Optimizing variable flip angles in magnetization-prepared gradient-echo sequences for efficient 3D-T1ρ mapping

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Purpose: To optimize the choice of the flip angles of magnetization-prepared gradient-echo sequences for improved accuracy, precision, and speed of 3D-T1ρ mapping.

Methods: We propose a new optimization approach for finding variable flip-angle values that improve magnetization-prepared gradient-echo sequences used for 3D-T1ρ mapping. This new approach can improve the accuracy and SNR, while reducing filtering effects. We demonstrate the concept in the three different versions of the magnetization-prepared gradient-echo sequences that are typically used for 3D-T1ρ mapping and evaluate their performance in model agarose phantoms (n = 4) and healthy volunteers (n = 5) for knee joint imaging. We also tested the optimization with sequence parameters targeting faster acquisitions.

Results: Our results show that optimized variable flip angle can improve the accuracy and the precision of the sequences, seen as a reduction of the mean of normalized absolute difference from about 5%–6% to 3%–4% in model phantoms and from 15%–16% to 11%–13% in the knee joint, and improving SNR from about 12–28 to 22–32 in agarose phantoms and about 7–14 to 13–17 in healthy volunteers. The optimization can also compensate for the loss in quality caused by making the sequence faster. This results in sequence configurations that acquire more data per unit of time with SNR and mean of normalized absolute difference measurements close to its slower versions.

Conclusion: The optimization of the variable flip angle can be used to increase accuracy and precision, and to improve the speed of the typical imaging sequences used for quantitative 3D-T1ρ mapping of the knee joint.

KEYWORDS
flip angles, pulse sequence, quantitative MRI, T1ρ relaxation
INTRODUCTION

The spin–lattice relaxation time in the rotating frame ($T_{1p}$) has shown to be useful in several applications, ranging from quantifying proteoglycan content of the cartilage\cite{1,2} to distinguishing between healthy and chronic liver disease subjects\cite{3} and with Alzheimer’s and Parkinson’s disease.\cite{4,5} One drawback is the undesirably long acquisition time required for $T_{1p}$ mapping, particularly when 3D and high-resolution (HR) mapping is desired. High accuracy, precision, and reduced acquisition time are fundamental for clinical use, improving diagnostic quality while avoiding long exams.

Significant efforts have been made to reduce scan time while maintaining good image quality. Fast pulse sequences such as fast gradient echo\cite{6-8} and fast spin echo,\cite{9} and sequences with long readouts such as EPI\cite{10} and spiral imaging,\cite{11} are examples of efficient sequences that capture more k-space data per unit of time. Another approach to reducing the scan time is undersampling. In parallel imaging,\cite{12-14} multiple receiving coils are used to capture more data in parallel, with different coil sensitivities, allowing for undersampling of the k-space to reduce acquisition time. Compressed sensing,\cite{15-17} which relies on incoherent sampling and sparse reconstruction, also reduces time by undersampling, while obtaining high-quality images from advanced nonlinear reconstruction. Recent advancements with data-driven approaches for learned reconstruction and sampling pattern have shown that k-space sampling can be optimized for specific anatomy and reconstruction methods\cite{18-22} for improved quality in accelerated MRI. All these improvements can be combined, allowing 3D MRI with short scan times. This study focuses on fast pulse sequences for quantitative mapping.

The 3D-$T_{1p}$ mapping methods discussed in this study are based on Cartesian magnetization-prepared gradient-echo (MPGRE) pulse sequences\cite{23} with RF and gradient spoilers,\cite{24} modified to include $T_{1p}$ preparation.\cite{25-28} In these sequences, a train of small flip-angle RF pulses combined with the action of the magnetic gradient system creates multiple gradient echoes that correspond to the acquisition of multiple k-space lines after a $T_{1p}$ preparation module. Although very efficient, in the sense that multiple k-space lines are acquired in each echo train, it still has limitations due to the loss of the prepared magnetization that happens as a result of the natural signal evolution (SE) during the transient state of the echo train.\cite{25,26,28} This phenomenon causes issues such as spin–lattice relaxation time ($T_1$) contamination and k-space filtering effect (FE),\cite{28,29} ultimately affecting the accuracy of measured $T_{1p}$ values.

