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MT Effects and T_1 Quantification in Single-Slice Spoiled Gradient Echo Imaging

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Abstract

We investigated magnetization transfer (MT) effects on the steady-state MR signal for a sample subjected to a series of identical on-resonance RF pulses, such as would be experienced while imaging a single slice using a spoiled gradient echo sequence. The MT coupling terms for a two-pool system were added to the Bloch equations and we derived the resulting steady-state signal equation and compared this result to the conventional signal equation without MT effects. The steady-state signal is increased by a few percent of the equilibrium magnetization because of MT. One consequence of this MT effect is inaccuracy in T_1 values determined via conventional steady-state gradient echo methods. (Theory predicts greater than 10% errors in T_1 for white matter when using short TR.) A second consequence is the ability to quantify the relaxation and MT parameters by fitting the gradient echo steady state signal to the signal equation appropriately modified to include MT effects. The theory was tested in samples of MnCl_2 , cross-linked bovine serum albumin (BSA), and cross-linked BSA + MnCl_2

Keywords

magnetization transfer; steady state; gradient echo; inversion recovery

Magnetization transfer (MT) is the exchange of spin magnetization between free water protons and macromolecular protons in biological systems (1,2). While it has long been recognized that MT may affect the signal in multi-slice imaging (3,4), the effects of MT on conventional single-slice imaging have largely been ignored. We examined here how these single slice MT effects influence image contrast and parameters quantification (such as T_1) and provide a new method for quantifying the inherent MT parameters.

T_1 is the spin-lattice relaxation time for spins to return to equilibrium in the longitudinal direction. T_1 is conventionally measured by multiple flip angle experiments or inversion recovery experiments. Inversion recovery measurements vary the time between RF pulses while multiple flip angle experiments vary the RF field intensity, which involves

significantly more experimental uncertainty. However, multiple flip angle measurements have the great advantage of not requiring long TR, and are therefore frequently used in vivo. We will examine the MT effects on T_1 determination via multiple angle methods.

MT is often quantified by the magnetization transfer ratio (MTR). MTR equals one minus the ratio of signal intensity with and without one or more off-resonance saturation pulses. While it provides novel contrast, MTR is a reduction of MT phenomenon to a single value. In addition, the MTR value is affected by non-MT phenomena, such as relaxation properties and pulse sequence details. Quantitative magnetization transfer (QMT) provides more specificity than MTR by determining the intrinsic MT parameters, such as the spin exchange rates and the ratio of the proton pool sizes. There have been some recent results indicating that some QMT parameters, such as the pool size ratio, show unique information on multiple sclerosis (MS) pathology that is not available via MTR measurements (5,6).

There are many groups measuring QMT parameters by different methods (2,7–13). The general ideas of these methods are similar: rotating/saturating the free pool and the restricted pool to different degrees, measuring the resulting magnetization in either a steady-state or transient condition, and fitting the measured data to a signal equation to determine the MT parameters. These methods differ chiefly in the RF power and offset and transient/steady-state signal acquisitions. Some of these methods are limited by specific absorption rate (SAR) (2) or scan time (7); some methods are based on strong assumptions (13); and some methods yield only a subset of MT parameters (8,10,12,13). It is still an open topic which QMT method is optimum. We will introduce a new QMT technique here and discuss its applicability and limitations.

THEORY

It is well known that MT occurs when applying an off-resonance RF pulse to samples with two proton pools (i.e., a free pool and a restricted pool, which are a good description for biological tissues). The thermal equilibrium between the pools is broken after an off-resonance RF pulse, resulting in spin exchange between these two pools. It is not well appreciated that MT also occurs when applying an on-resonance RF pulse. In fact, any pulse that affects the two proton pools differently (and nearly every RF pulse does) will induce MT. Off-resonance pulses saturate the restricted pool to a greater extent than the free pool; on-resonance pulses rotate the free pool while having little effect on the restricted pool (when at low power).

We consider a simple gradient echo pulse sequence with the excitation pulse set on resonance. Bloch equations are used to predict the steady-state signal of this sequence. For samples with only one free proton pool, the transverse steady-state signal derived from the Bloch equations is (14):

$$M_{xy,f,ss} = M_{0,f} \sin \alpha \frac{1 - E_1}{1 - E_1 \cos \alpha} \quad [1]$$

Where $M_{0,f}$ is the equilibrium longitudinal magnetization for the free pool, α is the excitation pulse flip angle, $E_1 = e^{-TR/R_1}$, TR is the repetition time, and R_1 is the longitudinal recovery rate. (The T_2^* relaxation term is normalized to 1 since constant TE is assumed.)

