Inversion recovery sequences that vary the inversion time \( t_i \) have been employed to determine \( T_1 \) and, more recently, quantitative magnetization transfer parameters. Specifically, in previous work, the inversion recovery pulse sequences varied \( t_i \) only while maintaining a constant delay \( t_d \) between repetitions. \( T_1 \) values were determined by fitting to a single exponential function, and quantitative magnetization transfer parameters were then determined by fitting to a biexponential function with an approximate solution. In the current study, new protocols are employed, which vary both \( t_i \) and \( t_d \) and fit the data with minimal approximations. Cramer-Rao lower bounds are calculated to search for acquisition schemes that will maximize the precision efficiencies of \( T_1 \) and quantitative magnetization transfer parameters. This approach is supported by Monte Carlo simulations. The optimal \( T_1 \) schemes are verified by measurements on MnCl₂ samples. The optimal quantitative magnetization transfer schemes are confirmed by measurements on a series of cross-linked bovine serum albumin phantoms of varying concentrations. The effects of varying the number of sampling data points are also explored, and a rapid acquisition scheme is demonstrated in vivo. These new optimized quantitative imaging methods provide an improved means for determining \( T_1 \) and magnetization transfer parameter values compared to previous inversion recovery based methods. 

Magnetization transfer (MT), or spin exchange between protons in different tissue pools, can serve as a contrast mechanism in biologic systems. MT between free water and a broad, immobile pool of protons on macromolecules was first demonstrated by Wolff and Balaban (1), who measured the equilibrium magnetization \( M_e \) of water protons after applying continuous irradiation. Subsequently, Henkelman et al. (2) developed a two-pool model and performed measurements on agar gels. By varying the radiofrequency offset frequency and amplitude, they determined the relaxation and exchange rates of the two proton pools. This determination of the underlying sample parameters is referred to as quantitative magnetization transfer (qMT).

Several qMT imaging methods have been developed. Sled and Pike (3,4) extended the technique of Henkelman et al. (2) to pulsed MT, in which off-resonance saturation pulses are interleaved with on-resonance excitation pulses. Ramani et al. (5) combined the method of Sled and Pike (3,4) with an analysis similar to Henkelman et al. (2). Gloor et al. (6) developed a qMT imaging method based on balanced steady state free precession (SSFP), while Ropele et al. (7) developed a method based on stimulated echoes. Gochberg et al. (8) and Gochberg and Gore (9,10) developed a selective-inversion-recovery (SIR) technique, a qMT imaging method based on measuring the transient response to an radiofrequency pulse that selectively inverts the free water protons. MT induces biexponential recovery of longitudinal magnetization in most tissue types, including in vitro collagen (11,12), muscle (11), cartilage (13), and lung (14), and in vivo white matter (WM), gray matter (GM), and muscle (10). Prantner et al. (15) examined and dismissed non-MT explanations for this biexponential behavior in brain matter. In the most recent version of the SIR method (16), a fast-spin-echo (FSE) readout is applied, which leaves both the liquid and solid proton pools saturated and therefore facilitates determination of qMT parameters, using shorter repetition times.

The precision and accuracy of the estimates of the qMT parameters depend on several experimental factors, such as the MT pulse power \( \omega_p \) and offset frequency \( \Delta \) for pulsed MT and the inversion recovery time \( t_i \) and pre-delay time \( t_d \) for SIR-FSE. In most published MT protocols, the set of sampling points is selected empirically. Cramer-Rao lower bounds (CRLB) (16) provide a general approach to assess this dependence on acquisition parameters by setting a lower limit on the variance of any parameter estimate based on model fitting. This method has been used to optimize acquisition schemes for \( T_1 \) measurements with constrained scan time (17), \( T_2 \) measurements (18), diffusion coefficients (19), and echo spacing for multiecho imaging (20). In Sled and Pike’s pulsed-MT work (4), they used only two values of \( \omega_p \), each with a range of \( \Delta \). Based on the Ramani et al. model (5), the pulsed-MT technique was optimized by Cercignani and Alexander (21) by calculating the CRLB to obtain optimal acquisition protocols.

Optimized Inversion Recovery Sequences for Quantitative \( T_1 \) and Magnetization Transfer Imaging

Ke Li,¹²∗ Zhongliang Zu,¹² Junzhong Xu,¹² Vaibhav A. Janve,¹,³ John C. Gore,¹,²,⁴ Mark D. Does,¹,²,⁴ and Daniel F. Gochberg¹–³

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Magnetization transfer (MT), or spin exchange between protons in different tissue pools, can serve as a contrast mechanism in biologic systems. MT between free water and a broad, immobile pool of protons on macromolecules was first demonstrated by Wolff and Balaban (1), who measured the equilibrium magnetization \( M_e \) of water protons after applying continuous irradiation. Subsequently, Henkelman et al. (2) developed a two-pool model and performed measurements on agar gels. By varying the radiofrequency offset frequency and amplitude, they determined the relaxation and exchange rates of the two proton pools. This determination of the underlying sample parameters is referred to as quantitative magnetization transfer (qMT).