To minimize k-space FE, several strategies have been implemented, such as the use of variable flip angles (VFAs)\cite{26,28} adjusted to minimize FE, the reduction of the number of echoes per train, also called view per shots (VPS), and the use of RF phase cycling\cite{28} shots. These techniques are combined with k-space data-collection ordering schemes that capture first phase-encoding positions near the center of k-space,\cite{28,30,31} preserving most of the desired contrast. The use of RF phase cycling shots incurs a time penalty by doubling the scan time. Reducing the VPS leads to an increase in total scan time because more shots are necessary. To balance between k-space FE and scan time due to multiple shots, most sequences use from 64 to 256 VPS. On the other hand, the use of VFA and proper k-space ordering incurs no time penalty and can be exploited to reduce FE.\cite{26,28}

In addition to FE and $T_1$ contamination, noise is also an important factor that affects the quality of $T_{1p}$ mapping. One way to reduce the sensitivity to noise is to improve the choice of spin-lock times (TSLs).\cite{32-34} Using optimized choices for TSLs improves the quality of $T_{1p}$ mapping, allowing a reduction of the number of TSLs with the same quality. Another way to improve $T_{1p}$ mapping by improving SNR is to modify the pulse sequence by using larger flip angles (FAs) combined with longer recovery times. Although larger FAs may be beneficial, longer recovery times usually lead to an increase in total scan time.

In this work, we propose an innovative data-driven optimization framework for $T_{1p}$ mapping with MPGRE sequences. Inspired by Johnson et al.\cite{26} and Li et al.,\cite{28} we optimized the VFA to improve the sequence. However, different from previous works, we used a target cost function that involves three components: (1) $T_{1p}$ mapping accuracy, (2) flatness of the SE (to minimize FE), and (3) signal strength (for improved SNR). The proposed optimization framework is applied to three different pulse sequences typically used for $T_{1p}$ mapping: (1) the magnetization-prepared angle-modulated partitioned k-space spoiled GRE snapshots (MAPSS) sequence,\cite{28}; (2) the tailored VFA MPGRE sequences with magnetization reset\cite{26} (called MPGRE-WR here), and (3) standard MPGRE sequences.\cite{27,35} As it will be shown later, the proposed framework can generalize the choices from Johnson et al.\cite{26} and Li et al.,\cite{28} which are available for MAPSS and MPGRE-WR, allowing us, for example, to improve SNR beyond previous limits,\cite{26,28} and also extending these benefits to standard MPGRE sequences. Finally, by properly choosing small recovery times and large VPS, one can obtain faster $T_{1p}$ mapping with similar quality measures as slower configurations, accelerating the acquisition even without undersampling.
2 | METHODS

2.1 | Three-dimensional T₁ρ MPGRE pulse sequence

The 3D-T₁ρ-weighted data sets are usually acquired with various TSLs. In this work, we will follow Zibetti et al., targeting T₁ρ of the human knee joint as an example, by using only two TSLs (1 ms and 35 ms) with spin-lock frequency = 500 Hz. The pulse sequence includes T₁ρ magnetization preparation, followed by a FLASH sequence. The 3D volumes are acquired with Cartesian sampling with two phase-encoding directions, the k_y-k_z plane, and one linear readout (frequency-encoding direction), denominated as k_x. The k_y-k_z plane may be undersampled.

2.1.1 | T₁ρ magnetization preparation

In the three sequences discussed here, the magnetization preparation (MP) step has some differences. As shown in Figure 1A,B, for MAPSS and MPGRE-WR, the MP step starts with resetting the longitudinal magnetization (Mz) by using an Mz reset pulse. The purpose of the Mz reset pulse is to eliminate previous longitudinal magnetization and start signal recovery all from the same initial condition at each shot. The next step is the Mz recovery (usually between 300 ms and 3000 ms), which is essentially a recovery time for the longitudinal magnetization. Then a spin-lock pulse, with specified TSL, is applied to generate T₁ρ contrast.

Note that the standard MPGRE does not have an Mz reset pulse (Figure 1C). Compared with the other two variants, this sequence relies on SE reaching a periodic steady-state condition, where the SE of each shot is essentially repeated. For this reason, the signal is not acquired in some initial shots, called dummy shots (usually taking a total time of 5000 ms), which are in the transient state.

In MAPSS, there are phase cycling shots, as shown in Figure 1A, where the spin-lock pulse is modified. The modification is equivalent to a 180° pulse after the spin-lock pulse, resulting in rotating the prepared Mz to the negative axis, in the opposite direction when compared with a regular shot.

2.1.2 | Gradient-recalled echo train

This part is similar in all three sequences, where a FLASH sequence is used and each acquired echo corresponds to one k-space line of the 3D volume. Standard MPGRE usually uses constant flip angles (CFAs), the same for all TSLs. In MAPSS, a variable FA (VFA) train is computed to reduce the FEs, usually with increased FA for each pulse in the train, with the last FA at 90°. The idea of using the VFA train was extended in Johnson et al. for MPGRE-WR sequences (with Mz reset), as shown in Figure 1B. However, in this pulse sequence, the VFA train is different for each TSL. This is necessary for MPGRE-WR because the SE of this sequence does not depend only on the initial state, as in MAPSS. In Johnson et al. the pulse train for the first TSL is increasing as in MAPSS, optimized for maximum flatness of the SE for predefined relaxation parameters (e.g., T₁, T₁ρ). However, for the following TSLs, the FA in the train may be decreasing to obtain similar levels of flatness (see examples of these FAs in Figure S5).

