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Simultaneous Multi-Angular Relaxometry of Tissue With MRI (SMART MRI): Theoretical Background and Proof of Concept

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Abstract

Purpose: Accurate measurement of tissue-specific relaxation parameters is an ultimate goal of quantitative MRI. The objective of this study is to introduce a new technique, simultaneous multiangular relaxometry of tissue with MRI (SMART MRI), which provides naturally coregistered quantitative spin density, longitudinal and transverse relaxation rate constant maps along with parameters characterizing magnetization transfer (MT) effects.

Theory and Methods: SMART MRI is based on a gradient-recalled echo MRI sequence with multiple flip angles and multiple gradient echoes and a derived theoretical expression for the MR signal generated in this experimental conditions. The theory, based on Bloch-McConnell equations, takes into consideration cross-relaxation between two water pools: “free” and “bound” to macromolecules. It describes the role of cross-relaxation effects in formation of longitudinal and transverse relaxation of “free” water signal, thus providing background for measurements of these effects without using MT pulses. Bayesian analysis is used to optimize SMART MRI sequence parameters.

Results: Data obtained on three participants demonstrate feasibility of the proposed approach.

Conclusion: SMART MRI provides quantitative measurements of longitudinal and transverse relaxation rate constants of “free” water signal affected by cross-relaxation effects. It also provides information on some essential MT parameters without requiring off-resonance MT pulses.

Keywords

MRI; T1 relaxation; T2* relaxation; magnetization transfer; variable flip angles; gradient echo; steady state

INTRODUCTION

Measurement of the biological tissue specific MRI relaxation parameters, such as longitudinal R_1 and transverse R_2 and R_2^* relaxation rate constants, magnetization transfer (MT) rates, etc., is a key for numerous MR applications as these parameters can serve as biomarkers reflecting tissue “health status.”

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Previously, we have introduced a gradient echo plural contrast imaging (GEPCI) technique (1) that is based on a gradient recalled echo (GRE) sequence with multiple gradient echoes allowing simultaneous generation of naturally coregistered multicontrast images (T_1 -weighted or spin density images, R_2^* maps and frequency maps) from a single MR scan and applied it for quantitative evaluation of tissue damage in multiple sclerosis (MS) subjects (2–6). Other examples of using R_2^* mapping include but are not limited to BOLD effect (7,8), and trabecular bone structure (9). R_2^* mapping using GRE sequences has many advantages. First, the acquisition is fast, and, therefore, suffers from fewer motion artifacts. Second, due to the low flip angle used in GRE sequences, they have lower radiofrequency (RF) power deposition and are more suitable for high-field MRI. However, to obtain tissue specific R_2^* maps, consideration should be taken of artifacts created by macroscopic field inhomogeneity effects (10) and physiological fluctuations (5). GRE sequences are also sensitive to the tissue-specific magnetic susceptibility effects (8,10–12) and, hence, can provide separate information on tissue cellular and hemodynamic properties (13).

The present study aims at expanding GEPCI capabilities to provide quantitative R_1 and spin density maps as well as a new quantitative indices characterizing “MRI-invisible” water protons associated with macromolecules. We focus on the interaction between MR-visible water compartments occupying intra- and extracellular spaces (“free” water, f -pool) and an MR-invisible water compartments, in which water molecules are “bound” to macromolecules (“bound” water, b -pool). Because T_2 relaxation time of bound water is very short ($\sim 10 \mu\text{s}$) (14,15) the bound water does not directly contribute to the measured MR signal. However, the cross-relaxation between the free- and bound-water compartments can substantially affect the free-water MR signal. Starting from pioneering publications of Wolff and Balaban (16) and Henkelman et al (17), this phenomenon has been widely used in magnetization transfer (MT) imaging [e.g., (16–26)].

Pike (27) has analyzed the influence of cross-relaxation effects on the signal behavior in GRE imaging and demonstrated quite substantial impact of the bound-water pool on the free-water signal. Similar effects were also analyzed for GRE sequence in Ou and Gochberg (28), for free precession steady state in Gloor et al (29), and inversion recovery sequence in Prantner et al (30).

In the present study, we revisit the subject of the influence of the cross-relaxation between free- and bound-water pools on the GRE signal formation and derive rather simple equations providing a basis for a SMARTMRI technique, which allows the simultaneous measure of relaxation-related parameters characterizing both free and bound water as well as cross-relaxation (MT) effects. The SMART MRI approach is based on the spoiled GRE sequence with multiple flip angles α , multiple GRE times TE , and a theoretical expression for the GRE signal, which will be derived in the Theory section:

$$S(\alpha, TR, TE) = S_0 \cdot \Psi(\alpha, TR) \cdot \exp(-R_2^* \cdot TE) \cdot \exp(i\Delta\omega \cdot TE) \quad [1]$$

$$\Psi(\alpha, TR) = \frac{1 - \exp(-R_1^{(app)} \cdot TR) - \frac{G_1 \cdot \alpha^2}{G_2 + \alpha^2}}{1 - \exp(-R_1^{(app)} \cdot TR) \cdot \cos \alpha} \cdot \sin \alpha$$

where S_0 is proportional to the magnetization of the free water compartment; the apparent longitudinal ($R_1^{(app)}$) and transverse (R_2^*) relaxation rate constants and the coefficients $G_{1,2}$ depend on the relaxation and cross-relaxation parameters of the free- and bound-water pools and sequence parameters (see definitions below); ω is the local frequency shift of the f -pool. Equation [1] can be considered as a generalized Ernst-Anderson expression (see Eq. [18]) accounting for the cross-relaxation effects with the bound-water pool. One of the major new features of this equation is the presence of the α^2 -terms and dependence on the parameters describing exchange effects with the bound water. Hence, the SMART MRI can provide quantitative measurements of parameters defining both longitudinal and transverse tissue specific relaxation properties as well as some cross-relaxation parameters between “free” and “bound” water compartments, which are usually evaluated by the MT experiments with off-resonance MT pulses. Preliminary experimental data on healthy human subjects demonstrate feasibility of the SMART MRI approach. We also use Bayesian probability theory to analyze the optimal choice of experimental sequence parameters for obtaining the best possible estimates of biological tissue parameters.

