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“Relaxation by Amplitude Modulation (RAM): A Rapid T_1 Measurement Method”

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Abstract

Purpose—A novel T_1 measurement method using complex amplitude modulation is presented.

Theory—The method applies a series of inversion pulses to the imaged region in accordance with a binary modulation sequence. The longitudinal magnetization acquired in a given TR interval is the sum of the individual longitudinal magnetization recovered during each previous TR interval, weighted by T_1 decay factors and the combined effect of all the RF pulses they have experienced. The demodulated signal for each voxel is an exponential curve with a decaying rate determined by T_1 and the acquisition flip angle θ .

Methods—Sequences using a 15-cycle pseudo-random binary code were implemented on Siemens 3T Trio with standard gradient echo readout and multi-slice gradient echo-planar imaging. The sequences were tested on T_1 phantoms and human and compared against inversion recovery method.

Results—Our studies on phantoms and a human volunteer show that T_1 estimated from this method is very accurate and well reproducible. The average scan time is ~1.6s per slice (full k-space gradient echo-planar imaging with matrix size 128×128).

Conclusion—The current protocol is almost twice as fast as two fastest existing methods. Optimizing protocols and incorporating common acceleration techniques will make it even faster.

Keywords

MRI; T_1 ; relaxation times; rapid measurement; amplitude modulation; brain; neuropathology

INTRODUCTION

The measurement of the longitudinal relaxation time constant T_1 has become increasingly important (1–6). However, the clinical utility of T_1 imaging has been limited by long acquisition times. Currently, there are three main categories of T_1 quantification methods: inversion recovery (IR), Look-Locker (LL) (7,8) which samples inversion recovery curve weighted by low flip angle, and varied flip angles (VFA) (9) which measures steady state

magnetization as a function of excitation angle. Among them, the two fastest methods are echo-planar imaging (EPI) (10) based LL approach (LL-EPI) (11,12) and time efficient slice ordering IR (TESOIR-EPI) (13). In both techniques the average scanning time per slice is approximate 3s.

In this article, we describe a novel measurement method for T_1 using a complex pattern of amplitude modulation. The method, which we term “relaxation by amplitude modulation” (RAM), is very time efficient for two reasons. First, the image acquired at each TR is a weighted sum of partially recovered magnetization from all the previous TR periods, so that it can continuously collect data without waiting for the fully relaxed equilibrium magnetization. Second, it is completely compatible with ordinary multi-slice mode and most gradient echo acquisition strategies, and therefore the time efficiency can be easily enhanced or tailored in particular experiment. RAM works by applying a series of inversion pulses to the imaged region in accordance with a binary modulation sequence. Because spin magnetization is a linear system which can be described by the Bloch equation, the longitudinal magnetization acquired in a given TR interval is the sum of the individual longitudinal magnetizations recovered in each earlier TR interval before t , weighted by different T_1 decay factors ($\exp(-nTR/T_1)$) and the combined effect of all the RF pulses they have experienced in the intervening time. By choosing appropriate modulation strategy and acquiring magnetization in each TR , it is possible to separate the individual components with different decay factors by inverting the modulate matrix. Therefore, these separated components at each voxel form an exponential curve with a decay rate determined by T_1 plus the effect of the acquisition flip angle θ , as in the LL method. The specific RAM modulation scheme can be chosen from a large family of binary sequences (14,15). Here we use maximum length sequences, also known as pseudo-random sequences. This specific implementation is therefore referred to as “pseudo-random amplitude modulation” (PRAM).

In the remainder of the paper, we present primary theory of RAM, evaluate the specific PRAM implementation and compared it against inversion recovery method. Results from a T_1 phantom and human brain show that PRAM is very accurate and highly reproducible. A 4-slice imaging protocol is developed on a human. The total scan time is 6.45s for either one or four slices using standard full k-space gradient echo EPI (matrix size 128×128) to collect 15 data points with 430ms temporal resolution. Because the method can continuously collect data and compatible with multi-slice acquisition, the average acquisition time per slice (~ 1.6 s) is almost twice as fast as LL-EPI and TESOIR-EPI. We further analyze time efficiency, SNR, and systematic errors in Discussion.

THEORY

The schematic RAM sequence diagram is depicted in Fig. 1. Within each TR , a non-selective inversion RF pulse, denoted by A_n , is applied to the imaged region, followed by a spoiler and gradient-echo readout module. $\{A_n\}$ is a binary sequence of length N , in which $A_n = 1$ if inversion pulse ON and 0 otherwise. The acquisition module can be any gradient echo readout such as single-shot EPI or one or more k-space lines. To be able to separate the individual components with different decay factors, each k-space line or segment must be acquired N times so that entire sequence of $\{A_n\}$ pulses is cycled through.

Simplified example, $T_I=0$

The principle of RAM can be understood by considering a simplified example where the imaging pulse occurs immediately after the inversion pulse, i.e. $T_I = 0$, $M(t_{n,img}^-) = M(t_n^+)$. Then the evolution of longitudinal magnetization M during one TR can be represented by the Bloch equation as:

$$\frac{dM(t)}{dt} = \frac{M_0 - M}{T_1}, t \in (t_{n-1,img}^+, t_n^-) \quad [1]$$

where T_1 is longitudinal relaxation time, M_0 is fully relaxed equilibrium value of M . Note that Eq. [1] implies only single T_1 component is considered. Let the excitation angle be θ and the inversion efficiency be α (1 for perfect inversion and 0 for saturation). Then the boundary conditions for Eq. [1] are:

$$M(t_n^+) = M(t_n^-)(-\alpha)^{A_n} \quad [2]$$

$$M(t_{n,img}^+) = M(t_{n,img}^-) \cos(\theta)$$

Solving the Eq. [1] [2] using simplification $M(t_{n,img}^-) = M(t_n^+)$ since $T_I=0$, we obtain:

$$M(t_{n,img}^-) = M(t_{n-1,img}^-) \cos(\theta) E_{T_1} (-\alpha)^{A_n} + M_0 (1 - E_{T_1}) (-\alpha)^{A_n} \quad [3]$$

where $E_{T_1} = \exp(-TR/T_1)$. Eq. [3] shows that the imaged magnetization consists of two components: (1) the last imaged magnetization, $M(t_{n-1,img}^-)$, modified by the excitation pulse ($\cos(\theta)$), the T_1 decay (E_{T_1}), and the last inversion pulse (A_n); (2) the newly recovered magnetization from the last TR interval, $M_0(1 - E_{T_1})$, only modulated by the last inversion pulse (A_n). Iterating Eq. [3] and using the fact that $M(t_{n-i,img}^-) \cos^i(\theta) E_{T_1}^i (-1)^{\sum_{j=n-i+1}^n A_j}$ approaches to zero as i increases to infinity, we find the signal of the n^{th} image is:

$$\begin{aligned} M(t_{n,img}^-) &= M_0 (1 - E_{T_1}) \left\{ \sum_{j=0}^{\infty} \cos^j(\theta) E_{T_1}^j (-\alpha)^{\sum_{k=n-j}^n A_k} \right\} \\ &= M_0 (1 - E_{T_1}) \left((-\alpha)^{A_n}, (-\alpha)^{\sum_{k=n-1}^n A_k}, \dots, (-\alpha)^{\sum_{k=n-j}^n A_k}, \dots \right) \\ &\quad \cdot \begin{pmatrix} 1 \\ \cos(\theta) E_{T_1} \\ \vdots \\ \cos^j(\theta) E_{T_1}^j \\ \vdots \end{pmatrix} \end{aligned} \quad [4]$$

where we explicitly express the sum of multiplication as inner product of two vectors. Eq. [4] shows that, the signal acquired at $t_{n,img}^-$ can be viewed as a linear combination of longitudinal relaxation magnetization recovered during different TR intervals, each of which has experienced a different number of inversion pulses while decaying by $\cos(\theta) E_{T_1}$ each TR period. Note the periodicity of $\{A_n\}$ implies that $A_n = A_{n+N}$, and the spins will reach a steady state such that $M(t_{n,img}^-) = M(t_{n+N,img}^-)$. Let $\vec{M}$ be the vector of signals measured sequentially at different imaging time and $\vec{H}$ the decay-weighted vector of dimension $N \times 1$. We have a matrix relationship:

$$\vec{M} = \kappa \mathbf{A}_\alpha \vec{H} \quad [5]$$

where

$$\vec{M} = \begin{pmatrix} M(t_{1,img}^-) \\ M(t_{2,img}^-) \\ \vdots \\ M(t_{N,img}^-) \end{pmatrix}$$

$$\mathbf{A}_\alpha = \begin{pmatrix} (-\alpha)^{A_1} & (-\alpha)^{\sum_{k=1-1}^1 A_k} & \dots & (-\alpha)^{\sum_{k=1-(N-2)}^1 A_k} & (-\alpha)^{S_A} \\ (-\alpha)^{A_2} & (-\alpha)^{\sum_{k=2-1}^2 A_k} & \dots & (-\alpha)^{\sum_{k=2-(N-2)}^2 A_k} & (-\alpha)^{S_A} \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ (-\alpha)^{A_N} & (-\alpha)^{\sum_{k=N-1}^N A_k} & \dots & (-\alpha)^{\sum_{k=N-(N-2)}^N A_k} & (-\alpha)^{S_A} \end{pmatrix}$$

$$\vec{H} = \begin{pmatrix} 1 \\ \cos(\theta) E_{T_1} \\ \vdots \\ \cos^{N-1}(\theta) E_{T_1}^{N-1} \end{pmatrix}$$

$$\kappa = M_0(1 - E_{T_1}) \left(1 + \sum_{i=1}^{\infty} \cos^{iN}(\theta) E_{T_1}^{iN} (-\alpha)^{iS_A} \right) = M_0(1 - E_{T_1}) \left(1 + \frac{\cos^N(\theta) E_{T_1}^N (-\alpha)^{S_A}}{1 - \cos^N(\theta) E_{T_1}^N (-\alpha)^{S_A}} \right)$$

$$S_A = \sum_{k=1}^N A_k$$

Comparing the expression of each element in Eq. [5] with Eq.[4], one can see that $\vec{H}$ is still a geometric sequence but of finite length N , while the scale constant κ is now an infinite sum. This rearrangement reflects the fact that, if $N \times TR$ is not long enough, the magnetization

from the previous modulation cycle has not decayed to 0 and therefore contributes to the signal. In any case, as long as modulation matrix $\mathbf{A}_\alpha$ is invertible, $\vec{H}$ can be solved using Eq. [5], and then its rate of decrease with respect to n can be used to calculate T_1 :

$$\beta_1(\theta) = \ln(\cos(\theta)) - TR/T_1 \quad [6]$$

General model, $TI \neq 0$

In the more general case, when TI is not 0, a similar analysis (see Appendix), shows the measured signal $\vec{M}$ can be written in the same form as Eq. [5]:

$$\vec{M} = \kappa \mathbf{A}_\alpha \vec{H} \quad [7]$$

where $\mathbf{A}_\alpha$ is identical as above, and

$$\vec{H} = \begin{pmatrix} 1 \\ \cos(\theta)E_{T_1} \\ \vdots \\ \cos^{N-2}(\theta)E_{T_1}^{N-2} \\ \cos^{N-1}(\theta)E_{T_1}^{N-1} + \frac{M_0(1-E_2)}{\kappa(-\alpha)^{S_A}} \end{pmatrix}$$

$$\kappa = \left(M_0(1 - E_1)E_2 + M_0(1 - E_2)\cos(\theta)E_{T_1} \right) \left(1 + \frac{\cos^N(\theta)E_{T_1}^N(-\alpha)^{S_A}}{1 - \cos^N(\theta)E_{T_1}^N(-\alpha)^{S_A}} \right)$$

$$E_1 = \exp(-(TR - TI)/T_1)$$

$$E_2 = \exp(-TI/T_1)$$

The first $N-1$ elements of $\vec{H}$ in Eq. [6] are still the terms of a geometric sequence with same rate as in Eq. [5]. The TI value is only involved in two places, the scale factor κ and the last element of $\vec{H}$. Therefore, if we only use the first $N-1$ data points in processing, Eq. [6] is still valid. This property enables the straight-forward application of multi-slice mode for volumetric measurement, since multiple readout modules can be used at different TIs .

Excitation flip angle

From Eq. [6], the demodulated result $\vec{H}$ has a similar form to a LL signal in that both longitudinal relaxation time and RF excitation pulses contribute to its decay. Therefore, the calculation of the T_1 from $\vec{H}$ also depends on excitation angle θ . Because of the speed of this technique, we can use small flip angles to avoid large excitation field (b_1) offset while acquiring multiple averages to maintain reasonable SNR if necessary. If the accuracy of the

b_1 field is a concern, we can also map it within a reasonable time using the double-angle method (16). In this paradigm, the same sequence is run sequentially with flip angle θ and 2θ . Then θ and T_1 can be solved for simultaneously through the two decay rates $\beta_1(\theta)$ and $\beta_1(2\theta)$.

$$\cos(\theta) = \frac{b + \sqrt{b^2 + 8}}{4}, b = \exp(\beta_1(2\theta) - \beta_1(\theta)) \quad [8]$$

$$T_1 = \frac{TR}{\ln(\cos(\theta)) - \beta_1(\theta)}$$

METHODS

Phantom studies

Phantom verification and validation studies were carried out on a 3T Siemens Trio scanner with 12-channel head coil. A T_1 phantom was constructed, constituting of five bottles containing Gadoteridol varying in concentration from 0 to 1mM. A maximum length sequence of degree 4 was used for a 15-cycle PRAM modulation. The PRAM module contained a 15.36 ms hyperbolic secant inversion pulse followed by a 10 ms gradient spoiler. One line in k-space from snapshot fast low-angle shot (FLASH) (17) was then acquired immediately afterwards. The delay time between the center of modulation pulses and excitation pulses was 19ms. The other imaging parameters were: $TR = 250$ ms, $TE = 4$ ms, $BW = 260$ Hz/px, $matrix\ size = 128 \times 128$, $FOV = 256 \times 256$ mm², $slice\ thickness = 5$ mm, $\theta = 15^\circ$ and 30° . The scan time was 8 min for each flip angle.

To measure the reproducibility and accuracy, the same PRAM sequence was repeated six times, and compared with a customized IR sequence as described below:

{90° sat and spoiler—25ms—90° sat and spoiler}—1s—180° and spoiler—TI—gradient echo acq

At the beginning of each TR , the imaging slice was pre-saturated by two pulses separated by 25 ms to minimize off-resonance effects. The same inversion pulse and spoiler as in the PRAM sequence was applied 1s later to allow sufficient recovery of the magnetization. The same one line FLASH readout kernel as in the PRAM sequence was executed at the specified inversion time. The effective TIs (in ms) defined from the center of inversion pulse to excitation pulse were [19, 269, 519, 769, 1019, 1269, 1519, 1769, 2019, 2269, 2519, 2769, 3019]. The other imaging parameters were: $TR = 5$ s, $TE = 4$ ms, $BW = 260$ Hz/px, $matrix\ size = 128 \times 128$, $FOV = 256 \times 256$ mm², $slice\ thickness = 5$ mm, $\theta = 90^\circ$. Total scan time was 2h 18 min 40 s.

To validate the theory for the general $TI = 0$ model, we used a multi- TI experiment with six different PRAM delay times (19, 39, 59, 79, 99, and 119 ms) to acquire data which was then compared with the six repetitions of single delay time (19 ms) experiment described above.

Human studies

Human studies were also performed on the 3T Siemens Trio scanner using a 12-channel head coil. A healthy subject was recruited with institutional review board approval and written informed consent. The same PRAM module as in the phantom studies was used, but the spoiler duration was increased from 10 to 20 ms. The readout kernel was changed from a single k-space line to a standard gradient EPI with fat suppression. The other imaging parameters were: $TR = 430$ ms, $TE = 49$ ms, $BW = 2298$ Hz/px, *matrix size* = 128×128 , *FOV* = 256×256 mm², *slice thickness* = 5 mm, *slice number* = 4, $\theta = 15^\circ$ and 30° , *number of average* = 10. Total scan time for each flip angle was 69s. The same sequence was repeated six times to measure reproducibility. EPI-based inversion recovery data with the same TR and TIs as in phantom studies and corresponding single slice PRAM data were also collected using the same readout parameters.

