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Sensitivity of Quantitative Relaxometry and Susceptibility Mapping to Microscopic Iron Distribution

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Abstract

Purpose: Determine the impact of the microscopic spatial distribution of iron on relaxometry and susceptibility-based estimates of iron concentration.

Methods: Monte Carlo simulations and in vitro experiments of erythrocytes were used to create different microscopic distributions of iron. Measuring iron with intact erythrocyte cells created a heterogeneous distribution of iron, whereas lysing erythrocytes was used to create a homogeneous distribution of iron. Multi-echo spin echo and spoiled gradient echo acquisitions were then used to estimate relaxation parameters (R_2 and R_2^*) and susceptibility.

Results: Simulations demonstrate that R_2 and R_2^* measurements depend on the spatial distribution of iron even for the same iron concentration and volume susceptibility. Similarly, in vitro experiments demonstrate that R_2 and R_2^* measurements depend on the microscopic spatial distribution of iron whereas the quantitative susceptibility mapping (QSM) susceptibility estimates reflect iron concentration without sensitivity to spatial distribution.

Conclusion: R_2 and R_2^* for iron quantification depend on the spatial distribution of iron. QSM-based estimation of iron concentration is insensitive to the microscopic spatial distribution of iron, potentially providing a distribution independent measure of iron concentration.

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CONFLICT OF INTEREST

Dr. Colgan has no relevant conflicts of interest.

Dr. Knobloch has no relevant conflicts of interest.

Dr. Reeder has no relevant conflicts of interest. Dr. Reeder consults for ArTara Therapeutics, and has ownership interests in Calimetrix, Reveal Pharmaceuticals, Cellerar Biosciences, and Elucent Medical.

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Keywords

chemical shift encoded MRI; iron quantification; R_2 estimation; R_2^* estimation; quantitative susceptibility mapping

1 | INTRODUCTION

MRI-based iron quantification has broad clinical and research applications. Quantifying iron concentration in tissue has many important clinical applications in the liver [1, 2, 3], heart [4], brain [5, 6] as well as in the detection of atherosclerosis [7, 8], inflammation [9, 10] and risk factors for hepatocellular carcinoma [11, 12]. In addition, quantitative assessment of the biodistribution of iron-based contrast agents has various cellular biology applications including detection and quantification of contrast uptake [13, 14], cell tracking [15] and detection of cellular injury [16].

Current MRI-based iron quantification methods typically consist of measuring either relaxation parameters, such as R_2 and R_2^* [17, 18, 19], or measuring susceptibility through quantitative susceptibility mapping (QSM) [3, 5, 20]. MR relaxation parameters such as R_2 and R_2^* are sensitive to the presence of iron [17, 18, 19]. Iron deposition results in microscopic B_0 field heterogeneity, which in turn accelerates the dephasing of nearby water protons, leading to increases in measured R_2 and R_2^* . MR relaxation parameters have been shown to correlate with iron concentration [17, 18, 19, 21]. However, these relaxation parameters have a complicated empirical relationship with iron deposition [22, 23]. In contrast, QSM-based susceptibility estimation may enable iron quantification based on a well understood, linear relationship between iron concentration and tissue magnetic susceptibility [24]. Therefore, QSM has the potential to overcome the complicated empirical relationship needed for relaxometry-based iron quantification.

A potential confounder to accurate iron quantification is the microscopic spatial distribution of iron. Iron in the body is often stored heterogeneously, especially in organs like the liver and brain. Previous work has demonstrated that relaxometry is sensitive to the type of iron stored in the liver (ferritin vs hemosiderin) [25, 26] as well as within hepatocytes and/or Kupffer cells. It has also been shown via Monte Carlo simulations that MR relaxation parameters depend on the microscopic spatial distribution of iron [22, 27] due to the complicated relationship between iron deposition and R_2 and R_2^* . This dependence may pose a challenge for accurate iron quantification since the same iron concentration would result in different MR relaxation parameters depending on the microscopic spatial distribution of iron.