THEORY

Let us consider a system comprising a pool of free water molecules (f -pool) and a pool of water bounded to macromolecules (b -pool), characterized by the magnetization vectors $\mathbf{M}^{(f)}$ and $\mathbf{M}^{(b)}$, respectively. Generally, in the presence of exchange between these two pools, the time evolution of $\mathbf{M}^{(f)}$ and $\mathbf{M}^{(b)}$ is described by a system of six coupled Bloch equations (17,19,20). In what follows, we consider a pulse sequence comprising repetitive short RF pulses of durations τ separated by repetition time (TR), $\tau \ll TR$, with the remaining transverse magnetization being destroyed before each consecutive RF pulse (spoiled GRE sequence). During time intervals between the RF pulses, evolution of the longitudinal and transverse components of magnetization are independent of each other, and the longitudinal components $M_z^{(f)}$ and $M_z^{(b)}$ satisfy a standard McConnell equations (31):

$$\begin{aligned} \frac{dM_z^{(f)}}{dt} &= -k_f M_z^{(f)} + k_b M_z^{(b)} - R_1^{(f)} \cdot (M_z^{(f)} - M_0^{(f)}) \quad [2] \\ \frac{dM_z^{(b)}}{dt} &= -k_b M_z^{(b)} + k_f M_z^{(f)} - R_1^{(b)} \cdot (M_z^{(b)} - M_0^{(b)}) \end{aligned}$$

where $R_1^{(f,b)} = 1/T_1^{(f,b)}$, $T_1^{(f,b)}$ are the T_1 -relaxation time constants of the compartments; $M_0^{(f,b)}$ are the equilibrium compartmental magnetizations, $M_0^{(f,b)} = \zeta_{f,b} \cdot M_0$, M_0 is the equilibrium magnetization of the whole system and $\zeta_{f,b}$ are the volume fractions of the compartments, $\zeta_f + \zeta_b = 1$. The cross-relaxation rate constants k_f and k_b are related to each other by the equilibrium condition (31): $k_b M_0^{(b)} = k_f M_0^{(f)}$. This relationship can be written in more symmetric notations (17) using an exchange parameter K that is independent of pools populations:

$$k_f = K \times \zeta_b, \quad k_b = K \times \zeta_f. \quad [3]$$

During a short on-resonance RF excitation pulse, the behavior of magnetizations in the f - and b -pools are substantially different. The magnetization vector of the f -pool $\mathbf{M}^{(f)}$ is well known to rotate over a flip angle α determined by the RF field B_1 : $\alpha = \omega_1 \tau$, $\omega_1 = \gamma B_1$ (for a nonrectangular RF pulse, ω_1 should be substituted by its average value, $\bar{\omega}_1 = [\int_0^\tau \omega_1(t) dt] / \tau$). The relaxation and exchange processes during the short RF pulse ($\tau \sim 1$ ms) are well known to have negligible effect on the f -pool.

In the b -pool the situation is substantially different. In this compartment, the longitudinal relaxation and exchange processes during the short RF pulse ($\tau \sim 1$ msec) still play negligible role, while the transverse relaxation (rate constant $R_2^{(b)} \sim 10^5 \text{ s}^{-1}$ [e.g., (14,21)]) substantially changes the dynamics of magnetization rotation. As shown in Appendix B, during a short on-resonance RF pulse of an arbitrary shape, $B_1 = B_1(t)$, and duration τ , the longitudinal magnetization in the b -pool can be described by a monoexponential function with the effective relaxation rate constant R' ,

$$M_z^{(b)}(\tau) = M_z^{(b)}(0) \cdot \exp(-R' \tau), \quad R' = \frac{\overline{\omega_1^2}}{R_2^{(b)}} \quad [4]$$

$$\overline{\omega_1^2} = \frac{\gamma^2}{\tau} \cdot \int_0^\tau dt B_1^2(t)$$

(for a rectangular RF pulse, $\overline{\omega_1^2} = \omega_1^2$). The transverse components of the b -pool are negligibly small, $M_{x,y}^{(b)} \sim (\omega_1 / R_2^{(b)}) \cdot M_z^{(b)} \ll M_z^{(b)}$. Note that a typical value of R' can substantially exceed $R_1^{(b)}$; indeed, for $\omega_1 \sim 1.5 \cdot 10^3 \text{ s}^{-1}$ and $R_2^{(b)} \sim 10^5 \text{ s}^{-1}$, $R' \sim 20 \text{ s}^{-1}$, whereas $R_1^{(b)} \sim 1 \text{ s}^{-1}$.

During the intervals between the RF pulses, the longitudinal magnetizations of the f - and b -pools are described by Eq. [2]. Introducing a two-component vector $\mathbf{m} = (M_z^{(f)}, M_z^{(b)})^T$ (T

denotes a transpose operation) (21,27), the solutions of Eq. [2] with the initial conditions $\mathbf{m}(t=0) = \mathbf{m}_0$ can be written in a convenient matrix form:

$$\mathbf{m}(t) = \hat{\mathbf{A}}(t) \cdot \mathbf{m}_0 + (\hat{\mathbf{I}} - \hat{\mathbf{A}}(t)) \cdot \mathbf{m}_{eq}, \quad \hat{\mathbf{A}}(t) = \exp(-\hat{\mathbf{R}} \cdot t) \quad [5]$$

where $\mathbf{m}_{eq} = (M_0^{(f)}, M_0^{(b)})^T = M_0 \cdot (\zeta_f, \zeta_b)^T$ describes the equilibrium state, $\hat{\mathbf{I}}$ is the identity matrix, the matrix $\hat{\mathbf{R}}$ is

$$\hat{\mathbf{R}} = \begin{pmatrix} r_f & -k_b \\ -k_f & r_b \end{pmatrix}, \quad r_{f,b} = R_1^{(f,b)} + k_{f,b} \quad [6]$$

and the elements of the matrix $\hat{\mathbf{A}}$ are:

$$\begin{aligned} A_{11} &= \frac{1}{q} \cdot (p_+ e_- - p_- e_+), & A_{12} &= \frac{k_2}{q} \cdot (e_+ - e_-) \\ A_{22} &= \frac{1}{q} \cdot (p_+ e_+ - p_- e_-), & A_{21} &= \frac{k_1}{q} \cdot (e_+ - e_-) \end{aligned} \quad [7]$$

where the following notations are introduced:

$$\begin{aligned} e_{\pm} &= \exp(\lambda_{\pm} \cdot TR), \quad \lambda_{\pm} = \frac{1}{2} \cdot [-(r_f + r_b) \pm q], \\ p_{\pm} &= \frac{1}{2} \cdot [(r_f - r_b) \pm q], \quad q = [(r_f - r_b)^2 + 4k_f k_b]^{1/2}. \end{aligned} \quad [8]$$