For samples that have a free proton pool and a restricted proton pool, coupling terms have to be added to the Bloch equations in order to accurately model the underlying magnetization transfer. The modified Bloch equations when there is no RF pulse are (2):

$$\frac{d}{dt}M_{z,f} = R_{1,f}(M_{0,f} - M_{z,f}) - K_f M_{z,f} + K_r M_{z,r}$$

$$\frac{d}{dt}M_{z,r} = R_{1,r}(M_{0,r} - M_{z,r}) + K_f M_{z,f} - K_r M_{z,r}$$

Subscripts f and r denote the free water pool and restricted macromolecular pool, respectively. R_1 is the longitudinal recovery rate, M_0 is the equilibrium magnetization, and M_z is the longitudinal magnetization. K_r is the exchange rate from the restricted pool to the free pool, $K_f = K_r \cdot F$ is the exchange rate from the free pool to the restricted pool, where $F = M_{0,r}/M_{0,f}$ is the ratio of the restricted pool size to the free pool size.

The solutions of these equations are (15,16):

$$\begin{aligned} M_{z,f}(t) &= M_{0,f} + C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} \\ M_{z,r}(t) &= M_{0,r} + C_1 \frac{R_{1,f} + K_f - \lambda_1}{K_r} e^{-\lambda_1 t} + C_2 \frac{R_{1,f} + K_f - \lambda_2}{K_r} e^{-\lambda_2 t} \end{aligned}$$

In which C_1 and C_2 are functions of the QMT parameters ($R_{1,f}, R_{1,r}, K_f, K_r$) and initial conditions (16), and:

$$\begin{aligned} \lambda_{1,2} &= \frac{1}{2}(R_{1,f} + K_f + R_{1,r} + K_r) \\ &\pm \frac{1}{2} \sqrt{(R_{1,f} + K_f + R_{1,r} + K_r)^2 - 4(R_{1,f}R_{1,r} + R_{1,f}K_r + R_{1,r}K_f)} \end{aligned}$$

λ_1 is the slow recovery rate and is the observed recovery rate (R_1^{obs}) in inversion recovery experiments that fit the signal to a single exponential. λ_2 is the fast recovery rate.

With the addition of the excitation pulse at the beginning of each repetition (we treat the RF pulses as simple rotations of the free pool magnetization, with no relaxation and magnetization transfer effects during the relative short pulse), the steady-state signal is obtained by solving the equations:

$$M_{z,f}(t) = M_{z,f}(t + TR)$$

$$M_{z,r}(t) = M_{z,r}(t + TR)$$

The resulting transverse steady-state signal for the free pool is:

$$\begin{aligned} M_{xy,f,MTss} &= \sin\alpha M_{z,f,MTss} \\ &= M_{0,f} \sin\alpha \frac{[(1 - E_1)(1 - E_2 S_r) + A(1 - S_r)(E_1 - E_2) - \frac{K_f}{\lambda_2 - \lambda_1}(1 - S_r)(E_1 - E_2)]}{(1 - E_1 S_f)(1 - E_2 S_r) + A(S_f - S_r)(E_1 - E_2)} \end{aligned} \quad [2]$$

where $A = \frac{R_{1,f} + K_f - \lambda_1}{\lambda_2 - \lambda_1}$, $E_1 = e^{-\lambda_1 \cdot TR} = e^{-R_1^{obs} \cdot TR}$ and $E_2 = e^{-\lambda_2 \cdot TR}$.

$S_f = \cos\alpha$ is the direct rotation of free pool magnetization by the RF pulse, and S_r is the factor accounting for direct saturation of the restricted pool magnetization by the RF pulse. S_r can be calculated from numerically simulating the signal before and after the pulse, where $M_{z,r}(\text{after}) = S_r \cdot M_{z,r}(\text{before})$.

Equation [2] is an exact solution of the steady-state signal equation with the only assumption that there are no relaxation and MT effects during the RF pulse. We can make two more approximations to simplify Eq. [2].

First, for gel samples and biological tissues, K_r is much greater than other rates (10,17,18),

such as $K_f R_{1,f}$ and $R_{1,r}$. To first order in $1/K_r$: $\lambda_2 \approx K_r$, $A \approx F/(1F)$, and $A - \frac{K_f}{\lambda_2 - \lambda_1} \approx 0$.

Second, we set $E_2 = 0$ in the calculation of $M_{xy,f,MTss}$, recognizing that for typical parameter values, E_2 is nonzero only for short TR 's, where E_1 is close to 1; and when E_1 is 1, $M_{xy,f,MTss}$ is independent of E_2 . Therefore, we will take $E_2 = 0$ for all TR values.

