# Earth-field magnetic resonance imaging - investigating magnetic nanoparticle contrast in ex vivo liver

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**INTRODUCTION:** Earth-field MRI (EFMRI) may provide an accurate means to detect contrast agent concentrations which are below the detection limit of clinical MRI ($B_0$>0.5T) [1,2]. However, the detected signal strength using EFMRI is low due to the low thermal polarization at $B_0$~50μT requiring long (up to 2s) prepolarising steps at 21mT. Hence imaging times are exceptionally long and imaging resolution is low. The aim of this project was to investigate the relaxation time contrast of magnetic nanoparticles (MNPs) in order to acquire images of gels and biological tissue samples at earth magnetic field strength with a view to quantify MNP concentration in tissue.

**METHODS:** All EFMRI experiments were carried out on a system with an inner diameter of 80mm (Terranova, Magritek, Wellington, New Zealand) which provided approximately 21mT polarization magnetic field strength using 7A polarization current. The maximum gradient strength was 80μT/m. First-order shimming was achieved by supplying the three axis gradient coil set with currents of up to 10mA. An autoshim algorithm was applied, employing a modified bisection approach to iterate towards the ideal shim by maximizing the peak height. The B1-coil was tuned by 10.9pF to 2080Hz Larmor frequency. *Maghemite ($\gamma$-$Fe_2O_3$) superparamagnetic nanoparticles* were synthesised using surfactant free thermal decomposition [3]. The diameter of the MNP was measured to be 8.8±1.6nm, by Transmission Electron Microscopy (TEM), Figure 1. For earth field nuclear magnetic resonance (EFNMR) and EFMRI experiments the MNPs were stabilised in water using (3-Aminopropyl) triethoxysilane (APTES) which resulted in positively charged, electrostatically stabilised MNPs (Zeta Potential = +52mV) with a hydrodynamic diameter of 17.21 nm and a polydispersity index of 0.173 as measured by dynamic light scattering (DLS). *Rat livers* were harvested from male whistar rats (300 ± 25g) 3 hours post MNP or saline administration and immediately fixed in 10% formalin solution. After 24, they were suspended in 45ml plastic vials containing 1% agarose gel. The experimental protocol was approved by the Local Ethics Committee and was performed in accordance with the European guidelines regarding the care and use of animals for experimental procedures. *The longitudinal relaxation time* in the polarizing magnetic field was measured in a simple pulse and collect experiment (EFNMR). The polarization time was varied from 50ms in 100ms steps up to 5000ms and 8092 samples were sampled in 1s acquisition time (TR=10s) for 0.00, 0.06 and 0.12 mM [Fe]. The step width was reduced to 30ms with an average of 10 steps recorded and 4046 samples were sampled in 0.5s acquisition time (TR=4.3s) for the high concentration samples containing 0.18m, 0.24, and 0.30 mM[Fe]. The spectrum was computed from the measured free induction decay (FID) and spectral magnitudes were integrated over a range of 5Hz. The pulse duration was 3 ms for a B1 gain of 1. Delay time between excitation and recording of the first data point was set to 25ms. The total scan time for each sample was 1hr40min. The $T_{1,pol}$ and calibration curve were processed offline using a routine written in MATLAB®. *EFMRI* of the control and MNP doped liver were conducted using a 3D gradient echo sequence with 8 samples in frequency encoding direction with a read-out bandwidth of 16Hz/FOV for a FOV of 480mm in z-direction. The FOV was 160mm x160 mm in phase direction with 16 x 16 phase steps resulting in a nominal voxel resolution of 5mm x 5mm x 30mm after two-fold zero-filling. The polarization time was chosen to be 1s with a repetition time of 3s, TE=35ms, and phase gradient duration of 30ms. Twenty averages were acquired per phase encoding step resulting in a total imaging time of 4hr16min. *3T MR* images were recorded for the same control and MNP-doped livers using a $T_1$-weighted turbo spin echo sequence (TSE factor 3) with TE/TR=10ms/450ms, MTX 236x169, 2mm slice thickness, 10 slices, FOV=170mm x 153mm x 20mm, acquisition voxel size = 0.72mm x 0.90mm x 2.00mm, reconstructed voxel size = 0.27mm x 0.27mm x 2.00mm, total scan time was 6min50sec.