The two-component vectors $\mathbf{m}$ before ($\mathbf{m}_-$) and after ($\mathbf{m}_+$) the RF pulse can be related by the diagonal matrix $\hat{\mathbf{C}}$,

$$\mathbf{m}_+ = \hat{\mathbf{C}}(\alpha) \cdot \mathbf{m}_-, \quad \hat{\mathbf{C}}(\alpha) = \begin{pmatrix} \cos \alpha & 0 \\ 0 & e' \end{pmatrix} \quad [9]$$

where according to Eq. [4]

$$e' = \exp(-R' \tau). \quad [10]$$

Under the steady-state condition for an ideally spoiled gradient echo sequence with the repetition time TR , the vectors $\mathbf{m}_+$ and $\mathbf{m}_-$ are also related by Eq. [5]:

$$\mathbf{m}_- = \hat{\mathbf{A}}(TR) \cdot \mathbf{m}_+ + (\hat{\mathbf{I}} - \hat{\mathbf{A}}(TR)) \cdot \mathbf{m}_{eq} \quad [11]$$

Combining Eqs. [9] and [11], we get the following expression for the steady-state vector $\mathbf{m}_s \equiv \mathbf{m}_-$ just before the RF pulses

$$\begin{aligned} \mathbf{m}_s(TR, \alpha) &\equiv \left(M_{zs}^{(f)}, M_{zs}^{(b)} \right)^T \\ &= \left[\hat{\mathbf{I}} - \hat{\mathbf{A}}(TR) \cdot \hat{\mathbf{C}}(\alpha) \right]^{-1} \cdot \left[\hat{\mathbf{I}} - \hat{\mathbf{A}}(TR) \right] \cdot \mathbf{m}_{eq}. \end{aligned} \quad [12]$$

Due to a very short T_2 (approximately 10 μs), the bound water does not contribute to the GRE signal in the ms range. The transverse component of the magnetization of the free water pool just after the RF pulse, $M_{\perp}^{(f)}$, is determined by the f -pool component of the vector $m_s(TR, \alpha)$, $M_{\perp}^{(f)} = M_{zs}^{(f)}(TR, \alpha) \cdot \sin\alpha$ and the measured GRE signal $S(TE)$ can be written as

$$S = \eta \cdot M_{zs}^{(f)}(TR, \alpha) \cdot \sin\alpha \cdot \exp(-\Gamma(TE)) \cdot \exp(i\Delta\omega \cdot TE) \quad [13]$$

where η is a proportionality coefficient between the signal and the transverse magnetization, depending on the RF coil sensitivity; $\Gamma(TE)$ is the attenuation function describing transverse relaxation of the GRE signal, and the last factor describes the MR signal frequency depending on the field inhomogeneities and local tissue-specific frequency shifts. The transverse MR signal attenuation function $\Gamma(TE)$ is contributed by the internal decay of f -pool water, characterized by a $R_2^{*(f)}$ relaxation rate constant, and the exchange effects with the b -pool:

$$\Gamma(TE) = R_2^* \cdot TE; \quad R_2^* = R_2^{*(f)} + k_f. \quad [14]$$

Under the actual experimental conditions, $\Gamma(TE)$ is also contributed from mesoscopic field inhomogeneities resulting from the presence of a blood vessel network (BOLD effect) and macroscopic field inhomogeneities (background gradients). Generally speaking, the attenuation function $\Gamma(TE)$ can depend on the echo time TE in a nonlinear way [e.g., (11)]; however, in what follows, we restrict our consideration to the linear dependence $\Gamma(TE)$ on TE as in Eq. [14]. Detailed discussion of these effects is beyond the scope of this study and can be found elsewhere (8,10,11,13,32).

After rather cumbersome but straightforward transformations, Eq. [12] for $M_{zs}^{(f)}$ component can be presented as follows:

$$M_{zs}^{(f)} = M_0^{(f)} \cdot \frac{1 - E'}{1 - E' \cdot \cos\alpha} + M_0^{(b)} \cdot \frac{1 - E''}{1 - E' \cdot \cos\alpha} \quad [15]$$

where

$$E' = \frac{A_{11} - \det \hat{\mathbf{A}} \cdot e'}{1 - A_{22} \cdot e'} = \frac{p_+ e_- (1 - e_+ e') - p_- e_+ (1 - e_- e')}{p_+ (1 - e_+ e') - p_- (1 - e_- e')} \quad [16]$$

$$E'' = \frac{A_{12} \cdot (1 - e')}{1 - A_{22} \cdot e'} = -k_b \cdot \frac{(1 - e') \cdot (e_+ - e_-)}{p_+ (1 - e_+ e') - p_- (1 - e_- e')} \quad [17]$$

In the absence of exchange between the pools ($K = 0$), the quantity $E'' = 0$, and Eq. [15] reduces to the classical Ernst's expression for the steady-state magnetization (33):

$$M_{zs}^{(f)} = M_0^{(f)} \cdot \frac{1 - E_1}{1 - E_1 \cdot \cos \alpha}, \quad E_1 = \exp(-R_1^{(f)} \cdot TR). \quad [18]$$

It is worth noting that $E'' = 0$ also when $e' = 1$. The latter case corresponds to the approximation when the longitudinal magnetization in the b -pool is assumed to remain unchanged during the RF pulses.