After these two approximations, Eq. [2] is simplified to:

$$\begin{aligned} M_{xy,f,MTss} &= \sin\alpha M_{z,f,MTss} \\ &= M_{0,f} \sin\alpha \frac{1 - E_1}{(1 - E_1 S_f) + A(S_f - S_r)E_1} \end{aligned} \quad [3]$$

We will test the accuracy of the steady-state signal Eq. [2] and the simplified Eq. [3] in the next section by numerical methods.

NUMERICAL SIMULATIONS

Numerically Testing the Signal Equation

Numerical integration of the complete Bloch equations (with both MT terms and RF terms) was performed to generate numerical steady-state data. MT parameters for white matter (5) and a series of repetition times and flip angles were used in the numerical data generation. To test the accuracy of our signal equation and the legitimacy of the approximations we made during the signal equation derivation, we generated numerical data by two steps.

In the first step, relaxation and exchange during the RF pulse were not considered in the numerical integration. For each repetition time and flip angle the integration was continued until signal change for consecutive repetitions was less than 0.001%. We found that the numerical data match the data calculated by Eq. [2] very well (the signal difference, which is due to the finite step size in the integration, is less than 0.01% of the equilibrium magnetization, as shown in Fig. 1). The coincidence of the numerical data and Eq. [2] data indicates that our signal equation accurately describes the steady-state signal if we ignore the relaxation and exchange effects during the RF pulse.

In the second step we evaluated the relaxation and exchange effects during the RF pulse by numerical simulation. The details are included in Appendix A. The results suggest that even with the consideration of the relaxation and exchange effects during the RF pulse, Eq. [2] is able to accurately model the steady-state signal.

To test the accuracy of the simplified signal Eq. [3], we compared the analytical solution results from Eq. [3] to the results from Eq. [2]. Figure 2 shows that the steady-state data deviation is less than 0.1% of the equilibrium magnetization $M_{0,f}$ and Eq. [3] is an excellent approximation of Eq. [2].

MT Effects Increase the Steady-State Signal

Figure 3 show that MT effects always increase the steady-state signal. The relative signal increase (compared to signal without MT effects) can be as high as 14%; the absolute signal increase (normalized to the equilibrium magnetization $M_{0,f}$) is up to about 3%, roughly two orders of magnitude greater than any systematic errors due to our analytical approximations (see Fig. 8, line (e) in Appendix A).

T_1 Quantification Is Inaccurate if MT Is Ignored

T_1 is often measured by setting a TR , varying the flip angle α , and fitting the gradient echo signal to Eq. [1]. However, the increased steady-state signal caused by MT will affect the estimation of T_1 . If we ignore the MT effects and fit the data to Eq. [1], while the actual signal is described by Eq. [2] we will end up with an apparent recovery rate (the reciprocal of T_1) that is a function of TR , S_f , and S_r :

$$R_{1,app,GE} = \frac{1}{TR} \ln \frac{(1 - S_f)(1 - E_2 S_r - A E_1 S_r + A E_2 S_r) + K_f S_f / \lambda_2 - \lambda_1 (1 - S_r)(E_1 - E_2)}{(1 - S_f)(E_1 - A E_1 + A E_2 - E_1 E_2 S_r) + K_f / \lambda_2 - \lambda_1 (1 - S_r)(E_1 - E_2)} \quad [4]$$

Therefore, the measurement of apparent recovery rate by gradient echo will be affected to a degree depending on TR and α if we ignore MT effects. If we instead consider MT effects and fit the data to Eq. [2], as we will below, the measured $R_{1,app,GE}$ is the true value, which is R_1^{obs} , and is independent to the choice of TR and α . (Note that for samples with zero pool

size ratio, Eq. [4] is reduced to $R_{1,app,GE} = \frac{1}{TR} \ln \frac{1}{E_1}$, matching the conventional case.)

This inaccurate T_1 quantification is not negligible for in vivo experiments. For example, the QMT parameters for frontal white matter and cortical gray matter in the brain of a healthy subject (5) were used to generate gradient echo steady-state data from Eq. [2]. If we choose a constant TR , vary the flip angle α , and fit the gradient echo data to Eq. [1], the fitted $R_{1,app,GE}$ can be up to 15% higher than the true R_1^{obs} value for the frontal white matter, and 7% higher for the cortical gray matter, as shown in Fig. 4.