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The SIR-FSE technique, Gochberg and Gore (10) used a constant \( t_d \) and varied \( t_i \) only. The experimental data were then fitted to a biexponential equation to determine first-order approximations of the qMT parameters. The current paper focuses on the optimization of this technique (10), introduces a new data analysis method as part of this optimization, and employs a new protocol that varies both \( t_i \) and \( t_d \) and fits the data with minimal approximations. CRLB are calculated to search for the variations in both \( t_i \) and \( t_d \) that will maximize the precision efficiency. The optimal schemes are supported by Monte Carlo simulations and confirmed by measurements on bovine serum albumin (BSA) phantoms. It is further demonstrated that, in practice, only five sampling points are required to determine qMT parameters and is confirmed with in vivo rat brain measurements.

SIR-FSE is essentially an inversion recovery method with the assumption of biexponential recovery due to MT. Independently varying \( t_i \) and \( t_d \) also improves the precision efficiency of simple \( T_1 \) measurements, when assuming a single exponential recovery. While this method is often replaced by the more rapid single-shot (22,23) and variable-flip-angle methods (24–26), we include a variable \( t_d \) analysis of \( T_1 \) here for its inherent interest and as an introduction to the more complex qMT case.

\section*{THEORY AND MATERIALS AND METHODS}

\subsection*{Inversion Recovery Imaging Sequence}

Conventionally, \( T_1 \) is determined by using an inversion recovery sequence (similar to Fig. 1) with \( t_d \geq 5 \ T_1 \), during which the magnetization returns to its equilibrium state before the next sequence repetition. Previous work has optimized \( T_1 \) measurement efficiency using constant \( t_d \) or constant pulse repetition time (17). Here we will take a more general approach by varying both \( t_i \) and \( t_d \) independently without constraint. For an inversion recovery with a spin-echo or FSE readout, the measured signal is:

\[
S = M_0 \left[ S_f (1 - e^{-t_i/T_1}) e^{-t_d/T_1} + 1 - e^{-t_i/T_1} \right]
\]

where \( M_0 \) is the magnetization of the equilibrium state, and \( S_f \approx -1 \) quantifies the effect of the inversion pulse.

\subsection*{SIR-FSE qMT Imaging Sequence}

The SIR-FSE pulse sequence (10) is illustrated in Fig. 1. In order to model the signal when pulse repetition time is short, an essential insight is that at the end of each repetition, both the macromolecular and free water pools have zero \( z \)-magnetization. The assumption has been discussed numerically and verified previously (10).

The qMT data analysis is based on a two-pool model. The coupling between the pools is modeled by adding coupling terms to the Bloch equations, as given in (9,10):

\[
\frac{d}{dt} M_j(t) = -R_j \left( \frac{M_j(t)}{M_j^{\infty}} - 1 \right) - k_{jm} \left( \frac{M_j(t)}{M_j^{\infty}} - \frac{M_m(t)}{M_m^{\infty}} \right)
\]

\[
\frac{d}{dt} M_m(t) = -R_m \left( \frac{M_m(t)}{M_m^{\infty}} - 1 \right) - k_{mf} \left( \frac{M_m(t)}{M_m^{\infty}} - \frac{M_j(t)}{M_j^{\infty}} \right)
\]

where \( M_j^{\infty} \) and \( M_m^{\infty} \) are the longitudinal magnetizations at time \( t, \) whose equilibrium values are \( M_j^{\infty} \) and \( M_m^{\infty}. \) \( R_j \) and \( R_m \) are the longitudinal relaxation rates of the free and macromolecular pools when there is no MT between them, and \( k_{jm} \) and \( k_{mf} \) are the rates of MT between them. The pool size ratio (\( \rho_{ms} / \rho_j \)) is defined by \( k_{mf} / k_{jm}. \) The recovery of the magnetization of the free pool is described by a biexponential decay function when there are no radiofrequency pulses:

\[
\frac{M_f(t)}{M_f^{\infty}} = b_1 e^{-R_f t} + b_2 e^{-R_s t} + 1
\]

where

\[
2R_f^2 = R_{1f} + R_{1m} + k_{fm} + k_{mf}
\]

\[
\pm \sqrt{(R_{1f} - R_{1m} + k_{fm} - k_{mf}) + 4k_{fm}k_{mf}}
\]

\[
b_f^2 = \pm \frac{(M_f(0)M_m^{\infty} - M_m(0)M_f^{\infty})k_{fm}}{R_{1f} - R_{1m}}
\]

where \( R_{1f} \) and \( R_{1m} \) are the fast and slow recovery rates, respectively. The magnetization of the macromolecular pool is described by a biexponential equation as well, by exchanging \( f \) and \( m \) subscripts in Eqs. 3 and 4.