Importantly, due to the presence of the function e' , both the functions E' and E'' depend on the flip angle α through the parameter R' . For an RF pulse of duration τ , the flip angle of a free pool is defined by the equation $\alpha = \bar{\omega}_1 \tau$, hence

$$e' = \exp\left(-\frac{\bar{\omega}_1^2}{R_2^{(b)}} \cdot \tau\right) = \exp\left(-\frac{\alpha^2}{\nu \cdot R_2^{(b)} \tau}\right) \quad [19]$$

where the factor $\nu = (\bar{\omega}_1^2)/\omega_1^2$ depends on the shape of the RF pulse ($\nu = 1$ for a rectangular RF pulse). Of interest, for a fixed flip angle, the function e' decreases as τ decreases. For a typical $\tau \sim 1$ msec, due to high transverse relaxation rate constant $R_2^{(b)} \sim 10^5 \text{ s}^{-1}$, the difference $(1 - e')$ is small and can be approximated as

$$1 - e' \approx \frac{\alpha^2}{\nu \cdot R_2^{(b)} \cdot \tau} \ll 1 \quad [20]$$

Using this inequality, the expression for the signal S , Eq. [13], under the steady-state condition can be presented in the form

$$S(\alpha, TR, TE) = S_0 \cdot \Psi(\alpha, TR) \cdot \exp(-\Gamma(TE)) \cdot \exp(i\Delta\omega \cdot TE) \quad [21]$$

$$\Psi(\alpha, TR) = \frac{(1-E) \frac{G_1 \cdot \alpha^2}{G_2 + \alpha^2}}{(1-E) \cdot \cos\alpha} \cdot \sin\alpha$$

where $S_0 = \eta M_0^{(f)}$; E and $G_{1,2}$ are the functions of the model parameters and the repetition time TR , see Eqs. [29] and [30] in Appendix A.

The function $\Psi(\alpha, TR)$ in Eq. [21] generalizes the Ernst's expression for the steady-state magnetization (33) in several ways. First, it contains an additional term in the numerator depending on the flip angle α ; this term is due to the presence of E'' in Eq. [15] and, as mentioned above, is equal to 0 if $K = 0$ (no exchange between the pools) and/or $e' = 1$ (the longitudinal magnetization in the b -pool during the RF pulses remains unchanged). Second, in contrast to the exponent E_1 in Eq. [18] with a single relaxation rate constant $R_1^{(f)}$, the function $E = E(TR)$ in Eq. [21] depends on the repetition time TR in a nonmonoexponential way. Moreover, it depends on four independent model parameters: $R_1^{(f)}$, $R_1^{(b)}$, $k_f = K \cdot \zeta_b$, $k_b = K \cdot (1 - \zeta_b)$.

In an analogy with Eq. [18], we can still introduce an *apparent* longitudinal relaxation rate constant of the free-water compartment, $R_1^{(app)}$, which, however, depends on TR :

$$R_1^{(app)} = -\frac{1}{TR} \cdot \ln E. \quad [22]$$

Figure 1 illustrates the TR -dependence of the parameter $R_1^{(app)}/R_1^{(f)}$ at different exchange rate K for some values of the model parameters ($R_1^{(f)} = 0.8s^{-1}$, $R_1^{(b)} = 1s^{-1}$, $\zeta_b = 0.2$).

At sufficiently short repetition time ($r_+ \cdot TR \ll 1$), the function $E(TR)$ linearly decreases with TR : $E \approx 1 - R_1 \cdot TR$, where R_1 is the relaxation rate constant of the free water compartment modified by the exchange with the b -pool:

$$R_1 = R_1^{(f)} + k'_f, \quad k'_f = k_f \cdot \left(1 + k_b/R_1^{(b)}\right)^{-1}. \quad [23]$$

Hence, for short TR , $R_1^{(app)} = R_1$. The parameter k'_f can be considered as an effective exchange rate constant.

At short TR , the functions $G_{1,2}$ in Eqs. [21] are proportional to TR , and $\Psi(\alpha, TR)$ can be presented as

$$\Psi(\alpha, TR) = \frac{(1 - E) - k'_f \cdot TR \cdot \frac{\alpha^2}{\lambda \cdot (\nu \cdot \tau \cdot TR) + \alpha^2}}{1 - E \cdot \cos \alpha} \cdot \sin \alpha \quad [24]$$

where

$$E = \exp(-R_1 \cdot TR); \quad \lambda = R_2^{(b)} \cdot (R_1^{(b)} + k_b). \quad [25]$$

The additional (as compared to Eq. [18]) term in the numerator in Eq. [24] is proportional to the exchange rate constant $k_f = \zeta_b \cdot K$. It should be mentioned that typical values of all the relaxation and cross-relaxation rate constants are approximately $\sim 1\text{s}^{-1}$ (except $R_2^{(b)} \sim 10^5\text{s}^{-1}$).

According to Eq. [23], the parameter k'_f is of the same order - $k'_f \sim 1\text{s}^{-1}$, whereas $\lambda \sim 10^5\text{s}^{-2}$.

The dimensionless product of λ and the sequence parameters, $\lambda \cdot (\nu \cdot \tau \cdot TR)$, appearing in Eq. [24], for typical values of $\tau \sim 1\text{ms}$, $TR \sim 10\text{ms}$, and $\nu \sim 1$, is also approximately 1, and can be of the same order as α^2 ; hence, it is important for data analysis.

As follows from Eq. [21] and [24], varying the flip angle α (for fixed TR), six independent parameters can be obtained by fitting the signal to experimental data: the amplitude S_0 , the longitudinal and transverse relaxation rate constants R_1 and R_2^* (accounting for the exchange with the b -pool), the local frequency shift ω , and the parameters k'_f and λ . According to Eq. [23], the difference $R_1 - k'_f$ gives $R_1^{(f)}$ - the longitudinal relaxation rate constant of the f -pool.

The quantity $\Psi(\alpha, TR)$ has a meaning of the normalized amplitude of the FID signal. The blue line in Figure 2 demonstrates the dependence of $\Psi(\alpha, TR)$ on flip angle α , simulated with the following values of the sequence and model parameters (blue line): $TR = 18\text{ms}$, $\nu = 1$, $\tau = 0.4\text{ms}$, $R_1 = 1.2\text{s}^{-1}$, $k'_f = 0.4\text{s}^{-1}$, and $\lambda = 0.8 \cdot 10^5\text{s}^{-2}$. For comparison, the red line corresponds to the case when the α^2 -term in Eq. [24] is absent, $k'_f = 0$. The function $\Psi(\alpha, TR)$ reaches its maximum at $\alpha = \alpha^*$; the angle α^* obviously deviates from its value $\alpha_*^{(0)}$, determined by the Ernst expression $\cos \alpha_*^{(0)} = E(33)$ due to the α^2 -term in Eq. [24]. However, for $k'_f \cdot TR \ll 1$, this deviation is rather small and α^* is equal to

$$\alpha_* \approx \alpha_*^{(0)} \cdot \left[1 - \frac{4\lambda' \cdot k'_f \cdot TR \cdot \cos^2 \frac{\alpha_*^{(0)}}{2}}{(\alpha_*^{(0)2} + \lambda'^2)} \right], \quad \lambda' = \lambda \cdot (\nu \cdot \tau \cdot TR). \quad [26]$$