MT Parameters Determination

As confirmed by numerical simulations, both Eqs. [2] and [3] are accurate descriptions for the spoiled gradient echo steady-state signal. It was found that MT parameters may be determined by fitting the signal to either equation. The detailed discussion of parameters determination is included in Appendix B. In general, fitting gradient echo steady-state data to either Eqs. [2] or [3] can potentially determine MT parameters; the preciseness of the fitting results depends on the sample parameters, the repetition times and flip angles chosen, and the signal-to-noise ratio (SNR) of the data. For this work we limit ourselves to sample parameters typical for white matter and to nonoptimized acquisition parameters. Under these conditions, if we are only interested in the determination of the equilibrium magnetization M_{0f} and the slow recovery rate λ_1 (equals the observed recovery rate R_1^{obs}), then $SNR = 50$ is good enough for determining the parameters with uncertainty less than 5% when fitting data to Eq. [3], an approximation with fewer free parameters; if we are also interested in the determination of A to the same level of uncertainty, then $SNR \approx 500$ is required, and we can choose either Eqs. [2] or [3] as the fitting function; if we want to accurately determine every QMT parameter including the fast recovery rate λ_2 and the exchange rate K_f , then $SNR > 1000$ is required and Eq. [2] is the fitting function.

EXPERIMENTAL METHODS

All experiments were done on a 4.7T Varian system. Three uniform samples were measured: sample 1 is 0.1 mM $MnCl_2$ ($T_1 \approx 400$ ms, $F = 0$), sample 2 is cross-linked 15% BSA ($T_1 \approx 1750$ ms, $F \approx 0.1$), and sample 3 is cross-linked 15% BSA mixed with 0.1 mM $MnCl_2$ ($T_1 \approx 720$ ms, $F \approx 0.1$). Each sample was put in an NMR tube of 8 mm diameter and 32 mm length. Three tubes were tied together in parallel and placed at the center of a 63-mm diameter quad coil. In all of the gradient echo pulse sequences TE was set to 5 ms; 32×32 data points in k -space were acquired for each scan. In all, 32 dummy scans were performed before each data acquisition in order to ensure a steady-state condition. To destroy spin and stimulated echoes, spoiler gradients with linearly changing magnitudes were placed after the data acquisition and a phase step of 84° was set to the excitation pulse for RF spoiling.

Determining T_1

To measure the effect of MT on T_1 quantification, gradient echo imaging experiments were performed with 12 repetition times ranging from 0.05–2 sec, 15 flip angles linearly ranging from 20° to 160° , and a 600 μ s square excitation pulse. No slice selection gradient was applied in order to avoid slice profile issues in this experiment. The data are fit to Eq. [1] with $\alpha = \alpha_{input} * b_1$, where b_1 accounts for linear RF field errors due to amplifier

miscalibration and B_1 spatial variation. That is, we fit the signal at each pixel to Eq. [5] to determine $M_{0,f}$, $R_{1,app,GE}$, and b_1 :

$$M_{xy,f,ss} = M_{0,f} \sin(b_1^* \alpha_{input}) \frac{1 - e^{-TR^* R_{1,app,GE}}}{1 - e^{-TR^* R_{1,app,GE}} \cos(b_1^* \alpha_{input})} \quad [5]$$

Note that fitting to b_1 will also effectively correct for T_{2f} effects on S_f , as discussed in Appendix A and Fig. 8.

Determining MT Parameters

To test the determination of MT parameters, 42 steady-state gradient echo images were acquired with three excitation angles $\alpha = 40^\circ, 60^\circ, 90^\circ$ and 14 repetition times ranging from 0.06–15 sec. (The choice of TR and α is not optimized).

We employed a 1.5-ms sinc pulse to excite a 2-mm slice. Since the sinc pulse does not have an infinite width, the resulting slice profile is not an ideal rectangle. Similar to the method used in other studies (19), we modified Eq. [2] to include signal variation caused by nonideal slice profile:

$$M_{xy,f,MTss} = \int M_{0,f} \frac{(1 - E_1)(1 - E_2 S_r) + A(1 - S_r)(E_1 - E_2) - \frac{K_f}{\lambda_2 - \lambda_1} (1 - S_r)(E_1 - E_2)}{(1 - E_1 \psi_{\cos}(z, b_1, \alpha_{input}))(1 - E_2 S_r) + A(\psi_{\cos}(z, b_1, \alpha_{input}) - S_r)(E_1 - E_2)} \times \psi_{\sin}(z, b_1, \alpha_{input}) dz \quad [6]$$

Where $\Psi_{\cos}$ and $\Psi_{\sin}$ are functions of position z in the slice selection direction, the b_1 correction factor, and the input excitation flip angle. $\Psi_{\cos}$ and $\Psi_{\sin}$ are M_z and M_y , respectively, after a single pulse as determined by numerically simulating the Bloch equations with the appropriate RF pulse shape and gradients and smoothing the effects of the discrete definition of pulse shape (the slice profile is therefore determined numerically without prior assumptions). We performed the numerical simulation and created a $\Psi_{\cos}$ lookup table and a $\Psi_{\sin}$ lookup table by using 101 z values that are uniformly distributed in the 2-mm-thick slice with 20- μ m intervals, and 501 α values which are uniformly distributed between 10° and 110° with 0.2° intervals. During the least-squared fitting, $\Psi_{\cos}$ and $\Psi_{\sin}$ values were linearly interpolated from the corresponding table and we fit the signal at each pixel to Eq. [6] to determine $M_{0,f}$, λ_1 , λ_2 , A , K_f , and b_1 .

