Prediction of iron-induced MRI relaxation by Monte Carlo modeling

N. Ghugre[1,2], J. C. Wood[1,2]

[1]Division of Cardiology, Childrens Hospital Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, CA, United States, [2]Department of Radiology, Childrens Hospital Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, CA, United States

Introduction: MRI is becoming increasingly important in non-invasive quantification of iron-loaded tissue but the underlying biophysics remains poorly characterized. Since iron is stored primarily as ferritin or breakdown products of ferritin (hemosiderin), some investigators have logically studied its magnetic properties as a "starting point" (1). However, transverse relaxivity of iron-loaded tissue is much greater than that observed for ferritin alone (aqueous or in gels), most likely as a result of ferritin aggregation and sequestration (2). Support for this hypothesis comes from our observation that ferritin bound to 0.4 µm radius liposomes exhibits six-fold stronger R2 relaxivity than free ferritin (3). Moreover, our recent electron microscopy studies (4) have demonstrated that human hepatocyte iron deposits have comparable length "scale". That is, hepatocyte siderosomes range in size from 0.1 µm to 1.6 µm with a modal radius of 0.4 µm. To examine the potential role of iron fluctuations at the lysosomal scale, we employed a Monte Carlo model to simulate the effect of particle size and aggregation on iron-induced MRI signal relaxation. We then compared the computational model with human liver tissue relaxometry.

Methods: The ferritin/hemosiderin deposits were modeled as homogeneous spheres of a given susceptibility, periodically distributed in the tissue environment. Susceptibility was modeled as a 4:1 mixture of hemosiderin and ferritin using literature values (5). Diffusion of water molecules (diffusion constant, D= 0.76 μm^2/ms) was freely isotropic in three dimensions but constrained not to pass into the spheres. Size distribution and volume fraction of spheres was measured in human liver biopsy specimens by electron microscopy (4). The magnetic field was then computed as a superposition of magnetic dipoles. Diffusing water protons differentially accumulated phase according to their path through the magnetic inhomogeneities. For each case the field induction decay (FID) was measured along with a single echo experiment to obtain relaxivities R2 (1/T2) and R2* (1/T2*). A background T2 decay of 50 ms was used. We also studied systemic particle grouping by allowing 8 nearest neighbors to aggregate.

Results: Simulated R2 and R2* relaxivities are summarized in Figure 1 for representative iron concentrations (HIC). R2 demonstrated classic biphasic behavior consisting of motional averaging at small iron scale and static rephasing at large iron scale. The modal relaxivity occurred at a radius between 0.4 and 1 µm and shifted leftward with increasing iron burden. Lacking static refocusing, R2* curves monotonically increased with iron burden but demonstrated the same scale and shift as iron load increased. R2 and R2* curves were shifted to the right by increasing volume fraction but did not scale (not shown). A similar effect was seen by changing the intrinsic proton mobility (D value, not shown). Figures 2 and 3 compare observed and predicted R2* and R2 as functions of HIC for 5 patients. R2 and R2* predictions were matched to patient-specific particle size histograms, volume fractions, and iron concentration. Solid lines represent best fit calibration curves from larger clinical trials (6, 7). Predicted R2* calibration was quite close to observed values. Predicted R2 significantly overestimated observed results and did not exhibit saturation at high iron concentration. This prediction error arises from the failure to account for secondary iron distribution; our simple model had perfect, periodic particle spacing. Figure 4 demonstrates R2 as a function of inter-center distance for spheres of 3 different radii. Relaxivity dropped two-fold from static refocusing as the particles approached one another, suggesting that magnetic field fusion from particle grouping has sufficient magnitude to account for observed R2 calibration curve overestimation.