Magnetic susceptibility is an intrinsic property of tissue that reflects the concentration of paramagnetic substances. Unlike R_2 and R_2^* , susceptibility is potentially independent of the microscopic distribution of iron in materials with isotropic susceptibility, such as iron sequestered in the liver. A recent study in a mouse model demonstrated that iron in the liver had a heterogeneous spatial distribution and that the estimated R_2^* was a nonlinear function

of the injected iron level [28]. However, the results of Simchick et al. [28] suggest that QSM-based susceptibility estimation may directly reflect iron level despite a heterogeneous microscopic distribution of iron [28]. These data support the supposition that susceptibility is independent of the microscopic distribution of iron. However, this behavior has not been established in a highly controlled in vitro environment. Therefore, the purpose of this work was to investigate the dependence of R_2 relaxometry, R_2^* relaxometry, and QSM-based susceptibility estimation on the spatial distribution of iron using Monte Carlo simulations and highly controlled in vitro experiments.

2 | METHODS

In this work, both computer simulations and in vitro samples of human erythrocytes and varying concentrations of an iron-based contrast agent were used to investigate the dependence of MRI-based iron quantification on the spatial distribution of iron. Varying concentrations of ferumoxytol (Feraheme, AMAG Pharmaceuticals, Waltham, MA), an ultra-small superparamagnetic iron oxide (USPIO) contrast agent, were added to human erythrocytes.

Erythrocytes are large (~6–8 μm) compared to USPIOs (~25 nm) and, importantly, USPIOs cannot penetrate the erythrocyte cell wall. This creates a compartmentalization effect where iron particles cannot enter the erythrocytes. Instead, iron particles are distributed outside the erythrocyte as shown in Figure 1A and 1C. This results in a heterogeneous spatial distribution of the iron when mixed with blood. In this work, MR acquisitions were then performed to measure R_2 , R_2^* , and QSM-based susceptibility estimation in the presence of such heterogeneous distribution of iron (see details below).

Repeating the same experiment after lysis of the erythrocytes results in an experiment with the same overall iron concentration and environment as before except without intact erythrocyte cell walls. In the absence of cell walls the iron will distribute freely around the volume as shown in Figure 1B and 1D, creating a homogeneous spatial distribution of iron. Consequently, comparing the two experiments will isolate the effects due to the spatial distribution of iron only. This experimental setup was replicated using Monte Carlo simulations and phantom experiments, as described below.

2.1 | Computer Simulations

Monte Carlo computer simulations were performed over a range of iron concentrations, each with and without an intact erythrocyte. A small volume with three erythrocytes [29] and a hematocrit of 35% was simulated for computational speed. Iron particles were uniformly distributed outside the erythrocytes and the diameters were normally distributed with a mean of 25 nm and a standard deviation of 3.5 nm, similar to ferumoxytol particles [30, 31]. The susceptibility of individual iron particles was fixed at 4,500 ppm, approximated from Bullivant et al [30] and Liu et al [32]. The number of iron particles was varied to simulate different iron concentrations.

A magnetic field inhomogeneity map was generated based on the distribution and susceptibility of the iron particles. The erythrocyte and background volume was assumed to

have $R_2 = R_2^* = 50\text{s}^{-1}$ [33] and zero susceptibility, relative to water, since no iron is present. A total of 5,000 water protons [22] were simulated to diffuse at a rate of $1.16\text{ }\mu\text{m}^2/\text{ms}$, based on experimental measurements of room temperature ($\sim 21^\circ\text{C}$) blood using diffusion weighted MRI. The water protons were modelled as having restricted diffusion in and out of an erythrocyte, where the probability that a water proton will pass through the cell wall was fixed at $10\text{e-}4$ [34]. Erythrocytes and iron particles were assumed to be stationary to reduce computational complexity. Diffusing water protons accumulated phase according to their path through the magnetic field inhomogeneity map and the corresponding single spin echo (for R_2 measurement) and spoiled gradient echo (for R_2^* measurement) signals were calculated as a function of echo time. These signals were subsequently used to estimate R_2 and R_2^* using a monoexponential fit [35, 36].

QSM was not used to estimate the susceptibility in simulation due to the computational complexity of modeling the surrounding region that is needed for QSM-based susceptibility estimation. Instead, the volume susceptibility (relative to water) was approximated as

$$\chi \approx \frac{\sum_{n=1}^k V_n \chi_p}{V_T} \quad (1)$$

where k is the number of iron particles, V_n is the volume of particle n , χ_p is the fixed susceptibility of each particle, and V_T is the total volume of the cube. This calculation will be compared to the experimental results in order to demonstrate the agreement between this distribution independent expression and the QSM-based susceptibility estimates.

