Modeling CPMG behavior in a realistic magnetically-heterogeneous tissue matrix

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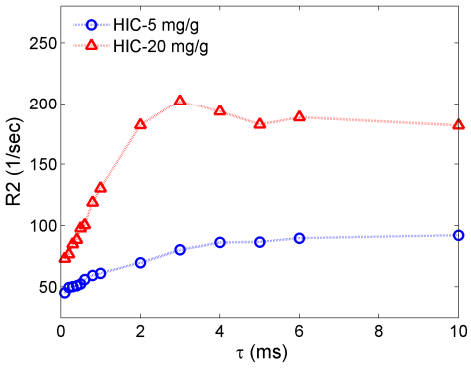
Introduction: Relaxivities R2* (1/T2*) and single echo R2 (1/T2) have been successfully calibrated for hepatic iron concentration (HIC) (1, 2) and adopted for routine clinical use. Alternatively CPMG sequences offer shorter echo times and greater insights regarding effective size of iron clusters (3) as well as diffusion and exchange times of proton pools (4). Due to these advantages, R2-iron calibrations have also been derived for multi-echo CPMG sequences (5, 6). However, influence of inter-echo spacing (τ) on relaxivity is not trivial in iron-overloaded tissues (3) and R2-iron calibration may vary with τ. Recent studies have also suggested that signal decay in iron loaded tissues has a non-exponential form (3, 7) and hence choosing an appropriate model is under question. In order to systematically interrogate the inner mechanisms of CPMG behavior, we employed a computational approach using a realistic anatomic model of liver iron overload. This study focused on validating the model by comparison with established R2-iron relationships. A validated computational model will complement existing theoretical predictions in understanding the underlying biophysics of proton-iron interaction in an iron-rich tissue matrix.

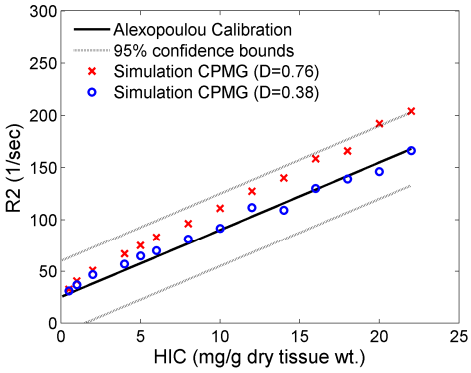
Methods: A realistic tissue matrix was simulated in the form of a 80 µm side cube consisting of 64 hepatocytes (liver cells). As previously described (8), impenetrable spherical iron deposits were distributed in this environment to mimic a HIC range of 0.5-22 mg/g dry tissue weight. Susceptibility was modeled as a 4:1 mixture of hemosiderin and ferritin using literature values. For each iron burden, multi-echo CPMG experiments were simulated with τ = 0.1-10 ms to observe R2-τ behavior. 5000 protons performed a random walk through the magnetic environment and phase accruals were converted to signal decay curves. Signals were fit to an exponential+constant model. To test sensitivity of R2, water diffusion was modeled with two different diffusion coefficients D=0.76 μm^2/ms (human liver) and D=0.38. As a first validation, R2 values at τ = 2.5 ms were compared to the calibration curve published by Alexopoulou et. al. (6). Secondly, the long echo condition (4) of R2 was tested where $\tau >> \tau_D$ (time to diffuse past a magnetized particle); τ was chosen as 6 ms. In this case, R2 values were compared to the single echo R2-HIC calibration curve (1).

Figure 1



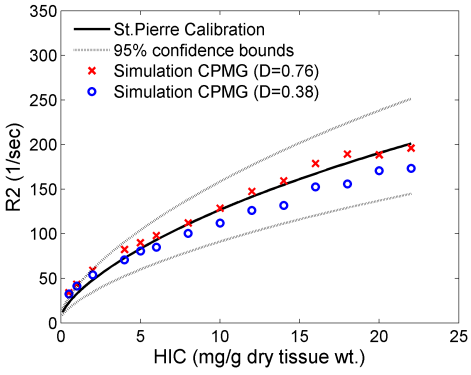
Results: Fig. 1 shows R2-τ behavior for two representative liver geometries with HIC in the low and high iron range (D=0.76 μm^2/ms). The behavior was sigmoidal in shape similar to that previously described (3) with curvature increasing with iron burden. Fig. 2 demonstrates model-predicted R2-HIC relationship at τ = 2.5 ms in comparison to calibration reported by Alexopoulou et. al. (6). Predicted R2, for both values of D, was within confidence bounds of the calibration, however the lower diffusion coefficient brought R2 much closer to it. Halving D dropped R2 by ~14.8% (±5.5%) with differences more apparent at higher HIC. The second validation for the model is demonstrated by Fig. 3; this represents R2 calibration in the long echo condition. Again, R2's for both diffusion coefficients were well within the calibration confidence bounds, over the observed range of HIC. R2 was lowered by 11.6% (±4.1%) when D was halved. R2 also followed the classic curvilinear trajectory with HIC as described previously (1, 2).

Figure 2



Discussion: The standard relaxation theory describes two types of scenarios, a) water protons diffuse past magnetic particles (outer sphere) and b) temporarily bind to them (inner sphere) (4). Our current model neglected any proton exchange or binding times and hence was based purely on an 'outer sphere' mechanism. The chemical exchange model (4) can provide approximate values for exchange/binding times and hence effective object size (3), although it is only a crude two-stage representation. These binding times can be easily incorporated in the model and a sensitivity analysis can be performed. In spite of their omission, model predictions were very close to in-vivo calibrations. The tissue model can also be helpful to interrogate the origins of the anomalous non-exponential signal behavior observed in iron loaded tissues (3, 7). Bi-exponential signal decay model divides the environment into magnetically distinct regions (fast and slow decaying components) while non-exponential model attempts to distinguish signals from ferritin and hemosiderin (different sized particles). The interpretations of these signal decay models can be tested by varying the conditions within the realistic tissue matrix (like iron compartments, diffusion, exchange times). Furthermore, the water diffusion coefficient of 0.76 μm^2/ms used here was measured in normal human liver and values for iron overloaded liver are lacking. CPMG sequences are sensitive to diffusion-based signal loss and hence the model may help quantify effective diffusion lengths of water protons as a function of iron burden. Finally, a tuned tissue-specific model of MRI relaxation will shorten the 'design cycle' for new MRI sequences and imaging conditions.

Figure 3



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