Applying Eqs. 3 and 4 to each free evolution period gives the signal as function of the qMT parameters, allowing us to investigate the problem and fit the qMT parameters without taking the first-order approximations utilized previously (8–10). Specifically, both pools have zero \( z \)-magnetization at the end of the FSE train, their magnetization at the end of \( t_d \) is written as

\[
\frac{M_j(t_d)}{M_j^{\infty}} = \frac{R_{1f} - R_{1m} + R_{1f} - R_{1m} e^{-R_{1f} t_d} + R_{1f} - R_{1f} e^{-R_{1f} t_d} + 1}{R_{1m} - R_{1m} e^{-R_{1m} t_d} + R_{1m} - R_{1m} e^{-R_{1m} t_d} + 1}
\]

\[
\frac{M_m(t_d)}{M_m^{\infty}} = \frac{R_{1m} - R_{1m} e^{-R_{1m} t_d} + R_{1m} - R_{1m} e^{-R_{1m} t_d} + 1}{R_{1f} - R_{1f} e^{-R_{1f} t_d} + R_{1f} - R_{1f} e^{-R_{1f} t_d} + 1}
\]

The effect of the inversion pulse is,

\[
\frac{M_f(t_d)}{M_f^{\infty}} = S_f \frac{M_f(t_d)}{M_f^{\infty}}
\]

\[
\frac{M_m(t_d)}{M_m^{\infty}} = S_m \frac{M_m(t_d)}{M_m^{\infty}}
\]

where \( S_f \) and \( S_m \) are the inversion coefficients of the free and macromolecular pools, and \( t_d \) and \( t_d’ \) are the time just before and after the inversion pulse, respectively.
The model discussed above contains seven parameters: $R_{1T}$, $R_{1m}$, $p_{ref}$, $p_j$, $k_{mf}$ ($k_{mf}$ is equal to $k_{ref} \times p_{ref}/p_j$), $S_f$, $S_m$, and $M_{fco}$. Among these parameters, the signal dependencies on $S_m$ and $R_{1m}$ are weak, as shown below. The weak dependence on $R_{1m}$ is also the case in the pulsed saturation sequence (3–5,21). In this work, $R_{1m}$ is set to be equal to $R_{1T}$ for data analysis. Previous results (10) calculated an $S_m$ of $0.83 \pm 0.07$ from numerical simulations, for a 1-ms hard inversion pulse on a solid pool with a Gaussian lineshape and a $T_2$ between 10 $\mu$s and 20 $\mu$s. There are then five remaining qMT parameters to fit: $R_{1T}$, $p_{ref}$, $p_j$, $k_{mf}$, $S_f$, and $M_{fco}$. $S_f$ is expected to be $-1$, but due to amplitude of static field and amplitude of radiofrequency field inhomogeneities, it has to be fit from experimental data. Finally, combining Eqs. 3–6 for each time period gives a signal function, which we use to fit the qMT parameters directly without first-order approximations.

CRLB Theory

The optimization technique presented in this work is similar to that of Cercignani and Alexander (21) but is applied to a different pulse sequence and includes acquisition time effects when calculating parameter precisions. For a set of particular qMT parameters, the CRLB for the objective function, which we use to fit the qMT parameters directly without first-order approximations, is given by:

$$V = \left( \sum_{j=1}^{Q} \left| J^{-1}_{jj} \right| p_j^{-2} \right) ^{-1} \times T_{\text{cost}}(\text{scheme})$$ \[7\]

where $Q$ is the number of fitted parameters, and $p_j$ is the $j^{th}$ parameter. $T_{\text{cost}}(\text{scheme})$ is given by:

$$T_{\text{cost}}(\text{scheme}) = \sum_{n=1}^{N} (T_n + T_d + T_{fse})$$ \[8\]

where $N$ is the number of sampling points, $T_{fse}$ is the length of the FSE train, and $T_n$ and $T_d$ are the $n^{th}$ $T_n$ and $T_d$ values. The Fisher information matrix $J$ is defined by its $j^k$th element

$$J_{jk} = \frac{1}{\sigma_n^2} \sum_{n=1}^{N} \left( \frac{\partial S(p_1, \ldots, p_Q; x_n)}{\partial p_j} \frac{\partial S(p_1, \ldots, p_Q; x_n)}{\partial p_k} \right)$$ \[9\]

where $p_j$ is the $j^{th}$ parameter, $x$ are the $(T_n, T_d)$ sampling points, and $S$ is the signal function. The standard deviation of noise, $\sigma_n$, is assumed to be independent of $x$. As pointed out by Cercignani and Alexander (21), the essence of the term $\sum_{j=1}^{Q} \left| J^{-1}_{jj} \right| p_j^{-2}$ in Eq. 7 is $\sum \sigma_j^2/p_j^2$, where $\sigma_j^2$ is the variance of the parameter $p_j$. By including the time cost term in Eq. 7, the objective function becomes essentially the inverse of precision efficiency (precision-per-unit-time (27)). The optimization process yields the maximum precision efficiency by searching for the minimum value of the objective function.

For optimization of heterogeneous samples, CRLB objective functions are constructed in a similar form as in Cercignani and Alexander (21):

$$V_{\text{max}} = \max \left\{ \sum_{l=1}^{Q} \left| J^{-1}_{ll} \right| p_l^{-2} \right\} \times T_{\text{cost}}(\text{scheme})$$ \[10\]

where $l$ indexes parameter sets that characterize different tissues. Minimizing $V_{\text{max}}$ by varying the sample points $x$ would maximize the precision efficiency for the worst combination of parameters.

