R2' and based on specific imaging strategies such as Gradient Echo Sampling of FID and Echo (GESFIDE)[6] and Gradient Echo Sampling of SE (GESSE)[7]. The applicability of the presented relaxation models to biological systems is not straightforward and depends among others on particle size (r) and shape, volume fraction (f), susceptibility difference (dχ), diffusion coefficient (D), B_0 field strength and imaging parameters such as the gradient echo time (TE) and the spin echo echo time (TE_{SE}). In this work the signal decay time course of FID and SE of an aqueous suspension of strongly magnetized micron-sized spheres is investigated in great detail both experimentally and using Monte-Carlo simulations. The findings are used to explore the validity and predictive value of the well-known static dephasing regime (SDR) as proposed by Yablonskiy et al.[8] and the strong field behavior (SFB) as proposed by Jensen et al.[9] for strongly magnetized micron-sized spheres subjected to unrestricted diffusion.

Methods- Phantom setup: An agarose gel (2%) HoMS dilution series with HoMS concentrations ranging from 1-15 mg/ml was prepared. HoMS contained 18.6% holmium by weight and possessed a volume susceptibility of 880ppm (SI units), a mean diameter of 30 µm and a density of 1.4 g/ml. The diffusion coefficient in the gel was determined to be 2 um^2/ms. MR imaging: GESFIDE was performed on the HoMS phantom in an interleaved fashion to characterize signal decay in great detail on 1.5T, 3.0T and 7.0T. For 1.5T and 3T the onset of the FID was sampled using ultrashort echo time (UTE) imaging. GESSE was performed on 1.5T while varying TE_{SE} (8.2; 13.9; 26.0ms). Other imaging parameters included FOV = 160x160mm; scan matrix = 120x160; slice = 10mm; TR = 500ms. Monte Carlo (MC) simulations: MC simulations were done as described by Weisskoff et al[10], using 20000 iterations, a random walk step size = 0.01ms, sampling interval = 0.1ms, SE_{TE} = (8.2; 14; 26.0ms) and system parameters similar to described above. The goal of the experiments and simulations was to describe the signal decay time course of FID and SE signal in terms of R_2, R_2' and R_2^*, to reveal the dependency on [HoMS], D and Bo and evaluate the applicability of SDR and SFB.

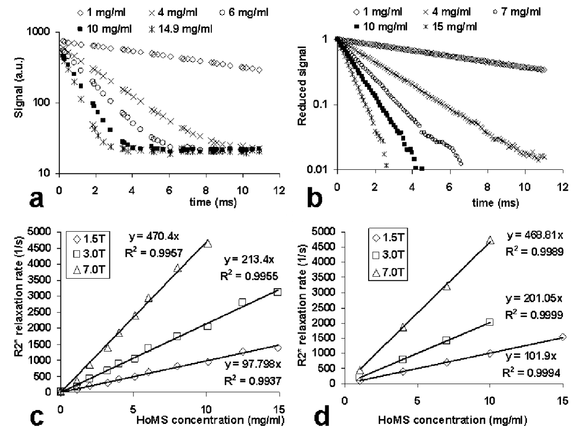

Fig 1. Monoexponential signal decay of FID at 1.5T. a) experimental; b) MC simulations. Linear relaxivity of HoMS for varying concentrations and field strengths. c) experimental; d) MC simulations.