Importantly, if the signal (in the short TR regime) is fitted by Eq. [18] rather than Eq. [24], the resulting relaxation rate constant, $R_{1e} = -(\ln E_1/TR)$, would differ from R_1 . It is easy to verify that for experiments with sufficiently small flip angle, $\alpha^2 < \lambda' = \lambda \cdot (\nu \cdot \tau \cdot TR)$,

$$R_{1e} \approx R_1 + 2 \cdot \frac{k'_f}{\lambda'}. \quad [27]$$

For the values of parameters used above, $\lambda' \approx 0.43$, Eq. [27] is valid for $\alpha < 30^\circ$, and $R_{1e} - R_1 \approx 1.6s^{-1}$, i.e., the error in determining the longitudinal relaxation rate constant may exceed 100%.

METHODS

Subjects

All studies were approved by the Institutional Review Board of Washington University. Three participants (P1, age 24; P2, age 57; and P3, age 75) are included in our preliminary study to demonstrate feasibility of the SMART MRI method.

MRI Acquisition

MRI data were collected using a 3 Tesla (T) Trio MRI scanner (Siemens, Erlangen, Germany) equipped with a 32-channel phased-array head coil. High resolution SMART MRI data with a voxel size of $1 \times 1 \times 1 \text{ mm}^3$ were acquired using a three dimensional (3D) multi-gradient-echo sequence with five flip angles of 5° , 10° , 20° , 40° , and 60° . Such a choice of the flip angles is based on the sequence optimization analysis provided in Appendix C. A rectangular RF pulse with $400 \mu s$ duration was used for signal excitation. For each acquisition, three gradient echoes were collected with echo time 2.26 ms, 6.19 ms, and 10.12 ms, respectively. A navigator echo was acquired for each phase encoding step and used to correct the artifacts caused by physiological fluctuations (5). By using $TR = 18 \text{ ms}$ and GRAPPA (34) with an acceleration factor of two and autocalibrating lines of 24 in each phase encoding direction, the acquisition time of each scan was 3 min 30 s, and the total acquisition time was 17 min 30 s.

Image Processing

The undersampled k-space data were corrected for physiological fluctuation induced artifacts (5). Then, an in-house developed GRAPPA package, the same as implemented in (35), was used to reconstruct the under sampled k-space. After applying the Fourier Transform to the reconstructed k-space, data from different channels were combined for each voxel in a single data set using the following strategy (3,36):

$$S(TE) = \frac{1}{M} \cdot \sum_{m=1}^M \eta_m \cdot S^*(TE_1) \cdot S_m(TE) \quad [28]$$

$$\eta_m = \frac{1}{M\sigma_m^2} \cdot \sum_{i=1}^M \sigma_i^2$$

where the sum is taken over all the channels (m), S^* denotes complex conjugate of S , η_m are weighting parameters, σ_m are noise amplitudes (r.m.s.); the index corresponding to voxel position is omitted for clarity. This algorithm allows for the optimal estimation of quantitative parameters, such as MR signal decay rate constants, and also removes the initial phase incoherence between the channels. To minimize artifacts caused by possible interscan motions, we registered multi-flip-angle scans using “FLIRT” (37,38) tool in “FSL” (39). Then, these multiple datasets with multiple flip angles were analyzed on a voxel-by-voxel basis using the theoretical model, Eqs. [24] and [25].

Fitting Procedure

To reduce noise and enhance fitting stability, the fitting procedure was divided into several steps: First, Eqs. [24] and [25] are fitted to experimental data to get preliminary estimate for all the parameters. As shown in Appendix C, the parameter λ has a rather high estimation error. To minimize this effect, for each voxel, we calculate the average λ -value using a surrounding spherical region with a radius of 5 mm which is a compromise between small characteristic sizes of tissue structure (a few mm) and the need to increase SNR, hence decrease measurement error. And, at last, this low-pass filtered λ -map is used to fit all other parameters in Eqs. [24] and [25]: S_0 , R_1 , k'_f and R_2^* .

RESULTS

Examples of SMART MRI maps obtained from a healthy subject are presented in Figure 3. The images ($R_1^{(f)}$, and R_2^*) demonstrate clear contrast between GM and WM. Note that R_2^* maps reveal bright WM tracts and, generally, improve the WM/GM contrast as compared to the previous results (2,3,5,40). This is because only short TEs in the SMART MRI approach are used, hence the signals are highly weighted by myelin water signals.

In Table 1, we present the SMART MRI parameters in WM and cortical GM for three subjects (averaged over the whole brain). In Table 2, we compare the R_1 -relaxation rate constants obtained by using the traditional model, Eq. [18], and the SMART MRI model, Eqs. [24] and [25].

Note that the traditional model underestimates the values of R_1 as compared to the SMART model. The mean values of R_1 obtained in SMART model correspond to T_1 -relaxation time ($T_1 = 1/R_1$) 855 ± 55 ms in WM and 1278 ± 76 in GM. These values are in a range of the results reported in previous publications [e.g., (26,41–43)]: 600–1000 ms in WM and 1000–1800 ms in GM.

DISCUSSION

Quantitative measurements of biological tissue relaxation properties (T_1 , T_2 , T_2^* , MT, etc.) have been used since inception of MRI in multiple publications to serve as biomarkers of biological tissue properties in health and disease. It is well appreciated that, due to the complicated structure of biological tissue comprised of different water compartments residing in numerous and varied cells and extracellular spaces, the measured values of water MR relaxation parameters always depend on the MRI pulse sequence type and settings used for measurements.

Among different water compartments, one should distinguish between the so-called “free” and “bound” water compartments. The latter have very short T_2 relaxation time [on the order of a few microseconds (17)] and do not directly contribute to the measured MRI signal. However, the bound water indirectly affects MRI signal through exchange effects with the free water. This phenomena is the basis of MT MRI (16,17) where long saturation off-resonance pulses are used to alter magnetization of bound water, thus affecting magnetization of free water which is used to gain information on cross-relaxation effects.