Optimization Technique

The optimization process searches for the optimal acquisition schemes, $x_1, \ldots, x_N$ that minimize $V$ and $V_{\text{max}}$ defined in Eqs. 7 and 10. A simulated annealing algorithm (28) was implemented in MatLab 2008b (The Mathworks, Natick, MA) to search for the optimal acquisition schemes. It evaluates 500 objective functions at each temperature $T$ by randomly varying $x_1, \ldots, x_N$, i.e., all $t_i$ and $t_j$ values. The objective function is randomly perturbed by using a Metropolis et al. (29) algorithm, which allows uphill transitions and increases the possibility of reaching a global minimum. The temperature decreases according to the annealing schedule

$$T(n+1) = T(n) \times (1 - \epsilon)$$ \[11\]

where $0 < \epsilon \ll 1$, until it reaches the final temperature. The initial and final temperatures are set as 100 and 0.001. To reduce the effects of local minima, the optimization is repeated from several random starting points. The scheme with a minimum objective function value is selected. The simulated annealing does not guarantee a global minimum, but we do not expect dramatic improvement in the objective function values.

By utilizing this technique, a series of optimization processes were performed. We optimized $T_1$ precision efficiency (using Eqs. 1 and 7–10) by varying all $t_i$ and a single $t_j$ values and by varying all $t_i$ and $t_j$ values. A set of typical parameters values is $M_f = 1$, $T_1 = 1$, and $S_f = -1$. The optimization of parameter ranges are $M_0 \in [0.5, 1.5]$, $T_1 \in [0.5, 1.5]$, and $S_f \in [-0.85, -1]$.

For qMT precision efficiency optimization, we searched for optimal acquisition schemes that have approximately the same total acquisition time as the original scheme given in Gochberg and Gore (10), by repeating the optimization process while varying the number of sampling points and then selecting the scheme that most closely matches the total acquisition time of the original. A set of typical qMT parameters (roughly those of WM) is $R_{1T} = 0.5$ Hz, $p_{ref}/p_j = 0.10$, $k_{mf} = 30$ Hz, $S_f = -0.95$, and $M_{fco} = 1.0$, with $R_{1m} = 0.5$ Hz and $S_m = 0.83$. $R_{1T}$ and $R_{1m}$ values are smaller than the values presented in Gochberg and Gore (9) because the measurements in this work are performed at higher magnetic field strengths. $M_{fco}$ is simply set to 1.0 since it is only a scaling factor. The optimization of parameter ranges is $R_{1T} \in [0.4, 1.0]$, $p_{ref}/p_j \in [0.05, 0.20]$, $k_{mf} \in (20, 40)$, $S_f \in [-1.0, -0.9]$, and $M_{fco} \in [0.6, 1.5]$. This process takes more time because it has to calculate 33 parameter combination sets ($2^3 = 32$ combinations of the listed parameter values plus one set of midpoint values). The lower limits of $t_i$ and $t_d$ are set as 4 ms and 10 ms, respectively. These parameter ranges encompass those of the WM and GM (10), so the optimal schemes are directly applicable to in vivo brain measurements.

Imaging Methods

In the SIR-FSE sequence diagrammed in Fig. 1, we applied 16 refocusing pulses with 10-ms spacing. We
acquired data only during the first eight echoes, applying an additional eight pulses in order to ensure zero z-magnetization in both the free water and macromolecular pools at the end of the echo train. The initial inversion pulse is a 1-ms 180° hard pulse. The 90° and 180° refocusing pulses are 1-ms five-lobe sinc pulses, with time bandwidth product of 5.92 and 4.44, respectively. For each measurement, two dummy scans were applied and four or eight acquisitions were averaged, with phase cycling of the 90° and acquisition but no cycling of the initial inversion pulse (in order to destroy residual transverse magnetization). Gradient spoilers were also applied after the inversion pulse.

$T_1$ measurements were made on a 9.4-T Varian (Varian, Inc., Palo Alto, CA) system with a 38-mm litz coil. MnCl$_2$ samples of 0.058 mM and 0.116 mM were prepared. Images were acquired with a field of view of $28 \times 28$ mm$^2$, slice thickness of 2 mm, and data matrix of $32 \times 32$. A conventional scheme, with a long $t_d$ of 6 sec and 10 logarithmic-spaced $t_i$ values varied between 4 ms and 6 sec, was applied, with four acquisitions averaged. In addition, eight optimized schemes were developed and applied. Four of the schemes were optimized for $M_0 = 1$, $T_1 = 1$ s, and $S_f = -1$, and four for the parameter ranges $M_0 \in [0.5, 1.5]$, $T_1 \in [0.5, 1.5]$, and $S_f \in [-0.85, -1]$. Each set of four consisted of one optimization of $t_i$ values with a single $t_d$ of 1 sec, and three optimizations where both $t_i$ and $t_d$ were allowed to vary among 10, 5, or 3 values. For ten-point optimal schemes, four acquisitions were averaged, while for five- and three-point schemes, eight acquisitions were averaged, to achieve roughly similar signal-to-noise-ratio (SNR) values for a comparison.