Until now, there was no optimized VFA for standard MPGRE sequences. One of the reasons may be because the lack of Mz reset pulse makes SE too complex to use shot-independent optimization schemes as proposed in Johnson et al. and Li et al.

2.1.3 | Acquisition time

As seen in Figure 1, the acquisition time for each TSL for the last two MPGRE sequences is given by

\[ T_{\text{tot}} = \sum_{q=1}^{T_{\text{TLS}}} [(D+S)\times(T_{\text{reset}}+T_{\text{rec}}+TSL(q)\times r + TR\times VPS)] \]

(1)

where D is the number of dummy shots, and S is the number of acquired shots, usually \( S = \lceil N/VPS \rceil \), where N is the number of acquired k-space lines in the k_y-k_z plane. In the fully sampled case, N is the total number of phase-encoding positions. The value of T_{TLS} is the number of TSLs. Other components of the scan time are described in Figure 1. The T_{tot} for MAPSS is twice what is in Eq. (1).

2.1.4 | k-Space ordering of data collection

The T₁ρ contrast is better right after the end of MP. This means that the first echoes have more of the desired contrast, whereas the later echoes are more contaminated by the changes in SE, which results in the FE. Following Johnson et al. and Li et al., we use a 3D Cartesian center-out approach. We used the one proposed in Zibetti et al. because it can handle both fully sampled as well as undersampled acquisitions (Figure 1D,E). This approach, combined with SEs, generates FE in the images that can be of low-pass filtering or high-frequency amplification.
Figure 1 Illustration of the pulse sequences used for $T_1\rho$ mapping in this study. (A) The magnetization-prepared angle-modulated partitioned k-space spoiled gradient echo snapshots (MAPSS) pulse sequence uses Mz reset and requires two shots for the same phase-encoding positions: one regular and one with phase cycling. (B) The magnetization-prepared gradient-echo with Mz reset (MPGRE-WR) does not use phase cycling. (C) The standard MGRE does not use Mz reset or phase cycling. Because it lacks Mz reset, the SE must achieve steady state, and some dummy shots may be necessary. (D) The acquisition is Cartesian 3D; at each shot, several phase-encoding positions given by view per shots (VPS) are acquired, according to the specified sampling pattern (SP) and ordering scheme. (E) Here a balanced center-out ordering is used, as shown.

This is important because the central area of the k-space is minimally affected by the changes caused by SE.

The VPS is a choice of the user. A larger VPS means fewer shots to acquire all the desired phase-encoding positions, resulting in a faster MRI scan, but probably more FE, as the SE will be longer. In this sense, the user must select sequence parameters to balance SNR, FE, $T_1$ contamination, and scan time.

2.2 Equations of the signal evolutions

In the first two sequences, where Mz reset is used, the SE can be described as:

$$M_{xy}(n) = A(n)M_{\text{prep}} + B(n),$$  \hspace{1cm} (2)

where $1 \leq n \leq \text{VPS}$, and

$$A(n) = e_{1} \left\{ \begin{array}{ll} 1 & \text{if } n=1 \\ \prod_{i=1}^{n-1} e_{1} \cos(a_{i}) & \text{if } n \neq 1 \end{array} \right\} e_{2} \sin(a_{n}).$$  \hspace{1cm} (3)

$$B(n) = M_{0} \left\{ \begin{array}{ll} 1 & \text{if } n=1 \\ (1 - e_{1}) \prod_{i=1}^{n-1} e_{1} \cos(a_{i}) & \text{if } n > 1 \end{array} \right\} + (1 - e_{1}) \left\{ \begin{array}{ll} 0 & \text{if } n=1 \\ 1 + \sum_{p=2}^{n-1} \left( \prod_{i=p}^{n-1} e_{1} \cos(a_{i}) \right) & \text{if } n > 2 \end{array} \right\} e_{2} \sin(a_{n}).$$  \hspace{1cm} (4)
where \( e_r = e^{-\frac{T_r}{T_1}} \), \( e_1 = e^{-\frac{T_S}{T_1}} \), and \( e_2 = e^{-\frac{T_{rec}}{T_1}} \). The SE is the same for each shot, and

\[
M_{\text{prep}} = M_0 \left( 1 - e^{-\frac{T_{rec}}{T_1}} \right) e^{-\frac{T_S}{T_1}}.
\]

(5)

In MAPSS, during the phase cycling shot, the SE is

\[
M_{\text{xy}}(n) = -A(n)M_{\text{prep}} + B(n),
\]

(6)

and the signal from Eq. (6) is subtracted from the signal in Eq. (2), resulting in \( M_{\text{xy}}(n) = 2A(n)M_{\text{prep}} \). Note that the MAPSS signal is free from \( T_1 \) contamination caused by \( B(n) \).