With the same approach we rewrote the approximate signal Eq. [3] to:

$$M_{xy,f,MTss} = \int M_{0,f} \frac{1 - E_1}{(1 - E_1 \psi_{\cos}(z, b_1, \alpha_{input})) + A(\psi_{\cos}(z, b_1, \alpha_{input}) - S_r) E_1} \times \psi_{\sin}(z, b_1, \alpha_{input}) dz \quad [7]$$

The experimental data were also fitted to Eq. [7] to determine $M_{0,f}$, λ_1 , A and b_1 .

A Comparison Measurement

To provide a separate measure of the observed recovery rate R_1^{obs} and the pool size ratio F , we also performed a selective inversion recovery experiment. A 180° inversion pulse followed by a conventional spin echo pulse sequence with $TR = 10$ sec, $TE = 10$ ms, and TI ranging from 6–9.8 sec was used. The measured data were fitted to a bi-exponential function to determine MT parameters (8).

RESULTS AND DISCUSSION

Inaccurate T_1 Quantification if MT Is Ignored

Figure 5 shows the fitted recovery rate when ignoring MT (and therefore fitting the data to Eq. [5]). The fitted $R_{1,app,GE}$ is a constant value and roughly equal to (R_1^{obs}) for samples with zero pool size ratio ($MnCl_2$), but it is a function of TR for samples with nonzero pool size ratio (BSA + $MnCl_2$ and BSA), as expected in Eq. [4] and Fig. 4. The measured recovery rates $R_{1,app,GE}$ approach R_1^{obs} as TR increases.

MT Parameters Determination

The SNR ratio for each pixel in our MT parameters determination experiment was about 500. We fitted the steady-state signal to Eq. [6] pixel by pixel. The fitted λ_2 and K_f values were inconsistent from pixel to pixel and the averages were skewed by outlying results. This lack of fitting robustness is qualitatively consistent with the simulation results (Fig. 9 in Appendix B). In distinction, the fits to Eq. [6] for $M_{0,f}A$ and R_1^{obs} were robust, also in agreement with the simulations. Figure 6 shows the fit to Eq. [6] for data from one pixel in the BSA $MnCl_2$ sample. Figure 7 shows the resulting map of parameter A . The pool size ratio was calculated pixel by pixel from $F = A/(1 - A)$. As an alternative approach, we also fitted the experimental data to Eq. [7] to determine the parameters $M_{0,f}A$ and R_1^{obs} . Table 1 compares the measured parameters for the two fitting methods for the three samples. The MT parameters measured from the separate selective inversion recovery experiment are also listed for comparison.

From the gradient echo experiment results, the $MnCl_2$ sample has a zero pool size ratio, the 15% BSA + $MnCl_2$ and 15% BSA samples have different recovery rates but similar pool size ratios. These results confirm that our gradient echo method is able to separate MT from relaxation effects.

For the BSA and BSA + $MnCl_2$ samples the pool size ratios measured by the gradient echo method are slightly different from the pool size ratios measured by the selective inversion recovery method. This is not surprising, since both methods determine the pool size ratio only to first order in $1/K_f$. For the $MnCl_2$ sample the measured pool size ratios from both methods are the same: $F \approx 0$, which is expected for samples with no MT effects.

The slow recovery rates (R_1^{obs}) determined via the gradient echo steady-state signal when including the effects of MT agree with those derived from the selective inversion recovery experiment. The total acquisition time (not optimized) for the QMT parameters

determination is about 2 hr. However, if we are only interested in the determination of R_1^{obs} it may be possible to make the measurement more time efficient by optimizing the choices of TR and α , and minimizing the number of dummy scans.

Systematic Error Management

While we correct for spatial variations in the flip angle and for imperfections in the slice profile, one systematic error that we ignore is RF power variations that are nonlinear with the programmed flip angle. The nonlinear RF field effect cannot be corrected by the linear b_1 correction factor. The magnitude band region of this problem are very system- dependent. In our experiments we chose the flip angles and pulse durations such that the nonlinearity is minimized, as determined by additional system performance test (data not shown). Another possible source of error is miscalibration of the slice select refocusing gradient. While the refocusing gradient is tuned separately for each flip angle, the uncertainty of this tuning may cause an error in some resulting MT parameters. For example, we found that a 1% deviation of the tuned refocusing gradient (which roughly equals the uncertainty in our experiments) results in almost no deviation on the fitted λ_1 but $\approx 10\%$ deviation on the fitted A .