A series of BSA samples served as test phantoms for the qMT measurements. The BSA samples have percentage weights of 10, 15, 20, and 25, with corresponding BSA to water ratios of 0.11, 0.18, 0.25, and 0.33. An additional sample of 15% BSA with 0.05 mM MnCl$_2$ was measured as well in order to separate MT from relaxation effects. All samples were cross-linked using 25% glutaraldehyde. Measurements on these BSA samples were performed on a 4.7-T Varian system with a 63-mm quad coil. Images were acquired with field of view of $40 \times 40$ mm$^2$, slice thickness of 2 mm, and data matrix of $64 \times 64$. Two sets of experiments were performed on the BSA phantoms: (1) a comparison of a previous method with two optimized methods with the same acquisition time (~1 h), and (2) a comparison of two optimized methods with five and ten sampling points (and eight or four averages) with the same 16-min acquisition time. All schemes were optimized for sample parameters that roughly match WM but are also a fairly good match for BSA. A measurement of $R_2$ was performed as well, by using a multiple-spin-echo imaging sequence (pulse repetition time/echo time = 15,000/12 ms, 15 echoes, and four averages).

To demonstrate that the optimized schemes are applicable to brain tissues, in vivo rat brain measurements were acquired using a five-point scheme optimized for parameter ranges. The measurement was performed on a 7.0-T Varian animal system, with a 38-mm litz coil. The field of view was $38 \times 38$ mm$^2$, with a slice thickness of 1 mm and matrix of $128 \times 128$. To increase SNR, eight acquisitions were averaged, giving a total time of around 32 minutes.

RESULTS

Optimal Schemes for Determining $T_1$

For a typical parameter set of $M_0 = 1$, $S_f = -1$, and $T_1 = 1$ s, and a conventional acquisition scheme, which consists of a constant $t_d$ of 6 sec and a ten-point logarithmic spacing of $t_i$ between 4 ms and 6 sec, the objective function value, calculated from Eqs. 1 and 7, is 286.1 sec. A ten-point scheme, which optimizes for $t_i$ and a single $t_d$ (1 sec), has an objective function value of 62.4 sec. The 1-sec $t_d$ value was found to be the optimal one by comparing objective function values of optimal schemes with different $t_d$ values. Finally, for an optimal scheme with 10 independently varied $t_i$ and $t_d$ values, the objective function value is 44.0 sec. There is little variation in the objective function when there are 10 (44.0 sec) or three (49.8 sec) $t_i$ and $t_d$ values; we plot below a similar lack of dependence on sampling point numbers in the qMT optimization case, shown in Fig. 2. Note that we have found that the minimum number of sampling points is three for $T_1$ determinations, with a total acquisition time of about 11 sec for one shot.

Optimal Schemes for Determining qMT Parameters

Table 1 lists three different schemes that have roughly equal acquisition times: the original scheme (column 1), the optimal scheme for typical qMT parameters (column 2), and the optimal scheme for qMT parameter ranges (column 3). For scheme 1, its objective function values are $V = 3.14 \times 10^4$ sec and $V_{\text{max}} = 7.82 \times 10^5$ sec. For scheme 2, its objective function values are $V = 1.39 \times 10^4$ sec and $V_{\text{max}} = 3.35 \times 10^7$ sec. For scheme 3, its...
objective function values are $V = 1.51 \times 10^4$ sec and $V_{\text{max}} = 3.25 \times 10^5$ sec. Note that for scheme 2, the
sampling points fall into seven groups, effectively making it a
seven-point sequence with variation in the SNR of each point. As
for the original scheme, the objective function does not reflect the
additional errors that come from the first-order approximations previously employed (9,10).

Investigation of Number of Sampling Points for qMT Measurements

As illustrated in scheme 2 in Table 1, we can determine qMT parameters with a much smaller number of sampling points. The optimization program was repeated while varying the number of sampling points, $N$. It is found that, for different $N$, the optimization processes yield similar objective function values, and only five sampling points are required to fit for five qMT parameters. In Fig. 2, plots of calculated relative precision efficiencies versus number of sampling points are shown, optimized for parameter ranges and the “typical” parameter set, respectively. Note that the precision efficiency is defined by the square root of the inverse of the CRLB objective function value, which is $1/V$. The precision efficiency decreases only slightly (2% drop for the parameter ranges and 4% drop for the typical parameter set) at small $N$, meaning that there is little penalty in the fitted parameter precision efficiencies when minimizing the acquisition time by decreasing the number of acquired images, assuming one employs the optimum $t_i$ and $t_d$ values at each $N$.