Data analysis

For both PRAM demodulation and IR fitting, complex rather than magnitude data is needed to calculate the relative phase changes. Complex output mode was available in the FLASH-based sequences. But for EPI sequences, we had to implement an offline reconstruction program, because the product EPI reconstruction forces all the images to have the same phase at $k=0$. The offline reconstruction was implemented in C++ based on the Fast Imaging Library developed by National Center for Image Guided Therapy with help from Dr. Scott Hoge.

The IR data was fit to a mono-exponential longitudinal relaxation curve using the standard Levenberg-Marquardt (18) least squares algorithm provided by MATLAB. The initial magnetization $M(0^+)$, equilibrium magnetization M_0 , and T_1 were free parameters.

To estimate T_1 from PRAM data, we apply the inverse matrix of A_α to the measured signal $\vec{M}$. The normalized result $\vec{H}_{exp}$ can be viewed as actual signal plus background noise with constant variance σ^2 . The logarithm of this result is fit on a voxel to voxel basis to the formula

$$\ln(\vec{H}_{exp}(n)) \approx \cos(\theta) E_{T_1}(n-1) + \eta \quad [9]$$

where η is background noise with $\text{var}(\eta) \approx \sigma^2 / (\vec{H}_{exp}(n))$. Note that the back ground noise is no longer uniform due to logarithm operation so that a weighted least square algorithm (18) provided by MATLAB was used.

An important factor in the inverse matrix of A_α is the inversion efficiency α . Both Bloch simulation and α maps estimated from the IR method reveal that the hyperbolic secant pulse used is nearly ideal on the phantoms and cerebral fluid (CSF), while for white matter (WM) and gray matter (GM) its inversion efficiency is 0.92 ± 0.02 . This is due to the T_2 in WM and GM being shorter than in the phantoms and CSF so that a larger magnetization is lost during the long adiabatic inversion procedure. Therefore, we used $\alpha=1$ in phantom data processing. For human data, we divided the processing into two steps. First we used $\alpha=0.92$ to obtain an initial T_1 map. Then for the voxels with $T_1 > 2.0$ s, we used $\alpha=1$ to reconstruct again.

RESULTS

Phantom studies

Fig. 2 shows the logarithm of PRAM reconstructed results, $\ln(\vec{H})$, as a function of n for two voxels taken from the phantoms with different longitudinal relaxation times in the reproducibility test experiment. The signal intensity of $\vec{H}$ decays exponentially with n , the shorter T_1 and the larger θ , the faster decay rate, as predicted by theory. Meanwhile, the apparent noise variance of logarithm signal increases as the signal decreases, as predicted by Eq. [9]. The lines fit to Eq. [9] demonstrate that our weighted least square estimation algorithm is appropriate and robust.

The mean and standard deviation maps for T_1 and b_1 field over six repetitions are given in Fig. 3. The estimated flip angle map (Fig. 3(e)) reveals that the average offset to the specified value $\theta = 15^\circ$ is approximate 4 degrees on this phantom, and that the deviation of the b_1 field is higher at the edges of bottles and head coil (Fig. 3(f)). Without b_1 -correction, T_1 is overestimated (compare Fig. 3(a) with (c)) as part of E_{T_1} decay is incorrectly attributed to $\cos(\theta)$. Fig. 3(b) and (d) illustrate that, though the percentage standard deviation increases as T_1 increases, it is well below 2% up to $T_1 \approx 2.71$ s.

Fig. 4 shows a scatter plot of the average T_1 (both corrected and uncorrected for b_1 variation) measured by the PRAM method (Fig. 3(a) and (c)) versus the T_1 measured by the inversion recovery method over 1211 voxels taken from the phantoms. The b_1 -corrected data points fall nicely on the unit slope line, demonstrating a nearly perfect agreement ($R = 0.99995$). The mean biases of b_1 -uncorrected T_1 in percentage are 1.0%, 2.3%, 4.1%, 5.8%, 20.0%, for T_1 (s) $\approx 0.20, 0.33, 0.58, 0.99, 2.71$, respectively. It is expected that the percentage deviation is proportional to T_1 (see Discussion).

The validation of the theory with $TI = 0$ is shown in Fig. 5. Using the same flip angle, the average T_1 (Fig. 5(a)) over six different TIs is almost identical to the average T_1 (Fig. 3(a)) over six repetitions of the same TI with a correlation coefficient 0.99993 (Fig. 5(c)). In addition, the percentage standard deviation map over six different TIs (Fig. 5(b)) is virtually the same as it over six repetitions of the same TI (Fig. 3(b)). Both of them demonstrate that different TI values do not influence our T_1 estimation, as predicted by the theory. To further confirm the theory, Fig. 5(d) shows that the measured last element of $\vec{H}$, $\vec{H}(15)$, at a given TI agrees well with theoretical value calculated using Eq. [7], with T_1 and θ estimated from double-angle PRAM method.

Human studies

The voxel-wise comparison between PRAM and IR method over the central brain (2875 voxels) is shown in Fig. 6, illustrating a good agreement ($R = 0.96268$). Deviations from the unit line appear to be from voxels with substantial partial volume effect, located at the boundaries of the ventricles where GM and CSF are. This pattern may be explained by the behavior of the scale factor κ in Eq. [7]. Because κ is a function of T_1 as well as TI and TR , the signal ratio between two components in PRAM is different from what it is in the IR method, resulting in different estimations in the two methods for voxels containing two or more types of tissue with different T_1 's.