CONCLUSIONS

In summary, for nonslice-selective pulse sequences we used a 600 μ s square pulse and for slice-selective pulse sequences we used a 1.5 ms sinc pulse with flip angles not larger than 90°. In both cases the powers of the RF pulses were in a region that was very linear for the amplifier. We also used a b_1 correction factor to compensate for power miscalibration and the B_1 variation between pixels. Furthermore, for slice-selective pulse sequences we included slice profile effects in our analysis. The combination of these techniques allows us to accurately model the gradient echo steady-state data as a function of the sequence repetition time and RF flip angle. By doing that we were able to show that T_1 quantification is incorrect if MT effects are ignored and that, for BSA, this error is on the order of 10%. On the other hand, after including MT effects in the data analysis, we were able to accurately quantify T_1 via the gradient echo method. In addition, some QMT parameters were able to be determined, including the pool size ratio. The use of this QMT method in vivo needs further investigation, which includes the optimization of the choice of TR and α to maximize the MT effects and to perform the experiment in a clinically applicable time. Although the requirements of high SNR make it difficult to accurately determine the pool size ratio in clinical studies, this method may prove well suited for accurate T_1 determination in vivo.

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APPENDIX A

Relaxation and MT Effects During the RF Pulse

To further test the accuracy of signal Eq. [2] in modeling the spoiled gradient echo steady-state signal, we included relaxation and exchange effects during the RF pulse in numerical simulations. During the RF pulse we added (a) MT exchange terms only; (b) R_1 relaxation terms only; (c) T_2 relaxation terms only; and (d) with all exchange and relaxation terms to the Bloch equations. In all cases all relaxation and exchange terms were included in the Bloch equations after the RF pulse. Figure 8 compares these four sets of numerical data to the analytical data generated by Eq. [2]. It was found that the magnetization exchange effect during the RF pulse is very small (on the order of $10^{-5} \times M_{0,f}$); the R_1 and $T_{2,f}$ relaxation effects during the RF pulse are also small but noticeable (on the order of a few parts per thousand).

Since the steady-state spoiled gradient echo signal difference caused by MT is usually on the order of $10^{-2} \times M_{0,f}$, as demonstrated below, the difference (greater than $10^{-3} \times M_{0,f}$) between Eq. [2] and the numerical simulations including relaxation effects during the RF pulse may need to be considered. This difference can be minimized by modification of TR and S_f in Eq. [2]. By using $TR = \text{inter-pulse delay} + \text{pulse width} / 2$, instead of $TR = \text{interpulse delay} + \text{pulse width}$, in Eq. [2], the effect of R_1 during the pulse can be largely compensated (data not shown). Differences originating in T_2 effects during the RF pulse can be mitigated by using $S_f = \cos(\text{factor} \times \alpha)$ instead of $S_f = \cos(\alpha)$ in Eq. [2], where the factor is determined by numerical simulation of a single RF pulse ignoring exchange (data not shown). Figure 8, line (e) illustrates that modifying TR and S_f reduces the difference between Eq. [2] and numerical simulation to less than $10^{-3} M_{0,f}$ (and the difference is almost two orders of magnitude less than MT effects after the RF pulse).

APPENDIX B

Validation of MT Parameters Fitting

From Eq. [2] the spoiled gradient echo steady-state signal equation including MT effects has the form: $M_{xy,f,MTss} = M_{xy,f,MTss}(\alpha, TR, M_{0,f}, \lambda_1, \lambda_2, A, K_f)$. It is a function of two experimental parameters (TR , α) and five MT parameters ($M_{0,f}, \lambda_1, \lambda_2, A, K_f$). We fitted the analytically generated steady-state data (with white Gaussian noise) to this function to determine the MT parameters $M_{0,f}, \lambda_1, \lambda_2, A, K_f$ and found that these five parameters can be determined by least-square nonlinear fitting. However, the robustness of the fitting results varies for each parameter. A Monte Carlo method was used to determine the standard deviation of the fitted parameters for different SNR values. The results are plotted in Fig. 9 and shown in Table 2. Note that some parameters have grossly non-Gaussian histograms. Such parameter fittings far from the input value indicate a lack of robustness in the fitting procedure. These misfittings are not due to fitting to a local, as opposed to a global minimum. Refitting these misfitted Gaussian noise sets by taking the minimum residue starting at 1000 randomly distributed initial parameter guesses did not significantly alter the fitted parameter histogram (data not shown).