Monte Carlo Simulations

Monte Carlo simulations were performed at different noise levels to measure the uncertainties of fitted parameters for the optimal schemes. At each noise level, 10,000 data sets were generated. Gaussian noise was introduced at each SNR level. Each data set was then

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<tr>
<th>Original and Optimal Schemes With Roughly the Same Total Acquisition Time</th>
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<td>(1) Original scheme</td>
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<tr>
<td>(1): $V = 3.14 \times 10^4$ sec, $V_{\text{max}} = 7.82 \times 10^5$ sec, Time cost = 105.54 sec, $t_i$ (sec) $t_d$ (sec)</td>
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<tr>
<td>0.191 2.410</td>
</tr>
<tr>
<td>0.191 2.443</td>
</tr>
<tr>
<td>0.193 2.437</td>
</tr>
<tr>
<td>1.635 0.010</td>
</tr>
</tbody>
</table>
fitted. The mean and standard deviation of the fits define the schemes’ systematic errors and uncertainties, respectively.

For $T_1$ simulations, the selected parameters are $M_0 = 1$, $S_f = C_0$, and $T_1 = 1$ sec. Fig. 3 shows a comparison between a conventional scheme, with ten-point logarithmic spacing of $t_i$ between 4 ms and 6 sec and $t_d$ of 6 sec, and a three-point optimal scheme, with both $t_i$ and $t_d$ varied. Only $T_1$ results are shown. The optimal scheme yields much less uncertainties in $T_1$ values than the conventional one, with uncertainties normalized to same total acquisition time.

For qMT simulations, the selected parameters used to generate the data are $R_{1f} = 0.5$, $p_m/p_f = 0.1$, $k_{mf} = 30$, $S_f = -0.95$, and $M_{f\infty} = 1$. The comparison of schemes 1 and 2 is shown in Fig. 4. Scheme 3 has similar performances as scheme 2, as reflected in their objective function values, and its simulation result is not shown. $M_{f\infty}$ is not shown either because both schemes produce similar results. $S_f$ is not shown either because it is not little interest. The simulation data of the original scheme 1 were processed both with and without first-order approximations. It is obvious that for the original scheme, this approximation causes systematic errors in the fitted $p_m/p_f$, $k_{mf}$, and these errors have a fractional size on the order of the pool size ratio. Schemes 1 and 2 without approximations avoid these systematic errors. Scheme 2 also produces more precise values of $p_m/p_f$, $k_{mf}$ than scheme 1, especially at low SNR. Additional simulations not shown here indicate that for the worst combination of parameter sets, scheme 3 yields the least uncertainties, as reflected in its $V_{\text{max}}$ value.

Measurements

The measured $T_1$ values of MnCl$_2$ samples by using different acquisition schemes are plotted in Fig. 5. The determined values and uncertainties are calculated from mean and standard deviation from pixels in the region of interest.

Fig. 6 shows corresponding plots of $R_{1f}$, $p_m/p_f$, $k_{mf}$, $S_f$, and $M_{f\infty}$. To show the effect of the new data processing technique, first-order approximations were employed to analyze the data acquired using scheme 1. The data from each pixel were fitted and qMT parameter values and uncertainties were set to the mean and standard deviation of the pixels in the regions of interest. The SNR of these measurements was around 270.

The comparison of measurement results using the five-point and ten-point optimal schemes is shown in Fig. 7. It shows that both schemes produce similar qMT parameters within error ranges. Similar results are obtained for the five-point and ten-point schemes optimized for parameter ranges as well.

The in vivo measurement results with the five-point scheme are show in Fig. 8. The determined qMT parameters of WM and GM are listed in Table 2.

DISCUSSION

In this paper, we have shown how to optimize the SIR-FSE sequences for $T_1$ and qMT imaging using CRLB
methods. The original qMT technique, presented elsewhere \((9,10)\), used fixed \(t_d\) and varied \(t_i\) only and employed first-order approximations for data fitting. According to Monte Carlo simulations, as shown in Fig. 4, first-order approximations will introduce systematic errors to \(p_{mf}/p_f\), \(k_{mf}\) and \(S_f\). The \(p_{mf}/p_f\) values, determined by the original technique will be lower than the true value, while \(k_{mf}\) will be larger. In the new method presented here, we varied both \(t_d\) and \(t_i\) and fitted the qMT parameters with minimal approximations. Both the precision and accuracy increase, as shown in simulations and experimental results.

\(T_1\) measurement has also been optimized using the same approach. By varying \(t_i\) and \(t_d\) independently, global optimal acquisition schemes were obtained with precision efficiencies, which are much greater than previous inversion recovery methods. This optimization is confirmed by Monte Carlo simulations, as shown in Fig. 3, by comparing a ten-point conventional scheme with a three-point optimal scheme with same total acquisition time. Fig. 5 shows a comparison of measured \(T_1\) values between the conventional scheme and a series of optimal schemes. It is shown that the optimal schemes yield consistent \(T_1\) values across schemes, which validates the optimization technique. It is also verified that only three sampling points are required to determine \(T_1\) value, as shown in schemes h and i in Fig. 5. The three-point scheme optimized for parameter ranges of \(M_0 \in [0.5, 1.5]\),