The results of multi-slice human experiment are displayed in Fig. 7. The estimated T_1 value of WM and GM is approximate 0.85s and 1.3s, respectively, consistent with previously reported values (19). The standard deviations ($\sim 3.9\%$ for WM and $\sim 8.8\%$ for GM) show a high reproducibility. Note the estimated field (Fig. 7(e)) is very close to ideal value., The average T_1 overestimation is 2.0% for WM and 2.9% for GM even without b_1 -correction, illustrating that b_1 may be less of concern in human brain experiment using $\theta=15^\circ$.

DISCUSSION

We have developed a general RAM theory applied to T_1 measurement. The PRAM implementation of RAM using pseudo-random modulation code shows high accuracy and reproducibility in both phantom and human studies, with the estimated T_1 values being completely consistent with those obtained by standard IR methods. We have also shown the feasibility of volumetric measurement on human brain with this method. The average scan time in the human brain for four slices (128×128 matrix size) using standard full k-space EPI readout was 1.6s per slice, in which effectively 15 relaxation data points were sampled at a temporal resolution of 430 ms, i.e. the effective total scan time to acquire only one slice was 6.45s.

Time efficiency, SNR analysis, and comparison to existing techniques

A major advantage of the RAM method is the high time efficiency. Let the number of k-space segments be M , and the number of readout kernels during one TR be L . The total scan time to complete the acquisition of L slices is $M \times N \times TR$, and therefore the average scan time per slice is $M \times N \times TR/L$. In multi-slice studies, the time efficiency of RAM is mainly limited by L , i.e. image acquisition speed. Given the same matrix size, the protocol acquiring full k-space EPI is approximately twice as fast as LL-EPI and TESOIR-EPI, the next two fastest T_1 quantification methods reported previously. It can be readily increased to 0.8s per slice with commonly used parallel imaging factor of 2 (20–22), or even higher using multi-band EPI acquisition (23).

The SNR of the RAM method depends on the specific modulation code used. As a T_1 recovery curve is scaled by its first data point, the RAM signal is approximate $M_0(1 - E_{T_1})\sin(\theta)$ (Eq. [5] and Eq. [7]). Assume the background noise from each imaging acquisition is independent with zero mean and constant variance σ^2 . Then each data point of the T_1 curve in RAM, i.e. $\tilde{H}(n)$, can be written as:

$$\tilde{H}(n) = \sum_{j=1}^N a_{nj} M(t_{j,img}^-) \quad [10]$$

where $a_{nj} = (\mathbf{A}_\alpha^{-1})_{nj}$. For the PRAM implementation, when $\alpha = 1$, $(N+1)/2$ of $\{a_{nj}\}_{j=1}^N$ are either $2/(N+1)$ or $-2/(N+1)$, with the rest being 0. Then the theoretical noise of each PRAM data point is:

$$\sigma_{PRAM}(\tilde{\mathbf{H}}(n)) = \sigma_{PRAM}\left(\sum_{j=1}^N a_{ij} M(t_{j,img}^-)\right) = \frac{2}{N+1} \cdot \sqrt{\frac{N+1}{2}} \cdot \sigma = \sqrt{\frac{2}{N+1}} \cdot \sigma \quad [11]$$

Therefore, the SNR of the PRAM implementation is approximate

$\sqrt{(N+1)/2} \cdot (1 - E_{T_1}) \cdot M_0 \sin(\theta) / \sigma$. By substituting $N = 15$ and $TR = 430\text{ms}$ used in the current human experiment protocol, the approximate SNR is $1.2 \cdot M_0 \sin(\theta) / \sigma$ for WM ($T_1 \approx 0.8\text{ s}$) and $0.8 \cdot M_0 \sin(\theta) / \sigma$ for GM ($T_1 \approx 1.3\text{ s}$). Thus the average SNR of this PRAM protocol is $M_0 \sin(\theta) / \sigma$, the same as in LL and IR methods if the same readout is used and full magnetization recovery is allowed.

A full SNR efficiency comparison between RAM, IR, and LL is very complex as there are many implementation possibilities for each of them under different circumstances, such as RAM modulation code, the excitation flip angle, the number of data points and their temporal distance, the number of k-space segments, the number of slices, and the number of repetitions. However, a general rule is that RAM doesn't need any waiting time so that every second can be straightforwardly used for data acquisition if not for modulation. The T_1 estimation process is exactly the same for all the slices collected at different TR 's. In multi-slice studies with one or more repetitions, the faster the acquisition, the higher the time efficiency. Although IR methods can have better SNR by using a 90° excitation pulse, they are limited by the inherent IR-type requirement that actual sampling time between two successive points has to be long ($\sim 15\text{s}$) for full restoration. TESOIR-EPI increases time efficiency by sampling many slices while waiting for the magnetization in each single slice to recover. For 12 data points, the total scan time for one slice is 3 minutes and thus it has to collect 60 slices in order to achieve the average scan time 3s per slice. LL doesn't require the $\sim 15\text{s}$ waiting time if the same slice is not excited more than once. Ideally, it can operate in a multi-slice mode and then use different sampling times for different slices in T_1 fitting. This requires extra effort and thus far most reports acquire multiple slices sequentially which restricts its efficiency even with accelerated readouts. In its best case that only one slice is desired ($L = 1$) using single-shot EPI readout ($M = 1$) with only one measurement, the total scan time for RAM and LL to collect the same number of data points separated by the same time distance is the same.

Systematic errors

The accuracy of estimated T_1 from RAM depends on the accuracy of flip angle θ and inversion efficiency α .