While the majority of measurements of cross-relaxation effects are focused on MT MRI [see for example (16–24)], a few papers (27–29,44) have analyzed the role of cross-relaxation effects on the signal behavior in gradient echo and inversion recovery MRI (30), demonstrating quite substantial influence of the bound-water pool on the free-water signal.

In the present study, we revisit the subject of the influence of the cross-relaxation between free- and bound-water pools on the GRE signal formation. We demonstrate that the exchange between the pools mediates the magnetization recovery in the f -pool after the RF pulse and significantly affects the f -pool T_1 -relaxation time. We derive rather simple equations providing a basis for the simultaneous measurements of relaxation-related parameters characterizing both free and bound water. Our approach is based on the spoiled GRE sequence with multiple flip angles α , multiple GRE times TE , and a theoretical expression we have derived for the MR signal, Eq. [21].

We present the expressions for the signal in a rather simple and clear analytical form allowing us to answer an important question: how many and what model parameters can be obtained by fitting the model to experimental data from the multiple flip angle measurements. This question is not trivial, especially, in models with numerous parameters. For instance, in the comparably simple model discussed in the present study, there are eight independent model parameters: the signal amplitude S_0 proportional to the tissue proton density, five relaxation and cross-relaxation rate constants $R_{1,2}^{(f,b)}$ and K , the local frequency shift in the f -pool ω , and the volume fraction of the b -pool ζ_b . It turned out that only 6 independent parameters can be determined from the SMART MRI experiments comprising measurements with varying flip angles and gradient echo times: the amplitude S_0 , the longitudinal R_1 and the effective cross relaxation rate constant k'_f , which is the combination of the intrinsic relaxation and cross-relaxation rate constants, Eqs. [23], the transverse relaxation rate constant R_2^* , the frequency shift ω in the f -pool, and the parameter λ , Eq.

[25], proportional to the transverse relaxation rate constant in the b -pool. It should be mentioned that, as follows from Eqs. [21], [29], and [30], more parameters can be found by including measurements with varying the repetition time TR .

It is important to note that the parameter λ is determined by the saturation effect of the longitudinal component $M_z^{(b)}$ in the b -pool during the on-resonance RF pulses, described by the quantity e' - the C_{22} -component of the matrix $\hat{C}(\alpha)$, Eq. [9]. In the studies using long off-resonance MT pulses, e' is usually put to 1 [e.g., (21)]. This makes sense because the saturation effect of $M_z^{(b)}$ during the short on-resonance RF pulse is negligible as compared to that during the long MT pulse. In the approaches without MT pulses, the on-resonance RF pulses are the only “source” for the saturation of $M_z^{(b)}$ and, therefore, should be taken into account. If all the water compartments are treated as free-water pools, their magnetization vectors during the on-resonance RF pulses are precessing “normally,” and $e' = \cos\alpha$. In contrast, in our approach, the parameter e' is related to α in a different way: $(1 - e') \sim \omega_1^2 \sim \alpha^2$, Eq. [4]. A more sophisticated approach (a so called super-Lorentzian form for R') required for describing experimental MT data with the off-resonance pulses (17,19) cannot be used for on-resonance pulses; it can be readily shown that the general expression for an arbitrary frequency shift Ω , proposed in (17,19), logarithmically diverges in the on-resonance limit $\Omega \rightarrow 0$.

Of course, our approach contains several assumptions and simplifications. First of all, we describe the brain tissue in the framework of the model comprising a single free-water pool and a single bound-water pool. In reality, the situation is much more complicated: multicompartment models are more adequate for description of brain tissue, in particular, WM [e.g., (45–50)]. For instance, in (25,51), three-compartment models, containing two bound-water pools were proposed. Incorporating such more complicated structures in our approach could be a subject of future work. Here, it should only be mentioned that in multicompartment systems, the model parameters in our equations are expected to depend on the sequence parameters (TE , TR , etc.).

Another important issue is the well-known problem of RF (B_1 field) inhomogeneities; an actual flip angle varies across the imaging object/subject and is different from an “ideal” value prescribed by a pulse sequence. These variations lead to well-known biases in quantitative parameter mapping and are usually addressed by incorporating different methods for the B_1 mapping [e.g., (52–56)]. In our future work the B_1 mapping will be incorporated in the SMART MRI.

CONCLUSIONS

In this study, we investigated the role of cross-relaxation effects between “free” and “bound” water on the MRI GRE signal. We have derived a simple analytical expression describing the GRE signal as a function of the GRE sequence parameters and tissue MR relaxation properties. This theory creates a basis for a new technique, SMART MRI, allowing simultaneous quantitative measurements of tissue specific longitudinal and transverse

relaxation rate constants as well as some essential parameters characterizing cross-relaxation processes. We also examine how the estimated model parameters in the GRE experiment with multiple gradient echoes and multiple flip angles depend on their “true values,” signal-to-noise ratio (SNR), and data sampling strategies. In the framework of Bayesian analysis, we found the optimal choice of experimental sequence settings for obtaining the best possible parameter estimates. Preliminary results obtained on three human volunteers demonstrate a feasibility of the SMART MRI for analyzing relaxation and cross-relaxation characteristics in the human brain.

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APPENDIX A

The Function $G_{1,2}$ Entering Eq. [21]

$$E = 1 - \frac{P_1}{P_2}, \quad G_1 = \frac{P_1}{P_2} - \frac{Q_1}{Q_2}, \quad G_2 = (\nu \cdot R_2^{(b)} \tau) \cdot \frac{P_2}{Q_2} \quad [29]$$

$$\begin{aligned} P_1 &= 2q \cdot [\cosh(r_+ \cdot TR/2) - \cosh(q \cdot TR/2)] \\ P_2 &= q[\exp(r_+ \cdot TR/2) - \cosh(q \cdot TR/2)] - r_- \cdot \sinh(q \cdot TR/2) \\ Q_1 &= q \cdot [\cosh(q \cdot TR/2) - \exp(-r_+ \cdot TR/2)] + (r_- - 2k_f) \cdot \sinh(q \cdot TR/2) \\ Q_2 &= q \cdot \cosh(q \cdot TR/2) + r_- \cdot \sinh(q \cdot TR/2) \end{aligned} \quad [30]$$

$$\begin{aligned} \text{where } r_{\pm} &= r_f \pm r_b; \quad r_{f,b} = R_1^{(f,b)} + k_{f,b}; \\ q &= \left[(r_f - r_b)^2 + 4k_f k_b \right]^{1/2} \end{aligned}$$

APPENDIX B

Nonrectangular RF Pulses

Generally, the time evolution of magnetization vectors $M^{(f)}$ and $M^{(b)}$ is described by a system of 6 coupled Bloch- McConnell equations (17,19,20,31). During time intervals between the RF pulses, evolution of the longitudinal and transverse components of magnetization are independent of each other, and the longitudinal components satisfy a standard McConnell equations (31), Eqs. [2], while the remaining transverse magnetization being destroyed before each consecutive RF pulse (spoiled GRE sequence).

