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MRI Contrast from Relaxation Along a Fictitious Field (RAFF)

Timo Liimatainen, Dennis J. Sorce, Robert O'Connell, Michael Garwood, and Shalom Michaeli*

Center for Magnetic Resonance Research and Department of Radiology, University of Minnesota, Minneapolis, USA

Abstract

A new method to measure rotating frame relaxation and to create contrast for MRI is introduced. The technique exploits relaxation along a fictitious field (RAFF) generated by amplitude- and frequency-modulated irradiation in a sub-adiabatic condition. Here, RAFF is demonstrated using a radiofrequency pulse based on *sine* and *cosine* amplitude and frequency modulations of equal amplitudes, which gives rise to a stationary fictitious magnetic field in a doubly rotating frame. According to dipolar relaxation theory, the RAFF relaxation time constant (T_{RAFF}) was found to differ from laboratory frame relaxation times (T_1 and T_2) and rotating frame relaxation times ($T_{1\rho}$ and $T_{2\rho}$). This prediction was supported by experimental results obtained from human brain *in vivo* and three different solutions. Results from relaxation mapping in human brain demonstrated the ability to create MRI contrast based on RAFF. The value of T_{RAFF} was found to be insensitive to the initial orientation of the magnetization vector. Finally, as compared with adiabatic pulse trains of equal durations, RAFF required less radiofrequency power and therefore can be more readily used for rotating frame relaxation studies in humans.

Introduction

As magnet technology continues to advance, the field strength (B_0) used for NMR has steadily increased. This trend has been fueled mainly by the quest for increased signal-to-noise ratio. On the other hand, as B_0 increases, the laboratory frame T_1 becomes less sensitive to slow molecular motions because T_1 is dominated by dipolar fluctuations occurring mainly near the Larmor frequency, $\omega_0 = \gamma B_0$ (1), where γ is the magnetogyric ratio. Reduced sensitivity to slow molecular motions is particularly relevant to the field of biomedical MRI, since tissue-specific differences in T_1 are relied upon for one of the most important forms of image contrast (i.e., T_1 -weighting) (2). Alternatively, it has been known for many years that relaxation in the presence of radiofrequency (RF) irradiation, i.e., the rotating frame longitudinal and transverse relaxation times ($T_{1\rho}$ and $T_{2\rho}$, respectively), can provide information about slow molecular motions at any field strength (3–8). Although $T_{1\rho}$ is also known to depend on B_0 , the relaxation rate increases when the spins experience dipolar fluctuations with relatively long correlation times ($\tau_c \gg \omega_0^{-1}$), and it is in this manner that $T_{1\rho}$ probes slow molecular dynamics. Although $T_{1\rho}$ and $T_{2\rho}$ measurements have

*Corresponding author: Shalom Michaeli, Ph.D., Center for Magnetic Resonance Research, University of Minnesota, 2021 Sixth Street SE, Minneapolis, MN 55455, USA, Tel. 612-626-2001, FAX: 612-626-2004, shalom@cmrr.umn.edu.

classically been performed with time-invariant RF pulses, these experiments can also be performed with pulses utilizing amplitude- (AM) and frequency-modulated (FM) functions which have been designed to execute adiabatic full-passage (AFP) (9–11). Some studies have shown that rotating frame relaxation times can be more informative than T_1 and T_2 in assessing specific tissue properties and in detecting certain pathologic changes (12–16). For example, in a recent pilot study of patients with Parkinson's disease, adiabatic $T_{2\rho}$ ($T_{2\rho,\text{adiab}}$) was more sensitive than T_2 to pathological changes occurring in the brain, which is likely due to iron accumulation in substantia nigra. In addition, adiabatic $T_{1\rho}$ ($T_{1\rho,\text{adiab}}$) reflected likely nigra neuronal degeneration (17).

A potential limitation to making rotating frame relaxation measurements in living systems is the required RF power (i.e., specific absorption rate (SAR)) and concern about tissue heating. In certain cases, only low RF power is required to measure $T_{1\rho}$ with the classical spin-lock experiment. For example, $T_{1\rho}$ measured with low spin-lock power ($B_1=2.0\cdot10^{-6}$ T) provided an excellent imaging biomarker to detect gene therapy response in a rodent glioma model (16). On the other hand, the RF power needed for spin-locking often limits the application of classical $T_{1\rho}$ experiments to studies of humans at high magnetic fields. To avoid off-resonance artifacts, the magnetization vector should be “locked” along a specified orientation in the rotating frame. To satisfy this requirement, the effective field should be larger than the local field gradients reflected by the linewidth of the resonance. To overcome the power limitation, the off-resonance $T_{1\rho}$ experiment is frequently used (18), although this method is sometimes limited by B_1 and B_0 inhomogeneities which are difficult to eliminate in MRI (19). Likewise, in some cases, the RF power required to fulfill the adiabatic condition for adiabatic $T_{1\rho}$ and $T_{2\rho}$ measurements may not be permissible within SAR guidelines.

In the case of frequency-modulated pulses (adiabatic and sub-adiabatic pulses alike), the analysis is performed in a tilting rotating frame in which the effective field also remains larger than the local frequency variations and is close to stationary despite these frequency variations. With this approach, we describe here a novel method to create and exploit a “fictitious” magnetic field for rotating frame relaxation studies. The fictitious field is created by a rapid, sub-adiabatic modulation of the RF amplitude and frequency, whereby the effective field consists of B_1 and B_0 components, as well as a fictitious field component. The method is called RAFF (relaxation along a fictitious field). Employing second order perturbation theory, we demonstrate the sensitivity of RAFF to long rotational correlation times, τ_c . Experimental measurements performed on solutions and human brain demonstrate the potential of RAFF to assess molecular dynamics and to generate contrast for MRI, while requiring less RF power than that typically used for $T_{1\rho}$ and $T_{2\rho}$ measurements.

Theoretical Description and Bloch Simulations of RAFF

An understanding of $T_{1\rho}$ and $T_{2\rho}$ methods utilizing AM and FM pulses can be facilitated by analyzing the magnetic field components and motion of the magnetization vector $\mathbf{M}$ in two different rotating coordinate frames. The first frame rotates in synchrony with the time-dependent pulse frequency ($\omega_{\text{RF}}(t)$), and is thus known as the ω_{RF} -frame with axis labels x' , y' , and z' (20). In the ω_{RF} -frame, during an AFP pulse the orientation of $\mathbf{B}_1$ is fixed (by

convention, $\mathbf{B}_1$ is along the x' -axis). The effective field ($\mathbf{B}_{\text{eff}}(t)$), which sweeps from $+z'$ to $-z'$ (or vice versa), is given by

$$B_{\text{eff}}(t) = \sqrt{B_1^2(t) + (\Delta\omega(t)/\gamma)^2}, \quad [1]$$

where $\omega(t)$ is the time-dependent offset frequency

$$\Delta\omega(t) = \omega_0 - \omega_{\text{RF}}(t). \quad [2]$$

The AM and FM functions of an AFP pulse produce a sweep of $\mathbf{B}_{\text{eff}}(t)$, with a tilt angle relative to the z' axis given by

$$\alpha(t) = \tan^{-1} \left(\frac{\omega_1(t)}{\Delta\omega(t)} \right), \quad [3]$$