First, let's consider the effect of θ . Since the decay rate of $\vec{\mathbf{H}}$ is the product of $\cos(\theta)$ and E_{T_1} , underestimating one will overestimate the other. This effect can be estimated by taking partial derivative of T_1 (Eq. [6]) with respect to θ :

$$\frac{\varepsilon_{T_1}}{T_1} = \frac{T_1}{TR} \tan(\theta) \varepsilon_\theta \quad [12]$$

Eq. [9] is consistent with phantom studies result. Given that $TR = 250$ ms and $\theta = 15^\circ$, and that the average excitation angle error is 4° , the approximate percentage errors for the five different relaxation times are: 1.5%, 2.5%, 4.3%, 7.4%, and 20.3%, similar to the errors observed in Fig. 4.

The results from human studies shows that b_1 may be less of concern in human brain experiment using $\theta=15^\circ$. The average b_1 offset is $\varepsilon_\theta \approx 2^\circ$. With $TR = 430$ ms and $\theta=15^\circ$, the percentage error for WM and GM is approximately 1.8% and 2.8%, while in CSF where T_1 is longest, the error is $\sim 8.7\%$. This may explain the highest variance of estimated T_1 map lying in CSF.

Though the effect of θ is small under regular imaging conditions, this issue can be improved by decreasing b_1 inhomogeneities, or using the double-angle method. In either case, a small flip angle is recommended for use as the error sensitivity is proportional to $\tan(\theta)$.

Now consider the effect of inversion efficiency. Suppose the actual inversion efficiency is α while the demodulation uses α_{recon} in Eq. [7]. Then the relationship between reconstructed $\tilde{\mathbf{H}}$ and actual $\mathbf{H}$ is $\tilde{\mathbf{H}} = [\mathbf{A}^{-1}(\alpha_{recon})\mathbf{A}(\alpha)]\mathbf{H}$. To illustrate the effect of efficiency error, suppose $\varepsilon_\alpha = \alpha_{recon} - \alpha > 0$, i.e. $\alpha_{recon} > \alpha$. In this case, the signal loss due to the true inversion efficiency is larger than we believe. For this reason the reconstructed $\tilde{\mathbf{H}}$ decays faster than it should, i.e. the true decay rate of $\mathbf{H}$, because of uncompensated signal reduction due to the imperfect inversion pulses. Consequently, T_1 is underestimated. Because only the efficiency difference and the number of inversion pulses experienced contribute to the uncorrected signal dispersion, it is natural to see that the decay rate error is mainly a function of ε_α and the modulation code, nearly independent of α and other parameters. Numerical simulation results are consistent with this qualitative understanding. And they further establish a quantitative relationship for PRAM implementation that:

$$\tilde{\beta}_1 \approx \beta_1 - 0.5\varepsilon_\alpha \quad [13]$$

where $\tilde{\beta}_1$ is the slope of $\ln(\tilde{\mathbf{H}})$ and β_1 is the slope of $\ln(\mathbf{H})$. The slope error does not affect the estimation of θ using Eq. [8], as $\tilde{\beta}_1(2\theta) - \tilde{\beta}_1(\theta) = \beta_1(2\theta) - \beta_1(\theta)$. However, it will cause biased T_1 estimation, regardless of whether b_1 is corrected or not. By taking the partial derivative of T_1 with respect to $\beta_1(\theta)$ using Eq. [6] or Eq. [8], and substituting the slope error using Eq. [13], we have:

$$\frac{\varepsilon_{T_1}}{T_1} \approx \frac{T_1}{TR}(-0.5\varepsilon_\alpha) \quad [14]$$

Both Bloch simulations and IR results show that the chosen hyperbolic secant pulse is nearly ideal on the phantoms and CSF, while its inversion efficiency is 0.92 ± 0.02 for WM and GM. Therefore, in a human experiment where $TR = 430$ ms, the approximate percentage errors for WM and GM are up to 2.0% and 3.0% given a maximum $|\varepsilon_\alpha| = 0.02$.

There are two additional issues involved in almost all tissue T_1 measurement methods in human studies. One is the presence of blood flow. However, since its fractional volume is on

the order of the measurement error, it can be effectively ignored. Another problem is partial volume effects. In this case, any mono-exponential model is no longer sufficient. Since the primary purpose of this article is to establish the theory of RAM and demonstrate its feasibility, the partial volume effects will be addressed in future work.

CONCLUSIONS

This paper presents RAM as a novel and rapid T_1 mapping technique. We have demonstrated that T_1 measurement using PRAM implementation can sustain reasonable SNR while operating twice as fast as the two fastest previously published methods LL-EPI and TESOIR-EPI. Our phantom results show that the resultant estimated T_1 maps have high accuracy and reproducibility. The error caused by imperfect inversion pulse and b_1 inhomogeneities can be controlled at low percentage levels. It is particularly useful in dynamic studies in which one can monitor T_1 change as well as have sufficient brain coverage. In the future work, multiple slabs and accelerated imaging techniques will be implemented for faster acquisition with larger volumetric coverage. Partial volume effects will be also considered in more detail.

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APPENDEIX

Here we outline the derivations of the theoretical results when $TI = 0$ presented under Theory.

When T_1 is not 0, the evolution of the longitudinal magnetization during one TR breaks into two pieces:

$$\frac{dM(t)}{dt} = \frac{M_0 - M}{T_1}, t \in (t_{n-1, img}^+, t_n^-) \text{ or } (t_n^+, t_{n, img}^-) \quad [A1]$$

Using the same boundary conditions in Eq. [2], the iterative formula becomes:

$$M(t_{n, img}^-) = M(t_{n-1, img}^-) \cos(\theta) E_{T_1}(-\alpha)^{A_n} + M_0(1 - E_1) E_2(-\alpha)^{A_n} + M_0(1 - E_2) \quad [A2]$$

where $E_1 = \exp(-(TR - TI)/T_1)$, and $E_2 = \exp(-TI/T_1)$.