![FIG. 5. Measured \(T_1\) values of MnCl\(_2\) samples of 0.058 mM and 0.116 mM by using several different acquisition schemes. a: A ten-point conventional scheme with \(t_i\) logarithmically varied between 4 ms and 6 sec and \(t_d\) of 6 sec. Schemes b and c are optimized by varying \(t_i\) values with a constant optimal \(t_d\) of 1 sec. Scheme b is optimized for parameter values of \(M_0 = 1\), \(T_1 = 1\), and \(S_f = -1\). Scheme c is optimized for parameter range values of \(M_0 \in [0.5, 1.5]\), \(T_1 \in [0.5, 1.5]\), and \(S_f \in [-0.85, -1]\). Schemes d-i are optimized by varying both \(t_i\) and \(t_d\) values. Schemes d, f, and h are optimized for a single parameter set, as in (b), with numbers of sampling points of ten, five, and three, respectively. Schemes e, h, and i are optimized for parameter range values as in (c), with numbers of sampling points of ten, five, and three, respectively. The determined values and uncertainties are calculated from the mean and standard deviation of the pixels in the region of interest.](image)

![FIG. 6. Measured \(R_{1f}\), \(p_{mf}/p_f\), \(k_{mf}\), \(S_f\), \(M_{fc}\), and \(R_2\) as a function of BSA weight versus water weight ratio using acquisition schemes 1 (black), 2 (red), and 3 (blue), where \(M_{fc}\) is plotted in arbitrary units. Data points are shifted for a clear comparison. For scheme 1, first-order approximations were employed to process data. Note that the results from two 15% BSA samples are plotted, both with and without MnCl\(_2\). The MnCl\(_2\) changes \(R_{1f}\) and \(R_2\) while having little effect on the fitted MT parameters, confirming that SIR-FSE is a true qMT sequence, and not just a function of the relaxation rates.](image)
$T_1 \in [0.5, 1.5]$, and $S_f \in [-0.85, -1]$, is given in Table 3, which requires about 11 sec per acquisition, so, depending on SNR requirements, an eight-shot clinical scan would take $11 \text{ sec/shot} \times \text{eight shots} \times \text{two averages} = 3 \text{ min}$ (two averages allow phase cycling that destroys any transverse magnetization remaining after the gradient spoiling; Using a single average and fewer shots will proportionally lower the acquisition time).

The qMT optimization results were confirmed by the experimental measurements of BSA samples, as shown in Fig. 6. The optimal schemes have less uncertainty in the measured qMT parameters, most notably in $k_{mf}$, which, due to its greater fractional uncertainty, tends to dominate the calculation in Eq. 7. The performances of schemes 2 and 3 are similar, which is not surprising, given their similar $V$ values in Table 1. Therefore, the optimal scheme for the set of typical parameters is applicable to a range of qMT parameters for BSA samples of different percentage weights. In other words, if the qMT parameters do not cover a very wide range, we will be able to optimize for a single parameter inside this range and apply the optimized scheme for all measurements. In addition, as in Gochberg and Gore (9), the $R_{1f}$, $p_m/p_f$, and $k_{mf}$ values increase linearly with the BSA-to-water ratios. Note that the results from two 15% BSA samples are plotted, both with and without MnCl$_2$. The MnCl$_2$ changes $R_{1f}$ and $R_2$ while having little effect on the fitted MT parameters, confirming that SIR-FSE is a true qMT sequence and not just a function of the relaxation rates.

To further confirm the optimization technique, experimental precision efficiencies were calculated. Examples are given for qMT schemes 1, 2, and 3, as listed in Table 1. The CRLB theory predicts precision efficiency ratios of 1:1.5:1.45, from their $V$ values. Monte Carlo simulations lead to precision efficiency ratios of 1:1.56:1.50, by extracting the simulation data at an SNR of 200. The experimental precision efficiency ratios of the qMT parameters of the 15% BSA are 1:1.69:1.35. These roughly similar ratios illustrate the advantage of the optimization technique. Consistent precision efficiency ratios were obtained for MnCl$_2$ samples $T_1$ measurements as well.

A detailed comparison of relative precision efficiencies, derived from CRLB, Monte Carlo simulations, and experimental results of $T_1$ and qMT, is given in Fig. 9. The experimental precision efficiencies were calculated from the 0.058-mM MnCl$_2$ and 15% BSA samples, respectively. By varying $t_i$ and $t_d$ simultaneously, the precision efficiencies of $T_1$ and qMT measurements have increased roughly 150% and 50%, respectively, compared with the conventional scheme and original technique. Fig. 2 shows that the precision efficiency has only a weak dependence on the number of acquisitions, $N$. This indicates that we can take as few as five sampling points to determine the qMT parameters. This conclusion is
confirmed by measurement of the BSA samples with five-point and ten-point schemes, as shown in Fig. 7. It is further confirmed by in vivo measurements using the five-point scheme, as shown in Fig. 8. The extracted qMT parameters of WM and GM are shown in Table 2. As shown in Monte Carlo simulations, the fitting process with first-order approximations leads to slightly larger $k_{mf}$ but lower $p_m/p_f$ values. This prediction is consistent with the differences between the qMT parameter values for WM in Table 2 and those in Gochberg and Gore (10).