where

$$\omega_1(t) = \gamma B_1(t). \quad [4]$$

Because $\mathbf{B}_{\text{eff}}$ is time-dependent during an AFP pulse, the adiabatic rotating frame relaxation time constants ($T_{1\rho, \text{adiab}}$ and $T_{2\rho, \text{adiab}}$) are also time-dependent. At any given time point during the pulse, the relaxation rate will depend on the orientation and amplitude of $\mathbf{B}_{\text{eff}}(t)$, as well as the orientation of $\mathbf{M}$ relative to $\mathbf{B}_{\text{eff}}(t)$ at that moment in time. When the adiabatic condition is well satisfied throughout an AFP pulse, the component of $\mathbf{M}$ that is initially aligned with $\mathbf{B}_{\text{eff}}$ will remain approximately aligned (or “locked”) with $\mathbf{B}_{\text{eff}}(t)$ during the pulse; accordingly, this magnetization experiences time-dependent $T_{1\rho}$ relaxation. In this manner, $T_{1\rho}$ contrast can be produced in MRI by transmitting a windowless train of AFP pulses prior to the excitation pulse (11). Likewise, if $\mathbf{M}$ is placed perpendicular to $\mathbf{B}_{\text{eff}}$ at $t = 0$, $\mathbf{M}$ will evolve with the effective frequency $\omega_{\text{eff}}(t) = \gamma B_{\text{eff}}(t)$ and will lie close to the plane perpendicular to $\mathbf{B}_{\text{eff}}(t)$ at all times during the AFP pulse. Hence, by first creating transverse magnetization (M_{xy}) and subsequently transmitting a windowless train of AFP pulses, $T_{2\rho, \text{adiab}}$ contrast can be generated (10).

The description above applies to the situation in which the adiabatic condition, $B_{\text{eff}}(t) \gg |\gamma^{-1} d\alpha/dt|$, is fulfilled throughout the pulse. Conversely, in the RAFF method the adiabatic condition is purposefully violated by choosing the modulation functions to satisfy the condition $B_{\text{eff}}(t) = |\gamma^{-1} d\alpha/dt|$. To facilitate an understanding of RAFF, the vector analysis must move to a second frame of reference (Fig. 1) which is a doubly rotating frame known as the ω_{eff} -frame, with axis labels x'' , y'' , and z'' (20). In the ω_{eff} -frame, by definition the orientation of $\mathbf{B}_{\text{eff}}$ remains fixed along the z'' axis. Initially ($t = 0$), the ω_{RF} -frame and ω_{eff} -frame are superimposed (i.e., $z'' = z'$), and at later times, the two frames are related by the $\mathbf{B}_{\text{eff}}$ rotation which takes place around $y' (= y'')$ of the ω_{RF} -frame. The time derivative of this rotation in the ω_{RF} -frame (i.e., $d\alpha/dt$) gives rise to a fictitious field in the ω_{eff} -frame directed along y'' and has a magnitude equal to $|\gamma^{-1} d\alpha/dt|$. The effective field vector $\mathbf{E}(t)$ in the ω_{eff} -

frame is thus the vector sum of $B_{\text{eff}}(t) \hat{z}'$ and the fictitious field, $[\gamma^{-1} d\alpha/dt] \hat{y}'$. As such, the magnitude of $\mathbf{E}$ is given by

$$E(t) = \sqrt{B_{\text{eff}}^2(t) + \left(\gamma^{-1} \frac{d\alpha}{dt}\right)^2}. \quad [5]$$

The angle between $\mathbf{E}$ and $\mathbf{B}_{\text{eff}}$ is defined as (20,21),

$$\varepsilon(t) = \tan^{-1} \left(\frac{\gamma B_{\text{eff}}(t)}{d\alpha/dt} \right). \quad [6]$$

The $\mathbf{E}$ field is utilized for spin-locking in the RAFF method. When $B_{\text{eff}}(t) = |\gamma^{-1} d\alpha/dt|$, a stationary $\mathbf{E}$ exists in the ω_{eff} -frame at an angle $\varepsilon = \pi/4$ relative to the z'' axis. To facilitate the theoretical analysis of the relaxation occurring with RAFF, a third frame of reference can be defined (the ω_E -frame with axes x''', y''', z'''), in which $\mathbf{E}$ remains stationary and collinear with z''' during the pulse (Fig. 1). Although $\mathbf{E}$ has been previously described (22) and used to excite magnetization (20), its usefulness in rotating frame relaxation experiments has apparently not been explored prior to this study.

Satisfaction of the condition $B_{\text{eff}}(t) = |\gamma^{-1} d\alpha/dt|$ with *sine* and *cosine* functions (SC) leads to the condition

$$\omega_E = \sqrt{2} \omega_1^{\text{max}}, \quad [7]$$

where $\omega_E = \gamma E$ and ω_1^{max} is the maximum value of the AM and FM functions, which are

$$\omega_1(t) = \frac{\omega_E}{\sqrt{2}} \left| \sin \left(\frac{\omega_E}{\sqrt{2}} t + \varphi_0 \right) \right| \quad [8]$$

$$\Delta\omega(t) = \frac{\omega_E}{\sqrt{2}} \cos \left(\frac{\omega_E}{\sqrt{2}} t + \varphi_0 \right). \quad [9]$$

Here, $\varphi_0 = 0$ when $t \in [0, T_p/4]$. T_p is the pulse length in seconds defined by

$$T_p = \frac{4\pi}{\omega_E}. \quad [10]$$

With this pulse, the frequency function (Eq. [9]) sweeps from its initial value ($\Delta\omega = \omega_1^{\text{max}}$) toward the resonance condition ($\omega = 0$) and beyond ($\omega < 0$), while the pulse amplitude (Eq. [8]) varies in a sinusoidal manner. The argument of both modulation functions must be the same ($2^{-1/2} \omega_E t + \varphi_0$) to create the condition $\varepsilon = \pi/4$. It should be noted that, with a given setting of ω_1^{max} , the effective field is larger with RAFF as compared with the on-resonance $T_{1\rho}$ spin-lock field (i.e. $\omega_E > \omega_1$).

Magnetization response to RAFF can be visualized by considering the motion of $\mathbf{M}$ in the ω_{eff} -frame, with $\mathbf{M}$ initially along the z'' axis (Fig. 2b). In this case, $\mathbf{M}$ evolves around the axis of a cone, which is defined by $\mathbf{E}$ and the angle $\varepsilon = \pi/4$ (20). When satisfying the conditions defined above, $\mathbf{M}$ undergoes a π rotation on the cone and thus attains a final orientation along y'' . This rotation is equivalent to a net rotation of $\pi/2$ in both rotating frames, since $y'' = y'$. Hereafter, the RF modulation functions producing this rotation will be denoted by the operator P , in accordance with nomenclature used previously (23).

After accomplishing the first P segment in the time interval $[0, T_p/4]$, the magnetization is returned to the z'' axis using the inverse pulse P^{-1} during the interval $[T_p/4, T_p/2]$ (Fig. 2). The inverse is created by performing a π phase shift and setting

$$\varphi_0 = -\pi \left(\sqrt{2} + 1 \right), \text{ when } t \in \left[\frac{T_p}{4}, \frac{T_p}{2} \right], \quad [11]$$

in Eqs. [8] and, [9]. In Bloch simulations of the SC pulse, the P^{-1} segment was necessary to compensate B_1 inhomogeneity.

To simplify the pulse and for ease of implementation, the FM function can be converted to the equivalent phase modulation function given by

$$\phi(t) = \int_0^t \Delta\omega(t') dt'. \quad [12]$$

In the AM and phase modulated format, P^{-1} is created by adding π to the phases of P and reversing the time dependencies of the AM and phase functions (Fig. 2a).