Repetitively iterating Eq. [A2], the signal at n^{th} image can then be written, similar to Eq. [4], as:

$$\begin{aligned}
& M(t_{n,img}^-) \\
& = M_0(1 \\
& \quad - E_2) + \left((-\alpha)^{A_n}, (-\alpha)^{\sum_{k=n-1}^n A_k}, \dots, (-\alpha)^{\sum_{k=n-j}^n A_k}, \dots \right) \\
& \quad \cdot (M_0(1 - E_1)E_2 \\
& \quad + M_0(1 \\
& \quad \quad - E_2)\cos(\theta)E_{T_1}) \begin{pmatrix} 1 \\ \cos(\theta)E_{T_1} \\ \vdots \\ \cos^j(\theta)E_{T_1}^j \\ \vdots \end{pmatrix}
\end{aligned} \tag{A3}$$

Applying the periodicity of $\{A_n\}$, we have a similar expression as Eq. [5], with an extra constant term $M_0(1 - E_2)$. However, notice that the last column of $\mathbf{A}_\alpha$ is a multiple of vector of ones, thus any constant term can be merged into the N^{th} element of $\vec{H}$. The final matrix representation is then Eq. [7]:

$$\vec{M} = \kappa \mathbf{A}_\alpha \vec{H} \tag{A4}$$

where

$$\begin{aligned}
\vec{M} &= \begin{pmatrix} M(t_{1,img}^-) \\ M(t_{2,img}^-) \\ \vdots \\ M(t_{N,img}^-) \end{pmatrix} \\
\mathbf{A}_\alpha &= \begin{pmatrix} (-\alpha)^{A_1} & (-\alpha)^{\sum_{k=1-1}^1 A_k} & \dots & (-\alpha)^{\sum_{k=1-(N-2)}^1 A_k} & (-\alpha)^{S_A} \\ (-\alpha)^{A_2} & (-\alpha)^{\sum_{k=2-1}^2 A_k} & \dots & (-\alpha)^{\sum_{k=2-(N-2)}^2 A_k} & (-\alpha)^{S_A} \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ (-\alpha)^{A_N} & (-\alpha)^{\sum_{k=N-1}^N A_k} & \dots & (-\alpha)^{\sum_{k=N-(N-2)}^N A_k} & (-\alpha)^{S_A} \end{pmatrix} \\
\vec{H} &= \begin{pmatrix} 1 \\ \cos(\theta)E_{T_1} \\ \vdots \\ \cos^{N-2}(\theta)E_{T_1}^{N-2} \\ \cos^{N-1}(\theta)E_{T_1}^{N-1} + \frac{M_0(1-E_2)}{\sigma(-\alpha)^{S_A}} \end{pmatrix}
\end{aligned}$$

$$\kappa = \left(M_0(1 - E_1)E_2 + M_0(1 - E_2)\cos(\theta)E_{T_1} \right) \left(1 + \sum_{i=1}^{\infty} \cos^{iN}(\theta)E_{T_1}^{iN}(-\alpha)^{iS_A} \right) \\ = \left(M_0(1 - E_1)E_2 + M_0(1 - E_2)\cos(\theta)E_{T_1} \right) \left(1 + \frac{\cos^N(\theta)E_{T_1}^N(-\alpha)^{S_A}}{1 - \cos^N(\theta)E_{T_1}^N(-\alpha)^{S_A}} \right)$$

When TI is 0, Eq. [A2] – [A4] are reduced to Eq.[3] – [5], respectively.

REFERENCES

1. MacDonald HL, Bell BA, Smith MA, Kean DM, Tocher JL, Douglas RH, Miller JD, Best JJ. Correlation of human NMR T1 values measured in vivo and brain water content. *The British journal of radiology*. 1986; 59(700):355–357. [PubMed: 3697613]
2. Fatouros PP, Marmarou A, Kraft KA, Inao S, Schwarz FP. In vivo brain water determination by T1 measurements: effect of total water content, hydration fraction, and field strength. *Magn Reson Med*. 1991; 17(2):402–413. [PubMed: 2062213]
3. Andersen C. In vivo estimation of water content in cerebral white matter of brain tumour patients and normal individuals: towards a quantitative brain oedema definition. *Acta Neurochir (Wien)*. 1997; 139(3):249–255. discussion 255–246. [PubMed: 9143593]
4. Larsson HB, Barker GJ, MacKay A. Nuclear magnetic resonance relaxation in multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 1998; 64(Suppl 1):S70–S76. [PubMed: 9647289]
5. Wick W, Kuker W. Brain edema in neurooncology: radiological assessment and management. *Onkologie*. 2004; 27(3):261–266. [PubMed: 15249715]
6. Manfredonia F, Ciccirelli O, Khaleeli Z, Tozer DJ, Sastre-Garriga J, Miller DH, Thompson AJ. Normal-appearing brain t1 relaxation time predicts disability in early primary progressive multiple sclerosis. *Arch Neurol*. 2007; 64(3):411–415. [PubMed: 17353385]
7. Look DC, Locker DR. Nuclear spin-lattice relaxation measurements by tone-burst modulation. *Physical Review Letters*. 1968; 20:987–989.
8. Look DC, Locker DR. Time saving in measurement of NMR and EPR relaxation times. *Rev Sci Instrum*. 1970; 41:250–251.
9. Homer H, Beevers M. Driven-equilibrium single-pulse observation of T1 relaxation. A reevaluation of a rapid “new” method for determining NMR spin-lattice relaxation times. *J Magn Reson*. 1985; 63:287–297.
10. Mansfield P. Multi-planar image formation using NMR spin echoes. *J Phys C*. 1977:L55–L59.
11. Gowland P, Mansfield P. Accurate measurement of T1 in vivo in less than 3 seconds using echo-planar imaging. *Magn Reson Med*. 1993; 30(3):351–354. [PubMed: 8412607]
12. Freeman AJ, Gowland PA, Mansfield P. Optimization of the ultrafast Look-Locker echo-planar imaging T1 mapping sequence. *Magn Reson Imaging*. 1998; 16(7):765–772. [PubMed: 9811142]
13. Clare S, Jezzard P. Rapid T(1) mapping using multislice echo planar imaging. *Magn Reson Med*. 2001; 45(4):630–634. [PubMed: 11283991]
14. Song, H-Y. Feedback Shift Register Sequences. *Wiley Encyclopedia of Telecommunications*: John Wiley & Sons, Inc.; 2003.
15. Park, SR.; Song, I. Polyphase Sequences. *Wiley Encyclopedia of Telecommunications*: John Wiley & Sons, Inc.; 2003.
16. Insko EK, Bolinger L. Mapping of the Radiofrequency Field. *J Magn Reson Ser A*. 1993; 103:82–85.
17. Haase A. Snapshot FLASH MRI. Applications to T1, T2, and chemical-shift imaging. *Magn Reson Med*. 1990; 13(1):77–89. [PubMed: 2319937]
18. Strang G. *Introduction to Applied Mathematics*. 1986