As we demonstrated in the numerical testing, signal Eq. [2] can be simplified to Eq. [3] with appropriate approximations. The steady-state signal calculated by Eq. [3] is almost the same as the signal calculated by Eq. [2] with the difference smaller than 0.1% of the equilibrium magnetization when calculated with parameters typical of white matter. Equation [3] is a function of two experimental parameters (TR , α) and three MT parameters ($M_{0,f}$, λ_1 , A).

Therefore, we can also use Eq. [3] to determine $M_{0,f}$, $R_1^{obs}(=\lambda_1)$, and A . The analytically generated steady-state-data (with white Gaussian noise) from Eq. [2] was also fitted to Eq. [3]. The results are plotted in Fig. 10 and shown in Table 3.

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FIG. 1.

Transverse steady-state signal generated from numerical methods for 32 different repetition times and three different excitation angles, comparing to the signal calculated from signal Eq. [2]. All data are normalized to $M_{0,f}$. The small figure is an example to show the small difference between the analytical data ($\alpha = 90^\circ$) and the numerical data. MT parameters for white matter (5) were used in the numerical data generation: $K_r = 30.26 \text{ s}^{-1}$, $F = 0.152$, $R_{1,f} = 1.8 \text{ s}^{-1}$, $R_{1,r} = 1 \text{ s}^{-1}$, $T_{2,f} = 0.038 \text{ s}$, $T_{2,r} = 1.14 \times 10^{-5} \text{ s}$. Unless specially noted, all of the numerical and analytical data in this paper were generated by these MT parameter values.

FIG. 2.

The comparison of analytically calculated steady-state signal from Eqs. [2] and [3] for different repetition times and flip angles. The small figure is an example ($\alpha = 90^\circ$) to show that the difference between them is much less than 0.1% of the equilibrium magnetization.

FIG. 3.

Left: The contour plot for $(\text{signal with MT} - \text{signal without MT}) / (\text{signal without MT})$ for different repetition times and flip angles. Right: The contour plot for $(\text{signal with MT} - \text{signal without MT}) / M_{0f}$. The signal with and without MT are from Eqs. [2] and [1], respectively, and sample parameters are for white matter (5). S_r , which will depend on the RF shape and duration, is taken equal to 1.

FIG. 4.

If MT effects are ignored in the data analysis, the fitted $R_{1,app,GE}$ value when varying the flip angle α depends on the choice of TR . The plot gives the expected results for white matter and gray matter (normalized by the R_1^{obs} results from inversion recovery experiment), as determined by Eq. [4] with $S_r = 1$.

FIG. 5.

The fitted recovery rate when ignoring MT by using a gradient echo imaging sequence (without slice selection) and fitting the data to Eq. [5] for MnCl₂ (O), MnCl₂ BSA (□), and BSA (△). The normalizing $R_1^{obs}=1/T_1$ is obtained from a separate inversion recovery experiment that used inversion times > 100 ms. The uncertainties were obtained by repeating the measurements three times.

FIG. 6.

Fit of the experimental data to Eq. [6] for one pixel in the BSA MnCl_2 sample: the fitting lines match well with the gradient echo steady-state data.

FIG. 7.
The parameter A map for $\text{MnCl}_2 + \text{BSA}$ (top), BSA (left bottom), and MnCl_2 (right bottom).

FIG. 8.

The difference between the analytical data generated from Eq. [2] (which ignores relaxation and MT during the RF pulse) and the numerical data generated with consideration of (a) MT, (b) R1 relaxation, (c) T_2 relaxation, (d) all relaxation and exchange terms, and (e) all terms (but with the repetition time starting from the center of the RF pulse and a numerically determined factor of 0.9921 multiplied to S_f) during a 1.5-ms square RF pulse.

Modifications in part (e) reduce the discrepancy between the numerical and analytical solutions by an order of magnitude. Note that the repetition time after modification is actually a better reflection of true TR since the RF pulse cannot be instant in real experiments; also the modification of S_f does not require additional numerical determination of the correcting factor when modeling experimental data, since a b_1 compensation factor will be implemented in experiments, as discussed in the Experimental Methods section. Flip angle $\alpha = 90^\circ$ is used in this figure.

FIG. 9.

The histograms of 1000 least-square fittings to Eq. [2] with different Gaussian noise sets (from left to right: SNR = 1000, 500, 100, 50). For each histogram, Y axis is the count; X axis is either the residue of the fitting or the fitted QMT parameter value normalized by its true value. Acquisition parameters are 32 repetition times exponentially distributed between $TR = 5\text{ms}$ and $TR = 5\text{ sec}$, and three flip angles $\alpha = 40^\circ, 60^\circ, 90^\circ$. The choice of TR and α is not optimized. The mean and standard deviation for each fitted parameter for each SNR is listed in Table 2. M_{0f} has a roughly Gaussian distribution at all SNR. The other parameters, however, have increasingly non-Gaussian distribution as the SNR drops. λ_2 is especially non-Gaussian.