To compensate other types of frequency shifts ($\mathcal{J}$) that can arise from imperfections such as B_0 inhomogeneity and magnetic susceptibility differences in the sample, the $P P^{-1}$ segment is followed by the segment $P_\pi P_\pi^{-1}$, which is formed by adding π to all phases in $P P^{-1}$. The resulting composite pulse, $P P^{-1} P_\pi P_\pi^{-1}$, with length T_p given by Eq. [10], defines the fundamental element from which RAFF trains are composed. In Bloch simulations of RAFF, satisfactory performance was obtained when using pulse trains composed of increasing numbers of the basic element, $P P^{-1} P_\pi P_\pi^{-1}$, despite the existence of B_1 inhomogeneity and frequency shifts ($\mathcal{J}$) larger than typical water linewidths (Fig. 3a). For comparison, simulations were performed using only the $P P^{-1}$ segment as the basic element of the RAFF train. As compared with $P P^{-1} P_\pi P_\pi^{-1}$ (Figs. 3c,e, solid line), the $P P^{-1}$ segment by itself exhibited poor off-resonance performance (Figs. 3b,d). In addition, when the frequency response profile of $P P^{-1} P_\pi P_\pi^{-1}$ was compared to the profile of a simple (square) π pulse train, a wider profile was achieved with the SC pulse (Figs. 3c,e, dashed line).

It can be shown that the fictitious field $\mathbf{E}$ acts as a locking field. This was demonstrated by performing Bloch simulations when placing $\mathbf{M}$ initially along the direction of $\mathbf{E}$ ($\mathbf{M}_0 = [0, 2^{-1/2}, 2^{-1/2}]$) and applying continuously the SC pulse according to Eqs. [8], and [9]. It can

be seen (Fig. 4) that the magnetization vector remains locked along $\mathbf{E}$ during the application of the SC pulse. This demonstrates that $\mathbf{E}$ effectively acts as a locking field.

Relaxation Calculations

Here we consider dipolar relaxation between two identical isolated spins. It has been shown that a complete description of the relaxation in the presence of AM and FM irradiation requires consideration of the time-dependence of the relaxation functions (24). The Wigner rotation matrices were used to transform between the various frames of interest with the following substitutions (24)

$$\begin{aligned}\alpha &\rightarrow \alpha(t) \\ \omega_{eff} &\rightarrow \omega_{eff}(t)\end{aligned} \quad [13]$$

These transformations have been used to describe relaxation that occurs during the execution of adiabatic π pulses belonging to the hyperbolic secant (HS) family (10,24). In the current work, for the calculation of the relaxation functions during RAFF an additional transformation to the third frame of reference (the ω_E -frame) is needed, which is performed by rotating the ω_{eff} -frame by the angle ε which for generality is allowed to be time-dependent.

Following the procedure of Abragam (3), the relaxation rate constants in the ω_E -frame were obtained using spectral density functions written in the laboratory frame and transformed first to the ω_{eff} -frame, and then to the ω_E -frame using Wigner rotation matrixes (24,25). The time-dependent spectral densities in this case are written in the frame rotating doubly at ω_0 and $\omega_E(t)$. The expansion for the dipolar Hamiltonian in the ω_E -frame is written as (24)

$$H_{dd}(t) * = \sum_{m=-2}^2 F_{2m}(t) A_{2m}^* \quad [14]$$

Here $F_{2m}(t)$ is a time-dependent stochastic function that models the interaction of the spin system with its environment and A_{2m}^* is a second rank irreducible spherical tensor transformed to the ω_E -frame. Following standard methods from angular momentum theory (25),

$$A_{2m}^* = \sum_{m'=-2}^2 A_{2m'} D_{m',m}^{(2)}(-\psi(t), -\alpha(t), \varepsilon(t), -\omega_0 t), \quad [15]$$

where $D_{m',m}^{(2)}$ are the second rank Wigner rotation matrices that are used to transform the second rank tensors from the laboratory frame to the ω_E -frame and ψ is the angle evolved around ω_E :

$$\psi(t) = \int_{t_0}^t \omega_E(\zeta) d\zeta. \quad [16]$$

The second rank Wigner rotation matrix elements are (24,25)

$$D_{m',m}^{(2)}(-\psi(t), -\alpha(t), \varepsilon(t), -\omega_0 t) = e^{im''\psi(t)} d_{m',m}^{(2)}(-\alpha(t)) d_{m'',m'}^{(2)}(\varepsilon(t)) e^{im\omega t}. \quad [17]$$

The second rank reduced Wigner matrix elements are

$$d_{m',m}^{(2)}(-\alpha(t)) = \sqrt{(2+m)!(2-m)!(2+m')!(2m')!} \\ \times \sum_l \frac{(-1)^l}{(2-m'-l)!(2+m-l)!(l+m'-m)!l!} (\cos(\alpha(t)/2))^{4+m-m'-2l} (-\sin(\alpha(t)/2))^{m'-m+2l}, \quad [18]$$

where the sum is over the values of the integer l for which the factorial arguments are

greater or equal to zero and the elements $d_{m'',m'}^{(2)}(\varepsilon(t))$ are calculated following Refs. (24,25). Therefore, the final expressions for the longitudinal and transverse relaxation rate constants in the ω_E -frame are

$$T_{1\rho,E}^{-1}(t) = \frac{3}{20} b^2 \sum_{m=-2}^2 \sum_{m'=-2}^2 \sum_{m''=-2}^2 \frac{\tau_c}{1 + (\tau_c(m\omega_0 + m''\omega_E(t)))^2} \times (d_{m',m}^{(2)}(\alpha(t)))^2 (d_{m'',m'}^{(2)}(\varepsilon))^2 m''^2 \quad [19]$$

$$T_{2\rho,E}^{-1}(t) = \frac{3}{40} b^2 \sum_{m=-2}^2 \sum_{m'=-2}^2 \sum_{m''=-2}^2 \frac{\tau_c}{1 + (\tau_c(m\omega_0 + m''\omega_E(t)))^2} \times (d_{m',m}^{(2)}(\alpha(t)))^2 (d_{m'',m'}^{(2)}(\varepsilon))^2 (m''+2)(3-m''), \quad [20]$$

where $b = -\mu_0 \hbar \gamma^2 / (4\pi r^3)$, μ_0 is the permeability of vacuum, $\hbar$ is Planck's constant, and r is the radius of dipolar interaction, with all measures given in SI units. When the SC pulse with $\varepsilon = \pi/4$ acts on magnetization that is initially along the z axis, $R_{\text{RAFF}} (\equiv T_{\text{RAFF}}^{-1})$ will be the average of $T_{1\rho,E}^{-1}(t)$ and $T_{2\rho,E}^{-1}(t)$ over the duration of the pulse as given by

$$R_{\text{RAFF}} = \frac{1}{2T_p} \int_0^{T_p} (T_{1\rho,E}^{-1}(t) + T_{2\rho,E}^{-1}(t)) dt. \quad [21]$$

To allow a comparison with the theoretical formalism above, Bloch equations were also used to simulate signal decay during the pulse train using SC pulses with the refocusing scheme $P P^{-1} P_{\pi} P_{\pi}^{-1}$. To obtain the τ_c dependence for dipolar interaction, T_1 and T_2 values corresponding to given values of τ_c were calculated based on existing theory (26) and then used as inputs to the Bloch equations. From the simulations, the time-dependence of the magnetization was obtained separately for $\mathbf{M}$ initially along $\pm z'$.

Experimental Methods

Phantom experiments

All phantom experiments were carried out using a 40-cm-bore 4.7 T magnet (OMT, Inc., Oxon, UK) with a Varian ^{UNITY}INOVA console (Varian Inc., Palo Alto, CA). RF power was transmitted and received using a home-built linearly-polarized surface coil.