Discussion: While intermolecular "exchange" mechanisms appear to be necessary to explain the relaxivity of ferritin in solution, susceptibility-based diffusional losses dwarf the contribution of contact mechanisms in vivo. Our simple dipole model explains this observation; iron deposits are exceptionally well "tuned" to produce R2 relaxation. Either larger or smaller iron deposits would produce less susceptibility mediated R2 relaxation and exchange mechanisms would become more important in that case. In fact, the systematic model overestimation of R2 at high iron concentrations suggests that larger iron scales ARE important in the R2-iron relationship. Our simple model neglected the uneven distribution of individual dipoles. This secondary structure or aggregation increases the overall magnetic scale perceived by diffusing water protons and leads to greater static refocusing (Figure 4). Intuitively, this phenomenon will increase at high iron loads (where lysosomal volume fractions approach 10%), leading to decreased R2 sensitivity to iron (nonlinearity). We are currently testing this hypothesis by extending the Monte Carlo model to account for more complicated dipole distributions, using various parametric approximations to liver histology. We are also continuing our in vitro studies with synthetic siderosome mimics to validate our models. Nonetheless, our model predictions suggest that mesoscopic relaxation dominates microscopic effects in iron overloaded human liver.

Acknowledgements: GCRC (RR00043-43), NIH (1 R01 HL75592-01A1)

References:

1. Brooks RA, Vymazal J, Goldfarb RB, Bulte JW, Aisen P., Magn Reson Med 1998; 40:227-235.
2. Gossuin Y, Muller RN, Gillis P., NMR Biomed 2004; 17:427-432.
3. Wood JC, Fassler J, Meade T., Mag Res Med 2004;51:607-611.
4. Ghugre N, Coates TD, Nelson MD, Wood JC, Mag Res Med 2005; 54:1185-1193
5. Michaelis J, Coryell C, Granick S., J Biol Chem 1943; 148:463-380.
6. Wood JC, Enriquez C, Ghugre N, et al., Blood 2005; 106:1460-1465.
7. St Pierre TG, Clark PR, Chua-anusorn W, et al., Blood 2005; 105:855-861.

Figure 1

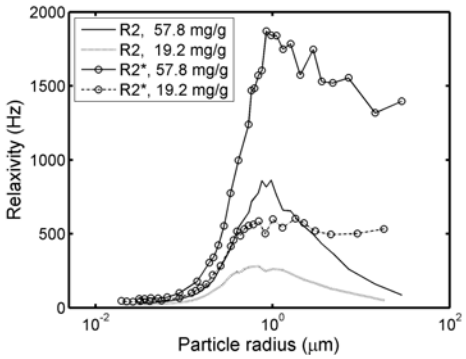

Figure 2

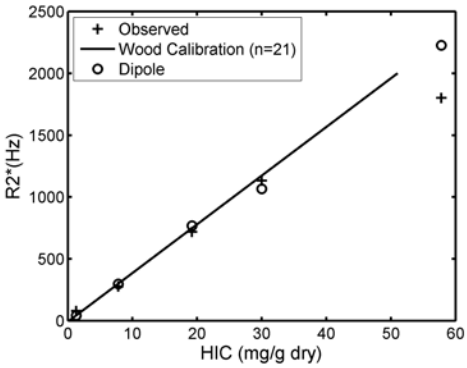

Figure 3

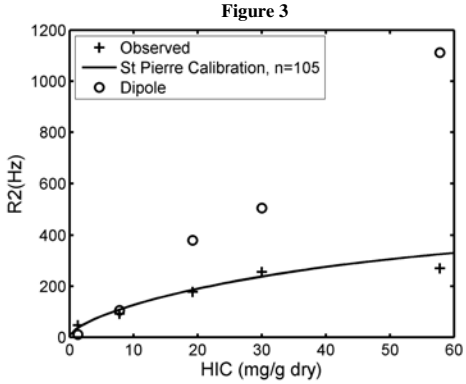
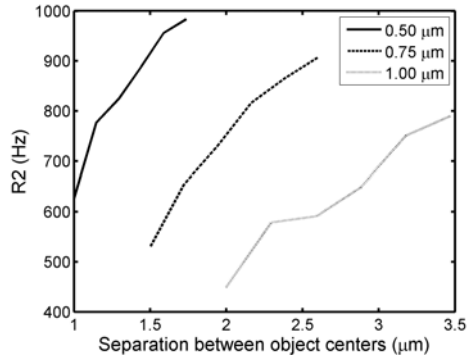
Figure 4