2.2 | In Vitro Experiments

One unit of fresh packed human erythrocytes and one unit of plasma were combined to reconstitute whole blood. The entire sample of whole blood was split into two equal volumes. One of the blood volumes was left intact, whereas erythrocyte membranes of the second volume were lysed by three 10-second sonication cycles (550 Sonic Dismembrator, Fisher Scientific, Hampton, NH) with 60 second cooling breaks between cycles to prevent protein heat damage. Complete cell membrane lysing was confirmed by light microscopic inspection. Next, the whole and lysed blood samples were separated into eight 20 mL vials and varying concentrations (0–2.7 mM) of ferumoxytol were added. The samples were placed in a room temperature water bath and placed in the scan room for 30 minutes to allow for temperature stabilization before MR imaging. The samples were gently inverted in between scans or at least every 15 minutes to prevent any settling in the vials.

MR exams were conducted using a 1.5T clinical MRI system (HDxt, GE Healthcare, Waukesha, WI) and an 8-channel phased array torso coil (USA Instruments, Cleveland, OH). For R_2 estimation, magnitude data was acquired using a 2D spin echo (SE) sequence with 20 echoes, imaging resolution of $2.3 \times 2.3 \times 6.0\text{ mm}^3$ (LR $\times$ AP $\times$ SI), a TR of 2000 ms, 3 slices, and echo times of 6–12, 15, 17, 20, 23, 26, 31, 41, 47, 55, 64, 74, 86, and 100 ms. For R_2^* and QSM-based susceptibility estimation, a 3D multi-echo spoiled gradient echo (SGRE) acquisition was performed with 12 echoes, imaging resolution of $2.0 \times 2.0 \times 2.0\text{ mm}^3$, a TR of 16.6 ms, 42 slices, a first echo of 1 ms, and an echo spacing of 0.9 ms.

Parametric maps were fit to the magnitude signal using a monoexponential fit for R_2 [35]. A previously proposed complex-fitting algorithm designed to be robust to large field inhomogeneities was used to estimate R_2^* [36, 37]. This same algorithm also provided B_0 field maps, which were used for QSM-based susceptibility estimation. The morphology-enabled dipole inversion (MEDI) QSM algorithm [38] was used, including background field removal based on a projection onto dipole fields (PDF) approach [39], in order to estimate susceptibility maps. Measurements of R_2 , R_2^* , and susceptibility were performed in each vial using regions of interest (ROIs) drawn inside each vial while avoiding any imaging artifacts and averaged over the entire volume of the vial.

3 | RESULTS

3.1 | Simulations

A central slice of the simulated field maps is shown in Figure 1C–D. B_0 field inhomogeneities are observed inside the erythrocyte due to its unique shape and the heterogeneous spatial distribution of iron.

The simulated SE and SGRE signal as a function of echo time are shown in Figure 2. The SE magnitude (used for R_2 estimation) and SGRE amplitude (used for R_2^* estimation) both depend on the presence of the intact erythrocytes, whereas the phase of the SGRE signal (as needed for QSM) is very similar between the two simulations.

The R_2 and R_2^* values estimated from the simulated SE and SGRE signals are shown in Figure 3. The estimated R_2 and R_2^* values (Figure 3A–B) are highly dependent on the presence or absence of an intact erythrocyte. In contrast, volume susceptibility (Figure 3C) does not depend on the presence or absence of an intact erythrocyte.

3.2 | In Vitro Experiments

The underlying echo data and estimated maps of R_2 , R_2^* , and field map are shown for a 2.7 mM ferumoxytol vial in Figure 4. The maps demonstrate large differences in the estimated R_2 and R_2^* between intact (first row) and lysed erythrocytes (middle row). However, no visually apparent differences are observed in the estimated field maps despite large variations occurring outside the vials. The underlying echo data (bottom row) is shown for the location marked by an X in the maps and a large difference is observed between whole blood and lysed in the SE magnitude and the SGRE magnitude but not the SGRE phase.