Confounding effects from B_1 inhomogeneity were minimized using localized spectroscopy. Immediately after executing a given preparation sequence (composed of either SC pulses for T_{RAFF} or AFP pulses for $T_{1\rho,\text{adiab}}$ measurements), the magnetization was rotated onto the transverse plane using a $\pi/2$ excitation pulse and then detected using single-voxel localization based on LASER (localization by adiabatic selective refocusing) (20). For $T_{2\rho,\text{adiab}}$ experiments, the $\pi/2$ excitation was applied prior to the AFP preparation pulses. Excitation was performed with an adiabatic half-passage (AHP) using $\omega_1^{\text{max}}/(2\pi)=4$ kHz and pulse length = 3 ms. The six HS pulses used for localization in LASER were transmitted with $\omega_1^{\text{max}}/(2\pi)=5$ kHz and pulse length = 3 ms, with a 1 ms delay between HS pulses giving an echo time 37 ms. The repetition time was 5 s. Voxel dimensions ranged from $4 \times 4 \times 4$ mm³ to $4 \times 6 \times 6$ mm³.

To assess dipolar relaxation, measurements were performed on 100 mM acetate in glycerol/water (ratio = 0.9/0.1 by weight). Sodium acetate (Sigma-Aldrich Inc., USA) and glycerol (99.9% grade, Fischer Scientific Inc., USA) were used as received. The signal intensity produced by the methyl protons of acetate (chemical shift = 1.9 ppm) was measured as a function of SC pulse train length (i.e., by increasing the number of $P P^{-1} P_{\pi} P_{\pi}^{-1}$ packets) using $\omega_1^{\text{max}}/(2\pi)=625$ Hz and $T_p \approx 2.263$ ms. The total number of SC packets was 2, 4, 8, 16, 24, 32, 40, 64, or 2, 16, 32, 48, 64, leading to pulse train lengths from 4.53 to 144.82 ms. With RAFF, the signal intensity evolves to a steady state. Therefore, a simple mono-exponential decay model cannot be used for the analysis. The contribution from the steady-state magnetization to the estimated R_{RAFF} value was examined by inverting **M** prior to applying the SC pulse train.

To investigate the possible existence of steady-state magnetization during the RAFF preparation sequence, experiments were performed on an aqueous solution of 5 mM gadolinium diethylenetriamine penta-acetic acid (Magnevist, Berlex Laboratories, Wayne, NJ). In separate experiments, the SC pulse train was applied immediately after an initial tip of the magnetization to the angle (α) = 0, $\pi/3$, $\pi/2$, and π . The initial tips of $\alpha = \pi/3$ and $\pi/2$ were performed with BIR-4 pulses (23) (length = 6 ms and $\omega_1^{\text{max}}/(2\pi)=3.5$ kHz), whereas the initial tip of $\alpha = \pi$ rad was performed using a HS pulse (length = 6 ms, bandwidth = 1667 Hz, and $\omega_1^{\text{max}}/(2\pi)=3.5$ kHz).

Measurements of $T_{1\rho,\text{adiab}}$ and $T_{2\rho,\text{adiab}}$ were performed with a preparation sequence composed of AFP pulses (27), as described previously (9,11). In all $T_{1\rho,\text{adiab}}$ and $T_{2\rho,\text{adiab}}$ experiments, the AFP pulses were HS pulses. In $T_{1\rho,\text{adiab}}$ measurements, the train of AFP pulses was placed prior to the AHP pulse in LASER, whereas in the $T_{2\rho,\text{adiab}}$ measurements, the train of AFP pulses was placed between the AHP pulse and the HS pulses of LASER.

Measurements of $T_{1\rho,\text{adiab}}$ and $T_{2\rho,\text{adiab}}$ were performed with number of AFP pulses = 4, 8, 16, 20, 24, 28 and 32, with each pulse having a length = 3.2 ms and $\omega_1^{\text{max}}/(2\pi)=3.5$ kHz. Inversion of $\mathbf{M}$ prior to the AFP pulse train in $T_{1\rho,\text{adiab}}$ and prior to the AHP pulse in $T_{2\rho,\text{adiab}}$ experiments was performed, as in the RAFF experiment, to investigate steady-state formation.

For comparison with RAFF, conventional continuous wave (cw) on- and off-resonance $T_{1\rho,\text{off}}$ measurements were also conducted, using an adiabatic spin-lock pulse (13). The adiabatic spin-lock pulse was composed of an AHP pulse followed by a cw spin-lock pulse. Magnetization was excited to $\alpha = \pi/2$ and $\alpha = \pi/4$ in the on- and off-resonance experiments, respectively, and locked at these angles by the cw portion of the adiabatic spin-lock pulse. After the spin-lock pulse, the magnetization was returned back to the z axis using a reverse AHP pulse and LASER was then used for signal localization. For the relaxation measurements, the spin-lock duration was incremented while the RF power was fixed at $\omega_1^{\text{max}}/(2\pi)=625$ kHz.

The sensitivity of R_{RAFF} to changes in RF amplitude (ω_1^{max}) and offset frequency (Ω) was investigated and compared with off-resonance $T_{1\rho}$ ($T_{1\rho,\text{off}} \equiv R_{1\rho,\text{off}}^{-1}$) using a 1:1 mixture of water and ethanol (>99.5%, Sigma-Aldrich Inc., USA). The value of R_{RAFF} and $R_{1\rho,\text{off}}$ were measured starting with $\mathbf{M}$ along $+z$ and $-z$ in separate experiments. The offset frequency was varied in 13 increments between ± 120 Hz, with 10 different settings of $\omega_1^{\text{max}}/(2\pi)$ in the range of 300 to 800 Hz.

Human experiments

All human experiments were performed according to procedures approved by the Institutional Review Board of the University of Minnesota Medical School. Healthy volunteers, (4 males and 1 female, ages 31 ± 15 years (mean $\pm$ std.)) were scanned after obtaining informed consent. The total scan time was approximately 60 minutes per subject.

The MRI system consisted of a Varian UNITYINOVA console (Varian Inc., Palo Alto, CA, USA) interfaced to a 90 cm bore 4 T magnet (OMT, Inc., Oxon, UK). A volume coil based on the transverse electromagnetic design (28) was used for RF transmission and reception. After global shimming, 11 transverse slices were acquired using a T_2 -weighted fast spin-echo sequence with repetition time = 4.5 s, matrix size = 256×128 , field-of-view = 20×20 cm², echo train length = 8, with echo spacing = 15 ms, and slice thickness = 3 mm. Following a preparation sequence to create T_{RAFF} , $T_{1\rho,\text{adiab}}$, or $T_{2\rho,\text{adiab}}$ weighting, the signal was measured in a single slice containing *striatum* using a TurboFLASH readout (29) with $TR = 10$ ms and echo time = 5 ms. Other parameters were: delay time between k-space segments = 5 s, number of segments = 4, number of excitations = 4, matrix size = 256×256 , field-of-view = 20×20 cm², and slice thickness = 3 mm. In obtaining relaxation maps with RAFF, the parameters of the SC pulses were chosen to be similar to those used in the solution experiments ($\omega_1^{\text{max}}/(2\pi)=625$ Hz and $T_p \approx 2.263$ ms), and the number of $P P^{-1} P_{\pi} P_{\pi}^{-1}$ packets = 2, 16, 32, 48, and 64. Measurements of $T_{1\rho,\text{adiab}}$ and $T_{2\rho,\text{adiab}}$ were performed with HS pulses using pulse length = 6 ms, bandwidth = 1667 Hz, $\omega_1^{\text{max}}/(2\pi) \approx 1300$ Hz, and number of HS pulses = 4, 8, 12, and 16. The RF amplitude was

calibrated in each human experiment using a square excitation pulse in LASER, with voxel coordinates matched to the position and size of the midbrain area. For T_1 mapping, images were collected with TurboFLASH following adiabatic HS inversion and a recovery period. This experiment was repeated using 6 different recovery delays evenly spaced between 0.3 and 1.4 s. To investigate whether a steady state contributed to any of the rotating frame signal decay curves ($S(t)$), the experiments were repeated with the inversion pulse placed prior to the SC and AFP pulse trains. Free-precession T_2 values were measured using an adiabatic double-spin echo pulse sequence and by varying the echo delays around the two AFP pulses (9). For the T_2 measurements, echo time was varied between 12 and 128 ms. B_1 maps were measured from two volunteers to ascertain B_1 homogeneity within the area of the deep brain structures. The B_1 maps were generated from 20 images that were acquired following the application of a square pulse of variable duration (30). The length of the square pulse was evenly incremented between 0.1 and 0.8 ms.