**RESULTS:** The EFNMR experiments resulted in measured $T_{1,pol}$ for water of 2459±107ms which reduced to 113±5ms for 0.06mM[Fe] MNP solutions. The signal evolution for different MNP concentrations is presented in Figure 2. Calibration via the difference in relaxation rates between MNP samples and water $T_{1,pol}$ resulted in a relaxivity of 29 $s^{-1}$ $mM^{-1}$ for these MNP (Figure 3). This relaxivity is comparable to the relaxivity as measured by fast field cycling nuclear magnetic relaxation dispersion (FFC-NMRD, Stelar, Italy) of 25 to 30 s-1 mM-1 when measured at comparable fields (i.e. 21mT). The EFMRI image (Figure 4) shows a clear separation between the two vials while the signal of the suspending gel remains comparable (56±6%max) for the MNP doped liver vial, 60±5%max for the control. The mean value computed for the MNP doped liver was 26±2%max while the control liver exhibited higher signal of 41±4%max.

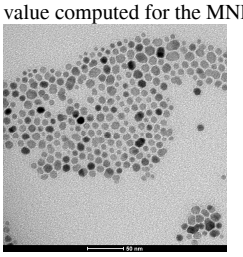

*Figure 1: TEM image of maghemite ($\gamma$-$Fe_2O_3$) super-paramagnetic nanoparticle.*

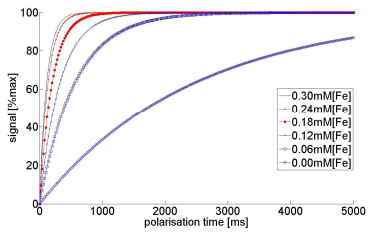


*Figure 2: EFMRI global magnitudes as a function of polarization time for different Fe concentrations.*

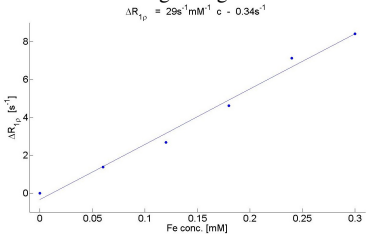


*Figure 3: calibration curve for various range of Fe concentrations in solution as measured via EFNMR of phantom experiments.*

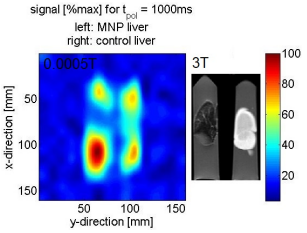


*Figure 4: EFMRI result (rgb) and 3T $T_1$-weighted image (black and-white) of the control (right vial) and the MNP-doped liver (left vial) in 1% agarose gels.*

**DISCUSSION:** The clear linear nature of the relaxation rate as a function of MNP concentration was observed which can allow for the precise quantification of MNPs using EFMRI. Clinical contrast agent concentrations need to range from 0.1 to 10mM to be picked up with high field MRI [1]. From our measurements it is clear that MNP concentrations of below 0.06mM[Fe] can be detected using EFMRI, demonstrating the potential for this technique. To date the imaging of gel and tissue like samples using EFMRI system had been regarded as challenging. Long $T_2$ samples have been imaged at earths field, e.g. Halse et al. imaged samples with long $T_2$ such as a pepper with TA=1.5hrs [4]. The imaging of non-liquid samples similar to tissue, e.g. gels has not been reported for EFMRI devices so far due to difficulties associated with short $T_2$s. EFMRI acquisition times are generally prolonged due to the required prepolarising step in the range of three times $T_1$ (appr. 7.5s for water @21mT) which can be significantly shortened through relatively low concentrations of magnetic nanoparticles. Cryogenic cooling of the highly resistive $B_1$-coil [6] can lead to more than ten-fold sensitivity improvement [6] and may enable EFMRI to become a well feasible imaging technique for clinical diagnostics in the future. Furthermore EFMRI could provide easy access to MRI for patients with contraindications such as metal implants.

**REFERENCES:** [1] Werner et al. *High-Relaxivity MRI Contrast Agents: Where Coordination Chemistry Meets Medical Imaging*, Angew. Chem. Int. Ed. 2008, 47, 8568 – 8580;[2] Lánczi et al., *Comparative examination of magnetic resonance contrast agents on low and high magnetic field, ESMRMB 2013, p.425;*[3] Ninjbadgar & Brougham 2011. Epoxy Ring Opening Phase Transfer as a General Route to Water Dispersible Superparamagnetic Fe3O4 Nanoparticles and Their Application asPositive MRI Contrast Agents. *Advanced Functional Materials, 21, 4769-4775.;[4]* Halse et al., A practical and flexible implementation of 3D MRI in the Earth's magnetic field, Journal of Magnetic Resonance 182 (2006) 75–83; [5] Dong et al. APPLIED PHYSICS LETTERS 102, 102602 (2013); [6] El-Abyad, Enhancing the Detector Sensitivity of a Radio-Frequency Surface Resonator for Potassium-39 MRI at 18.7 MHz: Probing Different Geometries at Various Temperatures, IEEE XPLORE, p444 – 7, (2012)