FIG. 10.

The histograms of 1000 least-square fittings to Eq. [3] with different Gaussian noise sets (from left to right: SNR = 1000, 500, 100, 50). For each histogram, Y axis is the count; X axis is either the residue of the fitting or the fitted QMT parameter value normalized by its true value. Acquisition parameters are the same as five parameters fitting: 32 repetition times exponentially distributed between $TR = 5$ ms and $TR = 5$ sec, and three flip angles $\alpha = 40^\circ, 60^\circ, 90^\circ$. The mean and standard deviation for each fitted parameter for each SNR is listed in Table 3. All of the resulting fitted parameters have a roughly Gaussian distribution, reflecting the greater robustness in fitting those data to Eq. [3] in comparison with Eq. [2].

Table 1

Measured QMT Parameters

		Five Parameters Fitting	Three Parameters Fitting	Inversion Recovery Method
BSA MnCl ₂	F	0.11 ± 0.01	0.09 ± 0.03	0.09 ± 0.01
	$R_1^{\text{obs}}(s^{-1})$	1.41 ± 0.03	1.43 ± 0.04	1.38 ± 0.03
BSA	F	0.11 ± 0.02	0.10 ± 0.04	0.09 ± 0.01
	$R_1^{\text{obs}}(s^{-1})$	0.57 ± 0.01	0.58 ± 0.01	0.57 ± 0.01
MnCl ₂	F	0.000 ± 0.001	0.02 ± 0.02	-0.005 ± 0.005
	$R_1^{\text{obs}}(s^{-1})$	2.56 ± 0.04	2.52 ± 0.06	2.46 ± 0.03

The measured slow recovery rate and pool size ratio from the gradient echo method (both five parameters and three parameters fittings) and the selective inversion recovery method. The mean and standard deviation of each parameter are determined by averaging all nonedge pixels in the sample.

Table 2

Results of Five Parameters Fitting

	SNR=1000	SNR=500	SNR=100	SNR=50
$M_{0,f} \left(\frac{\text{fitted}}{\text{true}} \right)$	1.0000 ± 0.0001	1.0000 ± 0.0003	1.000 ± 0.001	1.000 ± 0.003
$\lambda_1 \left(\frac{\text{fitted}}{\text{true}} \right)$	1.000 ± 0.002	1.000 ± 0.004	0.99 ± 0.03	0.96 ± 0.14
$\lambda_2 \left(\frac{\text{fitted}}{\text{true}} \right)$	1.00 ± 0.03	0.98 ± 0.16	1.17 ± 0.78	1.45 ± 1.00
$A \left(\frac{\text{fitted}}{\text{true}} \right)$	1.00 ± 0.02	1.00 ± 0.04	1.10 ± 0.31	1.38 ± 0.91
$K_f \left(\frac{\text{fitted}}{\text{true}} \right)$	1.00 ± 0.06	0.98 ± 0.21	1.11 ± 1.04	1.39 ± 1.77

The mean and standard deviation of the fitted QMT parameters for five parameters fitting. When SNR = 1000, all MT parameters can be determined with a relative small deviation; when SNR = 500, $M_{0,f}$, λ_1 , A are able to be determined. When SNR < 100, λ_2 , A , and K_f are hard to accurately determine, but $M_{0,f}$ and λ_1 are still able to be determined.

Table 3

Results of Three Parameters Fitting

	SNR = 1000	SNR = 500	SNR = 100	SNR = 50
$M_{0,f} \left(\frac{\text{fitted}}{\text{true}} \right)$	1.0000 ± 0.0001	1.0000 ± 0.0003	1.000 ± 0.001	1.000 ± 0.003
$\lambda_1 \left(\frac{\text{fitted}}{\text{true}} \right)$	1.002 ± 0.002	1.002 ± 0.004	1.00 ± 0.02	1.00 ± 0.04
$A \left(\frac{\text{fitted}}{\text{true}} \right)$	0.98 ± 0.02	0.98 ± 0.03	0.98 ± 0.15	0.97 ± 0.31

The mean and standard deviation of the fitted QMT parameters for three parameters fitting. It was found that $M_{0,f}$ and λ_1 can be reasonably determined for any case when SNR is not less than 50; A can be reasonably determined when SNR is around 500 or more. The systematic error on the parameters estimation caused by the approximation from Eqs. [3] to [2] is very small: the resulting A is about 2% smaller than the true value, and the resulting λ_1 is about 0.2% higher than the true value.