The RF power delivered to the coil was limited to a safe operating range using the hardware monitoring module of the Varian console. In addition, the RF power output over the full range of settings used in these experiments was measured with an oscilloscope connected to the coil port. From these measured values, the average RF power delivered to the coil was computed by integration of all RF pulses in the sequence, and SAR was estimated assuming a tissue load of 3 kg in the coil. When using the longest pulse train, the estimated SAR in RAFF and $T_{2p,adiab}$ experiments was 2.1 W/kg, and in the $T_{1p,adiab}$ experiment it was 1.7 W/kg. These SAR values are below the FDA limit of 3 W/kg averaged over the head for 10 min (<http://www.fda.gov/cdrh/ode/mri340.pdf>).

Data analysis

Analyses were performed on data obtained from Bloch simulations and experimentation, using initial magnetization along $-z'$ and $+z'$ separately. A non-linear least-squares fitting was performed simultaneously on data obtained with initial $-z'$ and $+z'$ magnetization orientations. An empirical equation was used to model the observed exponential decay and approach to steady state,

$$S_{\pm z}(t) = S_{0,\pm z} e^{-Rt} - S_{ss} (1 - e^{-Rt}). \quad [22]$$

Here S_0 is the initial intensity ($t = 0$), R is the relaxation rate constant describing the decay, and S_{ss} is the steady-state intensity at $t \rightarrow \infty$. The steady-state quantity (SS) is defined here by $SS = S_{ss}/S_0$. Note, the same formalism is usually applied in the estimation of T_1 from data acquired with rapid pulsing (31). Relaxation maps were generated by non-linear regression fits of pixel intensities using the model of Eq. [22]. A comparison was performed with RAFF maps generated using a single mono-exponential function for decay of $\mathbf{M}$ from $+z$. Regions of interests were outlined for *globus pallidus*, *putamen* and *caudate nuclei*. Relaxation time constants were determined from these regions of interest and average values over the subjects were calculated. All values are presented as mean $\pm$ standard deviation. Because there is no formation of the steady state during on-resonance T_{1p} measurements, a

simple two parameter mono-exponential function was used for fitting the on-resonance $T_{1\rho}$ data.

Estimation of τ_c in the glycerol water mixture was carried out using models given in Refs. (24,32,33), and by fitting modeled relaxation rates to experimentally obtained $T_{1\rho,\text{on}}$, $T_{1\rho,\text{off}}$, $T_{1\rho,\text{adiab}}$, and $T_{2\rho,\text{adiab}}$ values. Least square fitting with the trust-region-reflective Newton algorithm was used. Two strategies were used for τ_c estimation: i) separate estimates using each method, and ii) one estimate using all methods.

Results

Relaxation calculations

Relaxation rates expected from theory were calculated to investigate the relative sensitivities of the different relaxation methods (T_{RAFF} , T_1 , T_2 , $T_{1\rho,\text{on}}$, $T_{1\rho,\text{off}}$, and $T_{1\rho,\text{adiab}}$ and $T_{2\rho,\text{adiab}}$) to changes in τ_c . The calculations were performed for two isolated spins $\frac{1}{2}$ nuclei undergoing dipolar interactions. In figures 5a,b, respectively, the longitudinal and transverse rate constants are plotted as a function of τ_c . It can be seen that R_2 ($\equiv 1/T_2$) and $R_{1\rho,\text{on}}$ ($\equiv 1/T_{1\rho,\text{on}}$) exhibit the greatest sensitivity to changes in correlation time. As expected for this dipolar system (32), the plots show $R_{1\rho,\text{on}} = R_2$. With RAFF, the sensitivity to τ_c is similar to that of $R_{1\rho,\text{on}}$ when calculating longitudinal and transverse RAFF rate constants from Eqs. [19] and [20]. On the other hand, Bloch simulations yield slower RAFF relaxation rates than those predicted from Eqs. [19] and [20]. The value of R_{RAFF} calculated from Eqs. [19] and [20] is $\approx 70\%$ larger than the value obtained from Bloch simulations. Possible explanations for this difference are discussed further below.

Phantom experiments

Relaxation measurements of acetate ($-\text{CH}_3$ resonance) dissolved in glycerol/water mixtures were performed to probe a system undergoing dipolar relaxation. Comparisons were made between data measured with RAFF, $T_{1\rho}$, and $T_{2\rho}$ techniques. In Figure 6a, the results are shown for acetate dissolved in a 0.9:0.1 mixture of glycerol and water (a viscous solution, $\eta \approx 220$ cp (34)). The signal recovery after the inversion pulse demonstrates the formation of a steady state with RAFF. The results of the analysis using Eq. [22] reveal comparable rate constants for RAFF and adiabatic $T_{1\rho}$ methods ($R_{\text{RAFF}} = 6.6 \text{ s}^{-1}$, $R_{1\rho,\text{adiab}} = 6.5 \text{ s}^{-1}$). On the other hand, $T_{2\rho,\text{adiab}}$ and cw $T_{1\rho,\text{on}}$ and $T_{1\rho,\text{off}}$ methods yield similar rate constants ($R_{2\rho,\text{adiab}} = 10.5 \text{ s}^{-1}$, $R_{1\rho,\text{on}} = 9.9 \text{ s}^{-1}$, and $R_{1\rho,\text{off}} = 10.0 \text{ s}^{-1}$). The difference in relaxation rates between these two groups is $\approx 4 \text{ s}^{-1}$; thus, a more complex relaxation model may be needed.

From simulations (Fig. 5), the experimentally observed $R_{1\rho,\text{on}}$ and $R_{1\rho,\text{off}}$ values are consistent with τ_c values equal to $1.9 \cdot 10^{-10} \text{ s}$ and $2.2 \cdot 10^{-10} \text{ s}$, respectively. The slight difference between τ_c estimated based on $T_{1\rho,\text{on}}$ and $T_{1\rho,\text{off}}$ might be attributed to the experimental inaccuracies in the initial flip angle and phase during the $T_{1\rho,\text{off}}$ experiment, since this experiment is prone to errors in the initial preparation of **M**. With $T_{1\rho,\text{adiab}}$ and $T_{2\rho,\text{adiab}}$ methods, the τ_c values estimated from the simulations are $1.3 \cdot 10^{-10} \text{ s}$ and $2.1 \cdot 10^{-10} \text{ s}$, respectively. The combination of all reference methods ($T_{1\rho,\text{on}}$, $T_{1\rho,\text{off}}$, $T_{1\rho,\text{adiab}}$, and $T_{2\rho,\text{adiab}}$) yield $\tau_c = 1.9 \cdot 10^{-10} \text{ s}$. With RAFF, τ_c is $1.9 \cdot 10^{-10} \text{ s}$ based on the Bloch

simulations, whereas Eqs. [19], and [20] predict τ_c to be $1.4 \cdot 10^{-10}$ s. Potential reasons for this difference will be discussed later.