Results- For FID monoexponential signal decay and insensitivity to diffusion was observed over a large HoMS concentration range (1-15 mg/ml) and field strength (1.5T, 3T and 7T), as shown by experiments (Fig. 1a, c) and MC simulations (Fig 1b, d). Excellent agreement with the SDR was observed, which was expected since the well-known SDR criterion for FID ($\delta\omega << \tau_D$)[8] was fulfilled. Linear r_2^* relaxivity of HoMS was demonstrated as well, also in excellent agreement with both SDR and SFB theory (Table 1), using $R_2^* \sim R_2' = \eta.f.\gamma.\Delta\chi.B_0$, in which $\eta = 2\pi/9\sqrt{3}$ for both SDR and SFB. SE signal decay time course, however, was clearly influenced by diffusion, which acts as a dampening[2] effect during rephasing leading to lowering of the SE peak as shown both experimentally (Fig. 2a) and with MC simulations (Fig. 2c). The lowered SE peak caused a nonlinear decrease of the R_2^* after the SE peak with respect to both HoMS concentration and TE_{SE} (Fig. 2b, d). This was predicted by the SDR by Yablonskiy et al[8]. and Kiselev et al.[11]. R_2 relaxation as determined from single SE at different echo times was solely caused by diffusion in inhomogeneous fields, since intrinsic R_2 (spin-spin) due to micron-sized particles is negligible. The SFB theory successfully predicts R_2 relaxation concluded from the good correspondence with both MC simulations and experiments (Fig. 3). The r_2^* relaxivity following SE peak (Fig. 4a) and r_2 relaxivity (Fig. 4b) obtained from single SE's as determined experimentally for different TE_{SE} showed excellent agreement with MC simulations as well as with the theory of SFB, implying that the SBF can be used to predict both r_2^* and r_2 of strongly-magnetized micron-sized spherical particles.

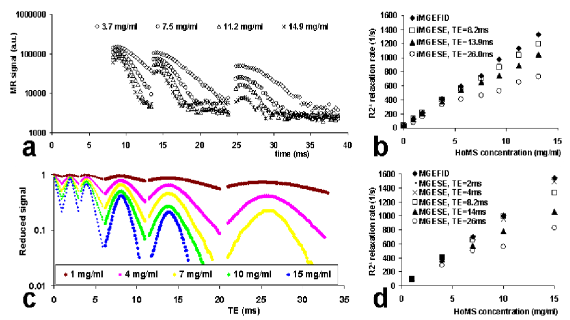

Fig 2. Signal decay time course of single SE at 1.5T as determined experimentally (a, b) and using MC simulations (c, d). A decrease of SE peak, R_2^* and r_2^* was observed with increasing SE_{TE} (b, d).

Discussion & conclusion- The signal decay time course of FID and SE of an aqueous suspension of strongly magnetized micron-sized spheres is was investigated in great detail. Excellent agreement between MR experiments, MC simulations and both SDR and SFB was demonstrated. Both theories were able to predict FID and r_2^* relaxivity, SFB also successfully predicted r_2 relaxivity for single SE experiments. Signal decay on both sides of the SE peak was influenced by diffusion, in spite of the validity of the generally used SDR criterion, which shows that it does not apply to SE experiments. This suggests that when quantifying magnetically inhomogeneous systems using R_2 determined by either GESFIDE or GESSE one should be extremely careful and sure of the validity of the used signal model. Criteria as defined by Yablonskiyet al.[8], Jensen et al.[9] and Kiselev at al.[11] may be useful to verify signal model validity. Further investigation on these criteria is needed to extrapolate the predictive value of both SDR and SFB as demonstrated in this work to other regions.

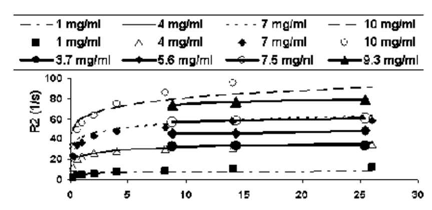

Fig 3. R_2 as a function of TE_{SE} obtained with single SE at 1.5T as determined experimentally and using MC simulations showed good agreement with the theory (lines) of strong field behavior.

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Table 1. R_2^* at 1.5, 3 and 7 T

B_0	1.5T	3.0T	7.0T
Exp.	98	213	470
Sims.	102	201	469
SDR+ SFB	102	203	474

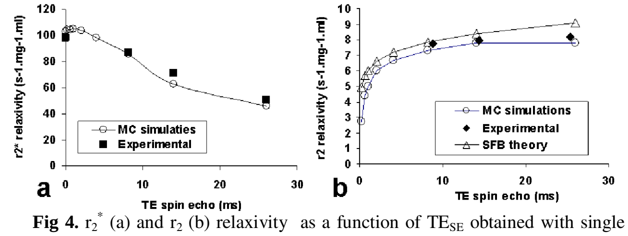

Fig 4. r_2^* (a) and r_2 (b) relaxivity as a function of TE_{SE} obtained with single SE at 1.5T showed good agreement with the theory of strong field behavior both experimentally and using MC simulations.