19. Rooney WD, Johnson G, Li X, Cohen ER, Kim SG, Ugurbil K, Springer CS Jr. Magnetic field and tissue dependencies of human brain longitudinal $1H_2O$ relaxation in vivo. *Magn Reson Med*. 2007; 57(2):308–318. [PubMed: 17260370]
20. Griswold MA, Jakob PM, Heidemann RM, Nittka M, Jellus V, Wang J, Kiefer B, Haase A. Generalized autocalibrating partially parallel acquisitions (GRAPPA). *Magn Reson Med*. 2002; 47(6):1202–1210. [PubMed: 12111967]
21. Pruessmann KP, Weiger M, Scheidegger MB, Boesiger P. SENSE: sensitivity encoding for fast MRI. *Magn Reson Med*. 1999; 42(5):952–962. [PubMed: 10542355]
22. Sodickson DK, Manning WJ. Simultaneous acquisition of spatial harmonics (SMASH): fast imaging with radiofrequency coil arrays. *Magn Reson Med*. 1997; 38(4):591–603. [PubMed: 9324327]
23. Feinberg DA, Moeller S, Smith SM, Auerbach E, Ramanna S, Gunther M, Glasser MF, Miller KL, Ugurbil K, Yacoub E. Multiplexed echo planar imaging for sub-second whole brain fMRI and fast diffusion imaging. *PLoS One*. 2010; 5(12):e15710. [PubMed: 21187930]

Figure 1.

Schematic sequence diagram of RAM. RF pulses are assumed to be sufficiently narrow that their action is instantaneous. In addition to inversion pulse time t_n and excitation pulse time $t_{n,img}$, superscript $-$ and $+$ are used to represent the time immediately before and after RF pulses, respectively.

Figure 2. Logarithm of the PRAM reconstructed H versus n of two voxels located in the highest and lowest Gd-concentration phantom bottles. The error bars indicate the standard deviation over six repetitions. The dotted lines are fits using Eq. [9]. Only the first 8 data points are shown.

Figure 3.

Estimated T_1 and b_1 maps from single TI PRAM experiment with six repetitions. $\theta=15^\circ$. (a) (c) are mean T_1 maps (in units of s) for b_1 -uncorrected and b_1 -corrected methods, respectively. (e) mean b_1 field map (in units of degree). (b) (d) (f) are percentage standard deviation maps to (a) (c) (e), respectively.

Figure 4.

Scatter plot showing the voxel-wise T_1 comparison between PRAM and IR method for 1211 voxels in the T_1 phantom. The red line indicates the line of unit slope. The correlation coefficient of b1-corrected PRAM and IR is 0.99994.

Figure 5.

b_1 -uncorrected PRAM reconstruction results using six different TI values, $\theta=15^\circ$: (a) (b) are mean and standard deviation (in percentage) maps for T_1 over multiple TIs ; (c) scatter plot of the mean T_1 averaged over six TIs versus the mean T_1 averaged over six repetitions with the same TI , $R = 0.99993$; the red line indicates the line of unit slope. The ROIs contain 1808 voxels total. (d) the measured last element of H , $H(15)$, for each TI versus the theoretical value for a single voxel.

Figure 6.

Scatter plot showing the voxel-wise T_1 comparison between the b1-corrected PRAM and IR method for human brain. The red line indicates the line of unit slope. The correlation coefficient of b1-corrected PRAM and IR is 0.96. The ROIs contain 2875 voxels in total.

Figure 7. PRAM reconstruction results of multi-slice experiment over six repetitions on human brain. $\theta=15^\circ$. (a) (c) are mean T_1 maps (in units of s) for b_1 -uncorrected and b_1 -corrected methods, respectively. (e) mean b_1 field map (in units of degree). (b) (d) (f) are percentage standard deviation maps to (a) (c) (e), respectively.