The steady-state fraction is similar for RAFF and off-resonance cw $T_{1\rho}$ methods ($SS = 0.4$ and 0.42 , respectively). In experiments with adiabatic $T_{1\rho}$ and $T_{2\rho}$ methods, negligible steady state formation is present ($SS = -0.03 - 0.04$).

The existence of a steady state contribution was also examined in experiments using gadolinium diethylenetriamine penta-acetic acid solution. This system was chosen because the water signal decays rapidly, and thus, the steady state could be attained with the pulse train lengths used in this work. As shown in Figure 6b, the experiment demonstrates how the signal always reaches the same steady-state level, despite using several different initial tip angles.

Measurements were also performed to investigate the robustness of the RAFF method to experimental imperfections. These measurements were performed on a 1:1 mixture of ethanol and water (a proton exchanging spin system) in order to have high dynamic range to define the signal decay over the pulse lengths used in this study and to have high signal-to-noise ratio to achieve accurate mapping of the relaxation dependencies on RF amplitude ($\omega_1^{\max}$) and offset frequency (Ω). With the same SC pulse pattern, the RAFF relaxation rate constant (R_{RAFF}) was measured in separate experiments using different settings of $\omega_1^{\max}$ and Ω . Immediately following the SC preparation sequence, LASER was used to measure the intensity of the water/ethanol hydroxyl resonance (a singlet due to fast proton exchange; e.g. in the absence of exchange, the chemical-shift between the proton resonances of water and the ethanol hydroxyl group is 0.85 ppm). For comparison, the experiment was repeated using off-resonance $T_{1\rho}$ preparation. Contour plots reveal the dependencies of the relaxation rate constant (percent change) as a function of $\omega_1^{\max}$ and Ω , when measured with RAFF (Fig. 7a) and $T_{1\rho, \text{off}}$ (Fig. 7b) methods. From Figure 7a, it is apparent that off-resonance variations larger than ± 50 Hz, due either to chemical shift or B_0 variation, will significantly affect the RAFF rate constant. It can also be seen that, as compared to the off-resonance $T_{1\rho}$ experiment (Fig. 7b), the RAFF method is less sensitive to chemical shift or B_0 variation in the range $-50 \text{ Hz} < \Omega < 50 \text{ Hz}$. On the other hand, RAFF is more sensitive to $\omega_1^{\max}$ variations. Thus, a relatively homogeneous B_1 is desirable in RAFF relaxation measurements. Despite these potential sources of experimental imperfections, R_{RAFF} values were highly reproducible between experiments, particularly when care was taken to minimize B_1 inhomogeneity (e.g., by limiting the volume) and by using a calibration procedure to attain the same $\omega_1^{\max}$ setting each time.

Human experiments

Although relaxation parameters are typically estimated by fitting data to a single mono-exponential function, this approach did not produce satisfactory estimates of T_{RAFF} . Specifically, when using Eq. [22] and simultaneous fitting of z and $-z$ data (i.e., magnetization initially unperturbed and inverted, respectively), the RAFF relaxation time constants (T_{RAFF}) in human brain tissue were $\approx 20\%$ smaller than the T_{RAFF} values obtained when fitting the $+z'$ data to a single mono-exponential function (Fig. 8). This difference is

due to neglect of the steady state contribution in the single mono-exponential analysis. Thus, Eq. [22] should be used in RAFF relaxation analyses even when a steady state is not reached with the longest pulse train length. The SS map (Fig. 8c) shows the spatial variation of the steady-state signal in the mid brain areas.

The feasibility to create MRI contrast based on RAFF was assessed in studies of healthy human brain at 4T, using the RAFF pulse train as a preparation sequence preceding image readout. For comparison, maps of T_1 , T_2 , $T_{1\rho, \text{adiab}}$, and $T_{2\rho, \text{adiab}}$ were generated from the same imaging slice as RAFF (Fig. 9). The values of T_{RAFF} were larger than T_2 and $T_{2\rho, \text{adiab}}$ and smaller than $T_{1\rho, \text{adiab}}$ and T_1 (Table 1), and these differences were significant ($p < 0.001$, paired student's t-test without correction for multiple comparisons).

Discussion

With an adiabatic pulse, a fictitious field component ($\gamma^{-1} da/dt \hat{y}''$) arises due to the rotation of $\mathbf{B}_{\text{eff}}$ in the $x'z'$ plane. When executing the pulse in an adiabatic manner, this additional field component can usually be neglected since $B_{\text{eff}} \gg \gamma^{-1} da/dt$ (the adiabatic condition). However, strict adherence to the adiabatic condition is not a requirement to rotate magnetization with FM pulses (20). For example, adiabatic full-passage can be performed under conditions which do not seem to be highly adiabatic (e.g., $B_{\text{eff}} \approx 5 \cdot \gamma^{-1} da/dt$) (35,36). During an adiabatic rotation, $\mathbf{M}$ experiences an effective field comprised of multiple field components including $\mathbf{B}_{\text{eff}}$, $\gamma^{-1} da/dt \hat{y}''$, and in some cases, additional higher order fictitious fields (also called higher order inertial fields (35)).

The objective of the current study was to consider the case in which a strong $\gamma^{-1} da/dt \hat{y}''$ field component exists (i.e., a FM pulse in a sub-adiabatic condition). To facilitate the study of relaxation in the presence of this strong fictitious field, the simplest case was chosen (the SC pulse) which produces equal and constant field amplitudes, $\gamma^{-1} da/dt = B_{\text{eff}}$, with no added complications from higher order inertial fields (i.e., $\gamma^{-1} d\epsilon/dt = 0$, because $\epsilon = \text{constant}$). In the current work, the effective field $\mathbf{E}$ is the resultant of the RF field ($\mathbf{B}_1$) and the fictitious components, $\gamma^{-1} \omega \hat{z}$ and $\gamma^{-1} da/dt \hat{y}''$. Thus, rotating frame relaxation occurs along the net field $\mathbf{E}$, which includes both fictitious and non-fictitious components.

When using the SC pulse described by Eqs. [8] and [9], the component of $\mathbf{M}$ initially along the direction of $\mathbf{E}$ will remain locked during the whole RF pulse. Likewise, rotation about $\mathbf{E}$ occurs for any components of $\mathbf{M}$ which are initially perpendicular to $\mathbf{E}$. Because frequency shifts and B_1 -inhomogeneities are difficult to avoid in practice, the RAFF pulse train must offer the ability to periodically refocus components of $\mathbf{M}$. In this regard, as demonstrated by Bloch simulations, the four segment SC pulse ($P P^{-1} P_{\pi} P_{\pi}^{-1}$) is needed to make the RAFF method usable *in vivo*. It is interesting to note that the $P P^{-1} P_{\pi} P_{\pi}^{-1}$ composite structure is the same as that used in the composite adiabatic pulse, BIR-4 (23), which also tolerates a reasonable amount of frequency shift and B_1 inhomogeneity.

In this work, a theoretical description of the effects of dipolar relaxation on RAFF has been introduced (Eqs. [19] and [20]). Bloch simulations and experimental data reveal some limitations of the proposed theory and point to the need for further work and understanding.