An evolution of the magnetization vectors during a RF pulse substantially depends on the relative scales of the relaxation and cross-relaxation rate constants and the nutation frequency $\omega_1 = \gamma B_1$. In the problem under consideration, typical values of all the relaxation and cross-relaxation rate constants are approximately $\sim 1\text{s}^{-1}$ (except $R_2^{(b)} \sim 10^5\text{s}^{-1}$), while a typical MR pulse duration of 1 ms, the value of ω_1 is approximately 10^3s^{-1} . Hence, the following inequality takes place:

$$R_{1,2}^{(f)}, R_1^{(b)}, K \ll \omega_1 \ll R_2^{(b)}. \quad [31]$$

For an arbitrary shape of an on-resonance RF pulse and the B_1 -field oriented along the X -axis in the rotating frame, the Bloch-McConnell equations for the magnetization vector $\mathbf{M}^{(b)}$ in the b -pool are:

$$\begin{aligned} \frac{dM_x^{(b)}(t)}{dt} &= -R_2^{(b)} \cdot M_x^{(b)}(t) - k_b \cdot M_x^{(b)}(t) + k_f \cdot M_x^{(f)}(t) \quad [32] \\ \frac{dM_y^{(b)}(t)}{dt} &= -R_2^{(b)} \cdot M_y^{(b)}(t) + \omega_1(t) \cdot M_z^{(b)}(t) \\ &\quad - k_b \cdot M_y^{(b)}(t) + k_f \cdot M_y^{(f)}(t) \\ \frac{dM_z^{(b)}(t)}{dt} &= -\omega_1(t) \cdot M_y^{(b)}(t) - R_1^{(b)} \cdot (M_z^{(b)}(t) - M_0) \\ &\quad - k_b \cdot M_z^{(b)}(t) + k_f \cdot M_z^{(f)}(t). \end{aligned}$$

where $\omega_1(t) = \gamma B_1(t)$. According to the inequalities (Eq. [31]), all relaxation and exchange processes, except the transverse relaxation in the b -pool, play negligible role during RF pulses and can be ignored. As a result, the evolution of the magnetization in the pools can be considered separately and Eq. [32] can be reduced to

The Function $G_{1,2}$ Entering Eq. [21]

$$\begin{aligned} \frac{dM_z^{(b)}(t)}{dt} &= -\frac{\omega_1^2(t)}{R_2^{(b)}} \cdot M_z^{(b)}(t) \quad [33] \\ M_y^{(b)}(t) &= \frac{\omega_1}{R_2^{(b)}} M_z^{(b)}(t) \ll M_z^{(b)}(t) \\ M_x^{(b)}(t) &= 0 \end{aligned}$$

The solution of Eq. [33] for $M_z^{(b)}(t)$ has the form

$$M_z^{(b)}(t) = M_z^{(b)}(0) \cdot \exp[-\Phi_b(t)] \quad [34]$$

$$\Phi_b(t) = \overline{\omega_1^2} \cdot t, \quad \overline{\omega_1^2} = \frac{1}{t} \cdot \int_0^t dt' \omega_1^2(t')$$

Thus, the longitudinal component in the b -pool during the on-resonance RF pulse is described by the effective relaxation rate constant $R' = \overline{\omega_1^2}/R_2^{(b)}$.

APPENDIX C

Sequence Optimization

Important practical questions also include (a) how does noise in the experimental data affect estimation of model parameters and (b) what is the optimal choice of experimental sequence parameters for obtaining the best possible parameter estimates (given restricted imaging time). To address these questions, we use Bayesian analysis (57,58) to examine how the estimated model parameters depend on their “true values,” SNR, and data sampling. In what follows, we restrict our analysis to the signal magnitude, $S_a(\alpha, TR, TE) = S \mid (\alpha, TR, TE)$ | ,

$$S_a(\alpha, TR, TE) = S_0 \cdot \Psi(\alpha, TR) \cdot \exp(-\Gamma(TE)) \quad [35]$$

In this study, we also restrict our consideration to an experiment with fixed TR and variable flip angles.

The basic quantity in Bayesian analysis is a joint posterior probability $P(\{p_j\} \mid Data, \sigma, I)$ for model parameters $\{p_j\} = S_0, R_2^*, R_1, k_f', \lambda$ given all of the data $Data$, the noise standard deviation σ , and the prior information I . In the high SNR approximation (57),

$$P(\{p_j\} \mid Data, \sigma, I) \propto \exp(-Q/2\sigma^2) \quad [36]$$

where

$$Q = \sum_{n,m} \left[\hat{S}_a(\{\alpha_n, TE_m\}; \{\hat{p}_j\}) - S_a(\{\alpha_n, TE_m\}; \{\hat{p}_j\}) \right]^2. \quad [37]$$

The double sum in Eq. [37] is over all the flip angles α_n and echo times TE_m used in experiment. The function $\hat{S}_a(\{\alpha_n, TE_m\}; \{\hat{p}_j\})$ represents Data and is determined from the model $S_a(\{\alpha_n, TE_m\}; \{\hat{p}_j\})$, Eq. [35], by substituting the parameters $\{p_j\} = \{S_0, R_2^*, R_1, k_f', \lambda\}$ with their “true” values $\hat{p}_j$.