Substantial differences between whole and lysed blood are seen in the estimated R_2 and R_2^* as a function of varying concentrations of ferumoxytol, as shown in Figure 5. In contrast, QSM-based susceptibility measurements are insensitive to the presence of whole versus lysed blood.

4 | DISCUSSION AND CONCLUSIONS

In this work, we have demonstrated the dependence of R_2 , R_2^* , and QSM-based susceptibility estimation on the spatial distribution of iron. Monte Carlo simulations and in vitro experiments based on erythrocytes were used to generate different distributions of iron. Measuring iron in the presence of intact erythrocyte cells created a heterogeneous distribution of iron, whereas lysing or removing the erythrocyte cell walls was used to create an analogous model except with a homogeneous distribution of iron. Measurements of both R_2 and R_2^* with a fixed concentration of iron resulted in different estimates for different iron distributions. However, the estimated susceptibility using QSM was independent of the iron distribution and produced the same susceptibility value regardless of the distribution of iron. These results suggest that the spatial distribution of iron is a confounder for R_2 and R_2^* relaxation measurements, whereas QSM-based susceptibility measurements are insensitive to the distribution of iron.

Accurate quantification of iron in tissue would ideally be independent of the microscopic distribution of iron since iron is typically stored heterogeneously in the body. In this study, iron was allowed to freely distribute outside of the fixed regions, i.e. the erythrocytes, which resulted in an increase of both R_2 and R_2^* in our simulations and in vitro experiments.

However, in a similar numerical study both the R_2 and R_2^* decreased when the iron was restricted to lie inside fixed regions with no iron particles between those regions [22]. This demonstrates that a simple overestimation or underestimation is not observed in the relaxation parameters due to the spatial distribution of iron. Consequently, the only way to remove this spatial distribution dependence would require knowledge of the underlying microscopic distribution of iron, which is not typically known and difficult to measure non-invasively. A similar problem would occur in longitudinal studies where the distribution of iron might vary over time through treatment or natural processes. For example, an in vivo study observed differences between R_2 and R_2^* iron estimates due to patient-specific differences in iron-distribution that occurred throughout chelation [23]. However, using an iron quantification method that is not sensitive to the spatial distribution of iron, e.g. susceptibility estimation through QSM, might enable unconfounded measurement of the true iron concentration.

Previous work has demonstrated similar results for the spatial distribution of iron and its effects on the MR signal. The fundamental basis for how inhomogeneous tissues and varying distributions of iron affect the MR signal has been thoroughly characterized in previous studies [40, 41, 42, 43]. A recent study characterized the relaxivity of ferumoxytol in saline, plasma, and blood and observed a large difference in the properties of blood compared to saline and plasma, similar to the enhancement seen in this study when compared to lysed blood [44]. The effect of different types of iron deposition in the liver has also been investigated and relaxometry was shown to be confounded by the different types of iron, i.e. hemosiderin versus ferritin iron [25, 26]. A recent study also observed a heterogeneous distribution of iron in the liver of a mouse model with varying levels of an injected iron agent and demonstrated a nonlinear trend in R_2^* as a function of iron concentration [28]. The

R_2^* behavior measured in the mouse model of Simchick et al. [28] matches the behavior predicted by Ghugre et al. [22] and agrees with the highly nonlinear behavior in relaxometry that we demonstrated with a heterogeneous distribution of iron. Further, Simchick et al. suggested that QSM-based susceptibility estimation was more robust than R_2^* estimation for iron quantification in the mouse liver, which is further supported by this work that demonstrates that QSM-based susceptibility estimation is insensitive to the heterogeneous storage of iron.

This work has several limitations. Computational complexity limited the design of our numerical simulations and may explain in part the quantitative discrepancies between our simulated and experimental results. The number of blood cells, overall domain size, and movement of both blood and iron were limited by computer hardware and computational time. Also, measuring iron in blood was a practical biological surrogate that allowed for highly controlled experiments investigating the spatial distribution of iron, but iron quantification in blood is not the desired clinical application. Developing experiments using actual liver or brain tissue might be more directly applicable to clinical applications but was outside the scope of this work. Further, only one iron particle size was investigated in this study and previous studies have shown that relaxometry can be sensitive to particle size [41, 42, 43]. The particles used in this study (25nm) were smaller than is typically seen in the liver (0.1–3.2 μ m) [22]. However, a previous study has shown using Monte Carlo simulations that particles similar to liver iron particles also saw changes in both R_2 and R_2^* depending on the distribution of iron [22]. Nevertheless, the highly controlled experiments conducted in this work may lay the groundwork for additional, more sophisticated, experiments.