Although the three spin system ($-\text{CH}_3$) was investigated, the application of two spin formalism is justified for the spin dynamics of this methyl group in liquid due to degeneracy of energy states (37). When using the experimentally determined relaxation rate constants obtained from acetate in a glycerol/water mixture as inputs to the Bloch simulations, good agreement between τ_c values was obtained despite using several different methods (RAFF, $T_{1\rho,\text{adiab}}$, $T_{2\rho,\text{adiab}}$, cw $T_{1\rho,\text{on}}$, and cw $T_{1\rho,\text{off}}$). However, the τ_c value of acetate calculated from Eqs. [19] and [20] is $\approx 27\%$ smaller than that predicted from Bloch simulations, when using the measured relaxation parameters as inputs. Most likely, the discrepancy between estimates made using Eqs. [19] and [20] versus Bloch simulation for RAFF originates from the assumption of initially averaged $T_{2\rho,E}$ in the plane perpendicular to $\mathbf{E}$ in Eq. [20]. With each $P P^{-1} P_{\pi} P_{\pi}^{-1}$ packet, the magnetization experiences two inversions (or flips) of $\mathbf{E}$. For the perpendicular components of $\mathbf{M}$, these $\mathbf{E}$ flips produce refocusing (a rotary echo) along the z' axis. Eq. [20] cannot account for the constrained evolution and periodic refocusing of the perpendicular components of $\mathbf{M}$. Hence, a more complete theoretical formalism, which includes the $\mathbf{E}$ flips, is still needed to allow accurate assessments of dipolar as well as other potentially important mechanisms such as exchange.

With RAFF, the RF irradiation has a periodical pattern which leads to the formation of steady-state magnetization. In this study, it was shown that in a viscous dipolar system where $T_1 \approx T_2$, the steady state has a significant influence on the signal decay and therefore has to be accounted for in the data analysis. All data measured in this study were readily fit with the empirical model which includes a steady-state term (Eq. [22]). Further investigation is needed to fully understand and utilize the steady state formation during SC pulse train. In the future, it may be possible to exploit the distribution of SS to enhance the contrast between different tissues.

The experiment performed using gadolinium diethylenetriamine penta-acetic acid water solution demonstrated that the relaxation rate constants of RAFF are not dependent on the initial tip angle. Hence, the RAFF experiment does not necessarily require an initial tip of the magnetization, unlike the classical cw $T_{1\rho}$ experiment in which a relatively uniform tip angle to the desired α value is needed prior to the application of the spin-lock pulse. For accurate estimation of steady state with short SC pulses, a measurement with the inversion prior to the SC pulses is expected to be beneficial.

Using the ethanol/water solution, the sensitivity of RAFF to common experimental imperfections (frequency offsets and B_1 -inhomogeneity) was studied and compared with the $T_{1\rho,\text{off}}$ experiment. The relaxation rate constants obtained using RAFF were more uniform as a function of frequency offset, whereas RAFF required a more homogenous B_1 field than $T_{1\rho,\text{off}}$. Hence, RAFF experiments may need to be performed with a relatively homogeneous RF coil or with volume selection.

The results from human brain show that T_{RAFF} maps can be obtained *in vivo* at 4 T and that the measured value of T_{RAFF} is between the values of $T_{1\rho,\text{adiab}}$ and $T_{2\rho,\text{adiab}}$, in agreement with theoretical predictions (Fig. 5). However, the exchange relaxation pathway may be a significant contributor to the *in vivo* brain contrast observed with RAFF, because in the viscous acetate solution (a dipolar system) the values of T_{RAFF} and $T_{1\rho,\text{adiab}}$ were

comparable (see Fig. 5a). Therefore, as mentioned above, the theoretical model of Eqs. [19] and [20] should be considered to represent a simplified treatment, rather than the complete relaxation model which will be needed to describe *in vivo* RAFF contrast.

The lower RF power required by RAFF is a significant advantage of this technique as compared to adiabatic $T_{1\rho}$ and $T_{2\rho}$ methods. Due to its amplitude modulation, the SC pulse deposits only 61% of the RF power (SAR) of a cw pulse, when transmitting for the same duration and with the same $\omega_1^{\max}$ setting. In this study, the average power delivered to the brain tissue during adiabatic $T_{1\rho}$, $T_{2\rho}$, and RAFF acquisitions were 1.07 W/kg, 1.48 W/kg, and 1.10 W/kg, respectively. Because the longest pulse train duration of RAFF was 1.5 times longer than that used in the adiabatic $T_{1\rho}$ experiment, the average power depositions were similar. The delivered RF energy during the pulse train unit time for RAFF irradiation was 83% and 63% of the energies of adiabatic $T_{1\rho}$ and $T_{2\rho}$ irradiations, respectively. In the future, an alternative to using the preparation sequence might be to use the SC pulse as an excitation pulse for an imaging readout, in which case it would be possible to obtain RAFF contrast with substantially improved acquisition efficiency.

Conclusions

In this work, a novel method based on the relaxation along fictitious field (RAFF) was developed. It was shown how MRI contrast based on rotating frame relaxation could be generated *in vivo* using frequency-swept pulses under a sub-adiabatic condition. The method eliminates the need for an initial tip of the magnetization vector to an angle α (as needed in conventional $T_{1\rho}$ experiments) and demands less RF power for implementation than other rotating frame relaxation methods. RAFF contrast was shown to be different as compared to T_1 , T_2 , adiabatic $T_{1\rho}$, and adiabatic $T_{2\rho}$, and therefore, may have use in detecting certain pathologies *in vivo*. It can be concluded that the RAFF method holds promise as a tool to access different time scales of molecular dynamics and to generate MRI contrast with sensitivity to long correlation times. In addition, the principles described herein are expected to have relevance to many types of experiments using adiabatic and sub-adiabatic rotations.

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Fig. 1.

The coordinate system used for describing the fictitious ω_E -frame of reference (x''' , y''' , z'''). The effective field $\mathbf{B}_{\text{eff}}$ (grey arrow) undergoes rotation with frequency $\omega_{\text{RF}}(t)$ relative to the laboratory frame. The rotation of $\mathbf{B}_{\text{eff}}$ in the $y'z'$ plane of the first rotating frame (not shown) leads to the fictitious field component $\gamma^{-1}d\alpha/dt$ along the y'' -axis in the ω_{eff} -frame (x'' , y'' , z''). The $\mathbf{B}_{\text{eff}}$ is aligned along $\pm z''$ -axis in the ω_{eff} -frame and the fictitious field $\mathbf{E}$ is the vector sum of $\mathbf{B}_{\text{eff}}$ and $\gamma^{-1}d\alpha/dt \hat{y}''$. The angle ε between $\mathbf{B}_{\text{eff}}$ and $\mathbf{E}$ depends on the magnitudes of ω_{eff} and $\gamma^{-1}d\alpha/dt$, and it is equal to $\pi/4$ with condition $B_{\text{eff}}(t) = |\gamma^{-1}d\alpha/dt|$. In the ω_E -frame, $\mathbf{E}$ field is collinear with the z''' axis.

Fig. 2.

a) Amplitude- and phase- modulated functions of the SC pulse used for RAFF. The π shift in the phase modulated function between P and P^{-1} (and between P_{π} and P_{π}^{-1}) is required for rotation of $\mathbf{M}$ from y'' back to z'' . b) The evolution of $\mathbf{M}$ during the P and P^{-1} portions of the pulse. The phase modulation during P is obtained by integrating the frequency modulation function given by Eq. [9] over the first quarter of the pulse duration (Eq. [10]) using Eq. [12]. With these definitions, the condition $B_{\text{eff}}(t) = |\gamma^{-1} d\alpha/dt|$ is fulfilled.