With the verification that only a five-point scheme is required to determine the five qMT parameters, this work provides more insight in rapid qMT acquisitions. For example, a five-point optimal scheme requires about 15 sec/acquisition, so, depending on SNR requirements, an eight-shot clinical scan would take 15 sec/shot × eight shots × two averages = 4 min, making clinical application a possibility. A five-point scheme, proposed in this work for clinical applications, is shown in Table 4, which is optimized for abovementioned parameter ranges.

A related issue for clinical application is the robustness of the standard FSE implementation on a given imaging system. Any ghosting or $T_2$ blurring will cause correlating effects in the SIR-FSE qMT imaging sequence. Also, given the significant MT effects from the off-resonance excitation and refocusing pulses (30,31), multislice acquisitions do not make sense for SIR-FSE. However, three-dimensional acquisitions are viable, at least in a research setting, e.g., a 128 × 128 × 32 three-dimensional volume could be acquired in two averages × 15 sec/excitation × 128 × 32 phase encodes/64 echoes = 32 min, not including benefits from partial $k$-space and parallel imaging effects. This acquisition time is comparable to pulsed saturation methods (32), but without the need for separate amplitude of radiofrequency field, amplitude of static field, and $T_1$ maps. Pulsed saturation has, however, been more extensively tested in vivo.

In this work, we have given equal weights to all fitted parameter uncertainties in Eqs. 7 and 10. Among the five qMT parameters, the pool size ratio ($p_m/p_f$) is of most interest. An alternative would be to optimize for $p_m/p_f$ only. Optimization results, which are not shown, indicate an increase in $p_m/p_f$ precision about 30% from such optimization, but at the cost of large systematic errors in the other qMT parameters, making it an unappealing alternative.

Fitting qMT parameters necessitates assumption about $R_{1m}$ and $S_m$. We performed Monte Carlo simulations to investigate the variances of fitted qMT parameters versus different underlying $R_{1m}$ and $S_m$ values. We found that the fitted $R_{1f}$, $k_{mf}$, $S_f$, and $M_f$ values are almost independent of $R_{1m}$ and $S_m$. The pool size ratios, $p_m/p_f$, have little dependence on $R_{1m}$ but a relatively large dependence on $S_m$. The simulated data were generated with $R_{1f} = 0.5$, $p_m/p_f = 0.1$, $k_{mf} = 30$, $S_f = -0.95$, and $M_f$ = 1, by using scheme 2 in Table 1 at an SNR of 100. For $S_m = 0.76$ and 0.9, the fitted $p_m/p_f$ values are 0.104 ± 0.005 and 0.096 ± 0.005, respectively. With these variations, the maximum uncertainty of $p_m/p_f$ is about 10%, which indicates that this technique is fairly robust to assumptions of $R_{1m}$ and $S_m$.

### Table 2

Measured qMT Parameters of WM and GM in a Live Rat Brain

<table>
<thead>
<tr>
<th></th>
<th>$R_{1f}$ (Hz)</th>
<th>$p_m/p_f$</th>
<th>$k_{mf}$ (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WM</td>
<td>0.677 ± 0.076</td>
<td>0.173 ± 0.023</td>
<td>13.1 ± 2.9</td>
</tr>
<tr>
<td>GM</td>
<td>0.550 ± 0.046</td>
<td>0.080 ± 0.008</td>
<td>20.8 ± 6.5</td>
</tr>
</tbody>
</table>

### Table 3

An Optimized Three-Point Scheme for Parameter Ranges of $M_0$ ∈ [0.5, 1.5], $T_1$ ∈ [0.5, 1.5] sec, and $S_f$ ∈ [−0.85, −1]

<table>
<thead>
<tr>
<th>$t_i$ (sec)</th>
<th>$t_d$ (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.004</td>
<td>4.781</td>
</tr>
<tr>
<td>1.480</td>
<td>3.454</td>
</tr>
</tbody>
</table>

### Table 4

An Optimized Five-Point Scheme Proposed for Clinical Applications, for qMT Parameters in Ranges of $R_{1f}$ ∈ [0.4, 1.0] Hz, $p_m/p_f$ ∈ [0.05, 0.20], $k_{mf}$ ∈ [20, 40] Hz, $S_f$ ∈ [−1.0, −0.90], and $M_f$ ∈ [0.6, 1.5]

<table>
<thead>
<tr>
<th>$t_i$ (sec)</th>
<th>$t_d$ (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.004</td>
<td>0.032</td>
</tr>
<tr>
<td>1.507</td>
<td>3.273</td>
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</tbody>
</table>
by measurements on MnCl₂ samples, BSA samples, and in vivo rat brain. Specifically, for qMT determinations, minimal approximations were applied to get rid of the systematic errors from first-order approximations in previous work (8–10). From the investigation of number of sampling data points, it is shown that five data points are enough to determine qMT parameters, and three data points are enough to determine T₁ parameters. This opens up the possibility of applying the SIR-FSE sequences to clinical two-dimensional and preclinical three-dimensional applications.

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REFERENCES