Finally, only one dipole inversion algorithm, one background field removal technique, and one set of regularization parameters were used for QSM in this work. However, different background field removal techniques and dipole inversion algorithms have been shown to produce different estimates in QSM-based susceptibility estimation [45, 46]. In this work we demonstrated that the underlying field map estimates were similar between different distributions of iron such that the resulting susceptibility estimates should be similar, despite any uncertainty in the QSM algorithm performance. The dependence of different QSM algorithms on the spatial distribution of iron and their accuracy in more complicated imaging environments, like those that occur in vivo, requires further investigation. In summary, there is a non-trivial trade-off between the advantages (including a direct relationship to iron concentration), and the disadvantages (including a more complicated data processing pipeline) of QSM-based susceptibility estimation compared to relaxometry. Ultimately, the clinical and research applicability of QSM-based susceptibility estimation may depend on the ability to develop reproducible, reliable, and computationally efficient acquisitions and computational reconstructions.

In conclusion, we have demonstrated that the spatial distribution of iron is a confounder to relaxometry-based iron quantification. Numerical simulations and in vitro experiments demonstrated that a given concentration of iron will lead to different relaxation parameters depending on the microscopic spatial distribution of iron. In contrast, QSM-based susceptibility measurements enable quantification of iron concentration, unconfounded by

the microscopic spatial distribution of iron. This work may have substantial implications for the accurate assessment of iron overload as well as imaging of iron-based contrast agents, both in clinical and research applications.

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FIGURE 1.

Iron cannot penetrate erythrocyte cell walls, which leads to a heterogeneous distribution of iron in the presence of intact erythrocytes. In contrast, the lack of intact erythrocytes results in a homogeneous distribution of iron. The images depict three human erythrocytes (modeled as a biconcave disk [29]) where no iron entered the erythrocytes (A), and the same number of iron particles distributed throughout the same volume without intact erythrocytes (B). A coronal slice through the simulated magnetic field map is shown with (C) and without (D) erythrocytes.

FIGURE 2.

Large differences between whole blood and lysed blood are seen in the magnitude of spin echo (SE) and spoiled gradient echo (SGRE) signals but only small differences are seen in the phase of SGRE signals. Plots show the simulated SE magnitude (left), SGRE magnitude (middle), and SGRE phase (right) for a simulation with intact and lysed erythrocytes.

FIGURE 3.

Simulations demonstrate that R_2 and R_2^* -based relaxometry depend on the spatial distribution of the iron particles, while the volume susceptibility does not. At each concentration, R_2 (A) and R_2^* (B) depend on the presence of erythrocytes despite having the same number of iron particles (i.e., same underlying iron concentration). The true volume susceptibility (C) is the same with and without the presence of erythrocytes, potentially enabling a more direct measure of iron concentration.

FIGURE 4.

The same concentration of ferumoxytol results in different relaxation properties but the same distortions in the field map, in a vial with intact erythrocytes versus a vial with lysed erythrocytes. The estimated R_2 (first column), R_2^* (second column), B_0 field map (third column), and estimated susceptibility (fourth column) for a vial with erythrocytes and 2.7mM ferumoxytol are shown in the top row. The middle row shows the estimated R_2 (first column), R_2^* (second column), B_0 field map (third column), and estimated susceptibility (fourth column) for a vial with lysed erythrocytes and the same concentration of ferumoxytol. The bottom row shows the normalized spin echo magnitude, spoiled gradient echo magnitude, and spoiled gradient echo phase from the locations marked in the images.

FIGURE 5.

Both the estimated R_2 (left) and R_2^* (middle) experience substantial differences between whole versus lysed blood in the presence of ferumoxytol, whereas QSM-based susceptibility measurements (right) are largely insensitive to the presence of whole versus lysed blood, and instead reflect only the ferumoxytol concentration.