To estimate any parameter in the model, a posterior probability for the parameters should be calculated, from which the estimated values of the parameters can be found in the form:

$$(p_j)_{est} = \hat{p}_j \pm \Delta p_j, \quad \Delta p_j = SNR_0^{-1} \cdot (\Delta_j / \Delta)^{1/2} \quad [38]$$

where p_j are the expected uncertainties of the estimated parameters, $SNR_0 = S_0/\sigma$ is the SNR; Δ is the determinant of the variance-covariance matrix $\hat{V}$ with the rank M equal to the number of model parameters, and Δ_j is the minor of this matrix corresponding to the diagonal element jj . The matrix elements of $\hat{V}$ are determined by the derivatives of the function $S_a(\{\alpha_n, TE_m\}; \{p_j\})$:

$$V_{ij} = \sum_{n=1}^{N-1} S_i(\{\alpha_n, TE_m\}; \{\hat{p}_j\}) S_j(\{\alpha_n, TE_m\}; \{\hat{p}_j\}), \quad [39]$$

$$S_i = (\partial S_a / \partial p_i)_{p_i = \hat{p}_i}$$

Obviously, an actual experimental SNR is much smaller than the quantity SNR_0 : the latter formally corresponds to the GRE signal that would be acquired at $\alpha = \pi/2$ and $TR \rightarrow \infty$. An actual amplitude of the GRE signal depends on TR and the flip angle α ; for the model parameters used in the previous section (see Figure 2), the SNR corresponding to the maximal amplitude of the GRE signal (achieved at $\alpha = \alpha_* \sim 11^\circ$) is approximately $SNR \approx 0.1 \cdot SNR_0$.

Optimal parameters of the pulse sequence correspond to a set of the sequence parameters α_n and echo times TE_m minimizing the expected uncertainties p_j . Obviously, the uncertainties p_j can be made smaller by increasing several acquired data points N . Roughly speaking, the uncertainties decrease as $1/N$. However, in real experiments, the total time is limited and a reasonable trade-off between a total number of measurements and precision should be used. Figure 4 illustrates the dependences of the relative uncertainties per a unit measurement, $\delta p_j = (\Delta p_j / p_j) \cdot \sqrt{N_\alpha}$, on the maximal flip angle α_{max} for different minimal flip angles α_{min} .

The relative errors (per unit measurement) of the signal amplitude S_0 (not shown) and the relaxation rate constant R_2^* have clear minima corresponding to the flip angles close to that at which the signal amplitude as a function of α has a maximum. The relative error of the parameters R_1 and k'_f have shallow minima at $\alpha \sim 60^\circ$, whereas the relative error of the parameter λ monotonically decreases as α increasing.

These results suggest that achieving the highest measurement precision for different model parameters requires different sequence design: for S_0 and R_2^* the highest precision can be achieved when the maximal flip angle α_{max} only slightly exceeds α_* ($\sim 11^\circ$ in our case), whereas the parameters R_1 , k'_f , and λ require much bigger flip angles.

As we see, all the relative uncertainties are smaller for smaller $\alpha_{\min}$ except δR_2^* . For the latter, the best estimates can be achieved at $\alpha_{\min} = 11^\circ$. Note that this value of the flip angle corresponds to the maximum of the normalized GRE signal amplitude $\Psi(\alpha, TR)$, see Figure 2.

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FIG. 1.

The ratio $R_1^{(app)}/R_1^{(f)}$ as a function of the repetition time TR at different values of the exchange rate constant K (in sec^{-1} , shown by numbers by the lines); $R_1^{(f)} = 0.8\text{s}^{-1}$, $R_1^{(b)} = 1\text{s}^{-1}$, $\zeta_b = 0.2$.

FIG. 2.

The function $\Psi(\alpha, TR)$ simulated with $TR = 18$ ms, $\nu = 1$, $\tau = 0.4$ ms, $R1 = 1.2 \text{ s}^{-1}$, $k'_f = 0.4 \text{ s}^{-1}$, and $\lambda = 0.8 \cdot 10^5 \text{ s}^{-2}$ (blue line). The red line corresponds to $k'_f = 0$.

FIG. 3.

Example of SMART maps from the participant P1. To minimize estimation errors and improve the SNR, the λ -map was averaged using a surrounding spherical region with a radius of 5 mm, which is a compromise between small characteristic sizes of tissue structure (a few mm) and the need to increase SNR.

FIG. 4.

The dependences of the relative uncertainties of the model parameters per a unit measurement on the maximal flip angle for different minimal flip angles $\alpha_{\min} = 1^\circ; 5^\circ; 9^\circ$ (black, red, and green lines, respectively). All curves are obtained using a 2° flip angle interval. Calculations are performed for $TR = 18$ ms, and three gradient echoes ($TE = 2, 6,$ and 10 ms).

Table 1
SMART MRI Parameters in WM and Cortical GM (Averaged Over the Whole Brain)

	White matter					Cortical gray matter				
	$R_1; s^{-1}$	$R_1^{(f)}, s^{-1}$	k_f', s^{-1}	$\lambda, s^{-2} (\times 10^5)$	R_2^*, s^{-1}	$R_1; s^{-1}$	$R_1^{(f)}, s^{-1}$	k_f', s^{-1}	$\lambda, s^{-2} (\times 10^5)$	R_2^*, s^{-1}
P1	1.23	0.73	0.50	1.08	23.82	0.82	0.55	0.27	1.01	19.04
P2	1.20	0.70	0.51	0.9	22.82	0.82	0.54	0.28	0.88	19.97
P3	1.09	0.64	0.46	0.86	23.83	0.74	0.50	0.24	0.83	21.85
Mean	1.17	0.69	0.49	0.95	23.49	0.79	0.53	0.26	0.91	20.29
STD	0.07	0.05	0.03	0.12	0.58	0.05	0.03	0.02	0.09	1.43

Table 2

R1-Relaxation Rate Constant (in s^{-1}) Obtained by Using the Traditional Model and SMART MRI Model in WM and Cortical GM (Averaged Over the Whole Brain)

	$R_1, s^{-1}, \text{white matter}$		$R_1, s^{-1}, \text{cortical gray matter}$	
	Traditional model	SMART model	Traditional model	SMART model
P1	1.01	1.23	0.71	0.82
P2	0.96	1.20	0.70	0.82
P3	0.88	1.09	0.63	0.74
Mean	0.95	1.17	0.68	0.79
STD	0.07	0.07	0.04	0.05