On the influence of particle size in MR iron quantification

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Target Audience: Physicists, biologists, technologists and physicians interested in MR iron quantification.

Introduction: Due to diffusion effects, the transverse relaxivity caused by small iron particles depends on the particles' size.[1] In the case of very small particles (<100 nm), the effective relaxivity (r_2*) is similar to the irreversible relaxivity (r_2), and r_2' is small. On the other hand, for large particles (>100 nm), r_2* is similar to the reversible relaxivity (r_2') and r_2 becomes small. Consequently, the same amount of iron can cause very different relaxation rates compromising relaxation-based iron quantification measurements. However, the bulk frequency shift is supposed to be determined by the average magnetic susceptibility of the solution and, therefore, independent of particle size, aggregation or distribution. The purpose of this work was to investigate this theoretical behavior in a phantom experiment and to discuss implications for future *in vivo* studies.

Methods: Two kinds of iron-oxide particles were investigated: Micromod (plain iron-oxide particles, 250 nm in diameter) and Feridex (dextran-coated iron-oxide cores, 5 nm in diameter). The smaller particles mimicked non-aggregated iron stores like freely dissolved ferritin (6 nm diameter)[2]. The larger particles mimicked agglomeration of iron stores in cells, like hemosiderin. The phantom consisted of a spherical bowl filled with 5L saline solution. Four 50 mL Falcon tubes were placed in the bowl's center parallel to the main magnetic field. The tubes were filled with saline and electrostatically and sterically stabilized iron-oxide particle suspensions resulting in homogeneous suspensions with iron concentrations (IC) of 0, 0.33, 0.67 and 1mg/kg. Irreversible (R_2), reversible (R_2') and effective (R_2*) transverse relaxation rates were assessed by analyzing magnitude images (e.g., left-most panel in Fig.1) acquired with a gradient echo sampled spin echo (GESSE) MRI sequence,[3] using 23 echoes with TE=46-134 ms, ΔTE=4 ms and spin echo time=82 ms. The MR frequency shifts caused by the iron particles were determined from background-field corrected GESSE phase images (e.g., right-most panel in Fig.1). Background-field correction was achieved by 7th degree 2D polynomial fitting of the tubes' surrounding.

Results: All MR-based quantities showed highly linear correlation with IC ($R^2>0.94$, $p<0.002$). Slopes of R_2, R_2' and R_2* with respect to IC, i.e., relaxivities r_2, r_2' and r_2*, were lower for the small particles (Feridex; Fig.2-left) and higher for the large particles (Micromod; Fig.2-right). In contrast to the relaxivities, linear regression of the frequency shifts revealed very similar slopes for small and large iron oxide particles (Fig.3).

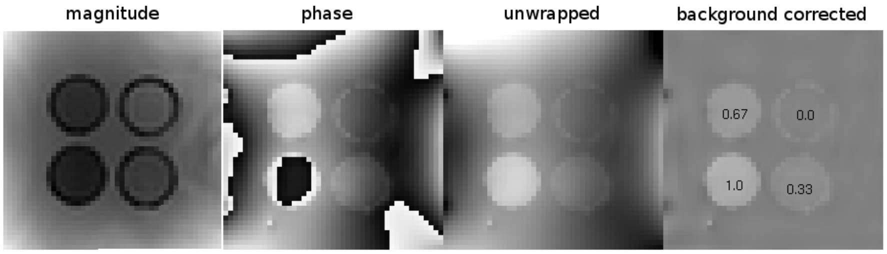

Fig.1: GESSE magnitude (left-most) and phase data (second from left). Phase was unwrapped (second from right) and corrected for background field (right-most). IC of tubes is denoted in mg/kg in right-most image.

Discussion: The much higher r_2 compared to r_2' of the small particles implies that in this case the transverse relaxation process is dominated by diffusion. The large particles showed nearly equal r_2 and r_2' relaxivities indicating that transverse relaxation of these particles is less affected by diffusion. The similar slopes of the linear regression of frequency shifts clearly demonstrate the insensitivity of this quantity with respect to particle size. However, the frequency shift is well known to be very sensitive to the shape of samples and their orientation with respect to the main magnetic field. To allow direct comparison between IC and frequency shift, orientation and shape was kept constant in this study. For heterogeneous samples, e.g., *in vivo* measurements, the phase may be converted to the underlying shape-independent magnetic susceptibility distribution using quantitative susceptibility mapping (QSM) techniques.[4]

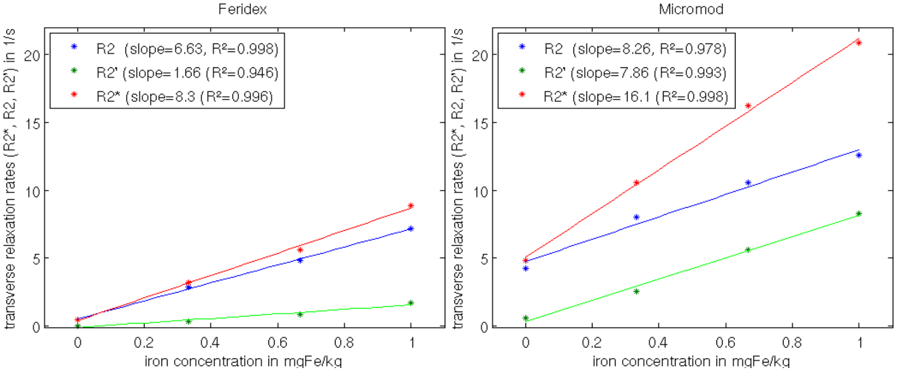

Fig.2: Transverse relaxation rates vs. iron concentration. Linear regression yielded relaxivities (slopes) that were different for the two different sized particles.

Conclusion: Results suggest that the use of MR phase data with subsequent QSM yields more robust estimates of the IC than R_2* and R_2. However, R_2* and R_2 may be useful to assess the aggregation and distribution of iron stores in the tissue matrix.

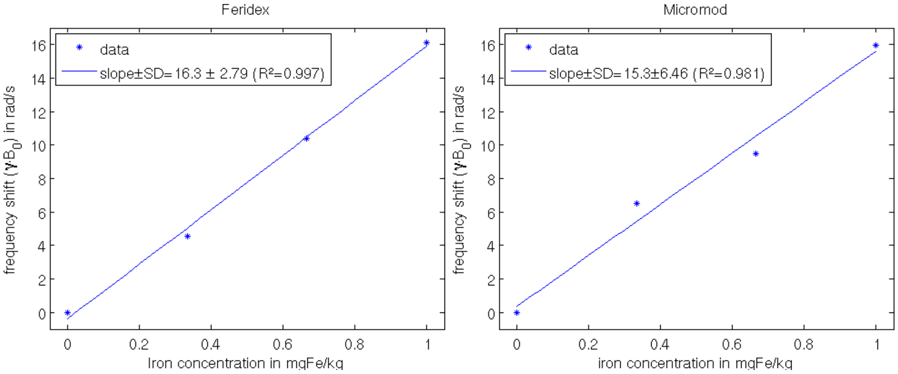

Fig.3: Frequency shift vs. iron concentration. Linear regression yielded equal slopes for both particle sizes.

References: [1] Ziener C et al. 2012. Phys Rev E Stat Nonlin Soft Matter Phys. 2012 May;85(5-1):051908. [2] Harrison PM and Arosio P, 1996. *BBA-Bioenergetics*, 1275(3), 161–203. [3] Yablonskiy DA. 1998. *Magn Reson Med.* 39: 417-428. [4] Schweser F et al., 2011. *NeuroImage*, 54(4):2789–2807.