Fig. 3.

a) The longitudinal magnetization profile (M_z/M_0) after several SC pulse durations as a function of pulse train length. The basic RAFF pulse packet $P P^{-1} P P^{-1}$, with the pulse train length of 4.53 ms (c) and 144.82 ms (e) are compared to the packet $P P^{-1} P P^{-1}$, with the same durations (b and d), respectively. The dashed lines in (c) and (e) are pulse train profiles for 8 and 256 hard π pulses ($\omega_1^{\max}/(2\pi)=625$ Hz) evenly spaced between 0 and 4.53 ms in (c) and 0 and 144.82 ms in (e). The simulations were carried out with 8 pulse train durations (a) and 500 off-resonance steps (a–e) using Bloch equations.

Fig. 4.

Trajectories of $\mathbf{M}$ (solid line), $\mathbf{E}$ (o), and $\mathbf{B}_{\text{eff}}$ (dotted line) during the execution of the SC pulse in the ω_{RF} -frame. The evolution of initial $\mathbf{M}$ along $\mathbf{E}$ (thick arrow) was calculated using Bloch simulation during one *sine/cosine* period with the parameters:

$\omega_1^{\text{max}}/(2\pi)=625$ Hz, 500 points during the length of one cycle of duration 1.6 ms.

Relaxations during the SC pulses were ignored. $\mathbf{E} (= \gamma^{-1}[\omega_1, da/dt, \omega])$ was plotted in every 6th point of the pulse. For comparison, $\mathbf{B}_{\text{eff}} (= \gamma^{-1}[\omega_1, 0, \omega])$ is shown.

Fig. 5.

Calculated relaxation rate constants a) for $T_{1\rho,\text{on}}$, $T_{1\rho,\text{E}}$, $T_{1\rho,\text{off}}$, T_{RAFF} , $T_{1\rho,\text{adiab}}$, T_{RAFF} , $T_{1\rho,\text{off}}$, and T_1 methods; and b) for T_2 , $T_{2\rho,\text{adiab}}$, $T_{2\rho,\text{off}}$, $T_{2\rho,\text{E}}$, $T_{2\rho,\text{on}}$, and T_{RAFF} methods. Inserts show expanded views for short τ_c range. The value of R_{RAFF} was estimated using Bloch simulation, whereas $R_{1\rho,\text{E}}$ and $R_{2\rho,\text{E}}$ were obtained using Eqs. [19] and [20], respectively. The other curves in the figure were calculated using the dipolar relaxation model based on reference (32). On- and off-resonance cw spin-lock were calculated with $\omega_1^{\text{max}}/(2\pi)=625$ Hz and additionally $\omega/(2\pi)=625$ Hz ($\alpha=\pi/4$) for off-resonance spin lock. The pulse modulation functions given in reference (20) were used for calculating $R_{1\rho,\text{adiab}}$ and $R_{2\rho,\text{adiab}}$ curves with pulse length = 3.0 ms and $\omega_1^{\text{max}}/(2\pi)=2.5$ kHz in a similar manner to that in Refs. (10,11). In all calculations, $\mu_0=4\pi\cdot10^{-7}$, $\hbar=1.0546\cdot10^{-34}$ Js, $\gamma=2\pi\cdot42.58\cdot10^6$ rad/(sT), $r=158$ pm and $B_0=4.7$ T were used.

a

b

Fig. 6.

a) Signal intensity decay curves of acetate (100 mM) dissolved in glycerol/water (0.9/0.1) mixture measured with RAFF pulse ($\circ$) with $\omega_1^{\max}/(2\pi)=625$ Hz, $T_{1\rho, \text{adiab}}$ ($\square$), $T_{2\rho, \text{adiab}}$ ($\triangle$), $T_{1\rho, \text{on}}$ ($\times$) with $\omega_1^{\max}/(2\pi)=625$ Hz, and $T_{1\rho, \text{off}}$ ($+$) with $\omega_1^{\max}/(2\pi)=\Delta\omega/(2\pi)=625$ Hz. Two independent acquisitions are presented for RAFF and adiabatic relaxation techniques. Top: $\mathbf{M}$ was not perturbed prior to the SC pulses; bottom: $\mathbf{M}$ was inverted prior to the SC pulses. Relaxation curves (solid lines) were fitted using Eq. [22]. b) Normalized decay curves $S(t)/S_0$ obtained with RAFF in 5 mM gadolinium diethylenetriamine penta-acetic acid in deionized aqueous solution. Magnetization ($\mathbf{M}$) was rotated to the different angles (0 , $\pi/3$, $\pi/2$, and π) relative to the z' axis prior to the application of the SC pulse trains. Solid lines represent fittings to the experimental data using Eq. [22]. The relaxation rate constants and the SS values were independent of the initial angle between $\mathbf{M}$ and z' . The results are normalized to the fitted S_0 obtained from the 0 rad experiment. In the present sample, $R_{\text{RAFF}} = 30.7 \pm 1.4$ s (mean $\pm$ sd) and $SS = 0.684 \pm$

0.001. The BIR-4 pulse (20) (pulse length = 6 ms, $\omega_1^{\max}/(2\pi)=3.5$ kHz) was used to excitation of angles $\pi/3$ and $\pi/2$, and the HS pulse (pulse length = 6 ms, $\omega_1^{\max}/(2\pi)=3.5$ kHz) for angle π . Note that the additional SC pulse train of duration 289.64 ms was added to better observe steady-state formation.

Fig. 7.

Contour plots of the relaxation rate constants of a) RAFF and b) off-resonance cw spin-lock $T_{1\rho,\text{off}}$ in ethanol/water mixture. Every contour line designates a 2.5% change in the rate constant from the nominal values measured with $\omega_1^{\max}/(2\pi) = 625$ Hz and $\Omega = 0$. The nominal rate constants were $R_{\text{RAFF}} = 5.3 \text{ s}^{-1}$ and $R_{1\rho,\text{off}} = 3.9 \text{ s}^{-1}$. The horizontal and vertical profiles from the dashed lines are presented on the top and left side of the contour plots, respectively. Fittings for both methods were performed using the model given in Eq. [22].

Fig. 8. The RAFF relaxation time maps calculated a) with a single mono-exponential fitting and b) using Eq. [22] with c) a map of the fractional steady state ($SS = S_{SS}/S_0$) obtained from the fitting in (b).

Fig. 9.

Representative relaxation time maps from human brain obtained using a) T_1 , b) $T_{1\rho, \text{adiab}}$, c) RAFF, d) $T_{2\rho, \text{adiab}}$, and e) T_2 relaxation mapping techniques.

Table 1

Comparison of the RAFF Relaxation Time (T_{RAFF}) with T_1 , T_2 , $T_{1\rho,\text{adiab}}$ and $T_{2\rho,\text{adiab}}$ in Representative Midbrain Areas of Normal Human Brain at 4 T
(n = 5)*

	T_1 (ms)	$T_{1\rho,\text{adiab}}$ (ms)	T_{RAFF} (ms)	$T_{2\rho,\text{adiab}}$ (ms)	T_2 (ms)
GP	1045.4 ± 42.2	161.3 ± 2.8	105.4 ± 2.2	55.4 ± 3.1	46.5 ± 1.8
P	1324.9 ± 37.5	189.2 ± 3.4	126.8 ± 3.1	65.7 ± 1.9	51.4 ± 3.2
CN	1420.5 ± 48.2	221.0 ± 8.1	134.8 ± 3.1	76.6 ± 3.0	64.8 ± 2.1

* GP = globulus pallidus; P = putamen; CN = caudate nuclei.