In the third sequence, the standard MPGRE without Mz reset, the SEs of different shots are connected, as follows:

\[
M_{\text{xy}}(s, n) = A(n)M_{\text{prep}}(s) + B(n),
\]

(7)

where \( s \) represents the shot index:

\[
M_{\text{prep}}(s) = \left[ M_c(s-1, VPS)e^{-\frac{T_{rec}}{T_1}} + M_0 \left( 1 - e^{-\frac{T_{rec}}{T_1}} \right) \right] e^{-\frac{T_S}{T_1}},
\]

(8)

and

\[
M_c(s, n) = C(n)M_{\text{prep}}(s) + D(n),
\]

(9)

where \( 1 \leq n \leq VPS \), and

\[
C(n) = e_r \left[ \prod_{i=1}^{n} e_1 \cos(a_i) \right],
\]

(10)

\[
D(n) = M_0 \left\{ (1 - e_1) \left[ \prod_{i=1}^{n} e_1 \cos(a_i) \right] + (1 - e_1) \left[ 1 + \sum_{p=2}^{n} \left( \prod_{i=p}^{n} e_1 \cos(a_i) \right) \right] \right\},
\]

(11)

being \( M_{\text{prep}}(1) = M_0 e^{-\frac{T_S}{T_1}} \).

Note that some imperfections in the Mz reset pulse may happen when some residual Mz magnetization remains after the pulse. This can cause imprecision in MPGRE-WR sequences. To correct for this imperfect Mz reset pulse, instead of Eq. (5), the following model can be used in combination with Eq. (9):

\[
M_{\text{prep}}(s) = \left[ c.M_c(s-1, VPS)e^{-\frac{T_{rec}}{T_1}} + M_0 \left( 1 - e^{-\frac{T_{rec}}{T_1}} \right) \right] e^{-\frac{T_S}{T_1}},
\]

(12)

where \( 0 \leq c \leq 1 \) is a constant corresponding to the amount of residual magnetization after Mz reset in the MPGRE-WR sequence (see Figure S5 with illustrations of the VFA optimized for both models). Note that any pulse sequence, imperfection can be included in the SE model. For example, \( T_1 \) contamination is already included in the terms \( e_r \) and \( (1 - e_r) \). This way, the optimization will take these imperfections under consideration and find FAs that minimize their effects.

Figure 2 illustrates the SE of three shots with VPS = 128, TR = 6 ms, TE = 3 ms, \( r = 3 \) ms, and Trec = 1110 ms for each sequence considering three different materials with different relaxation values, assuming \( M_0 = 1 \). Note that because the SE in the MPGRE sequence or MPGRE-WR with imperfect Mz reset pulse is coupled between shots, it is more complex to model, and consequently, to optimize. In Figure 2, the MAPSS and MPGRE-WR SEs already include VFA with optimization for maximum flatness following their original methods in Li et al. and Johnson et al. for the component \( (T_1, T_2^*, \ \ T_{1p}) = (1200, 35, 40 \text{ ms}) \). The MPGRE shown in Figure 2 uses a constant FA of 9° (MPGRE-CFA). Note the optimization of MAPSS and MPGRE-WR can be carried out using only one shot, because Mz reset clears past SE history, whereas the optimization of MPGRE (without Mz reset) or MPGRE-WR with imperfect Mz reset needs to include all shots, including the dummy ones, because SE depends on past SE history.

Note that SE also depends on the relaxation parameters, such as \( T_1 \), \( T_2^* \), and \( T_{1p} \). In the optimization process, we may be interested in optimal performance on several different sets of relaxation values. We will use \( M_{\text{xy}}(k, q, s, n) \) to denote the SE with relaxation sets indexed by \( 1 \leq k \leq K \), where \( K \) is the number of relaxation sets, being \( \left[ T_{1}(k), T_{2}^{*}(k), T_{1p}(k) \right] \), with the TSLs indexed by \( 1 \leq q \leq T_{\text{TSL}} \), where \( T_{\text{TSL}} \) is the number of TSLs, and with the shots indexed by \( 1 \leq s \leq S + D \), after the FA pulse indexed by \( 1 \leq n \leq VPS \).

### 2.3 Proposed optimization of the VFAs

The proposed optimization tries to find the best VFA for different TSLs that maximize a surrogate function of the precision and accuracy in \( T_{1p} \) mapping. More precisely, we maximize a function that consists of three SE terms and one constraint-like term that can deal with different imperfections in the SE of the \( T_{1p} \) mapping sequences. The general form of the cost function is:

\[
\hat{\alpha} = \arg \max_{\alpha} \left[ \sum_{k=1}^{K} \left( A(k, \alpha) + F(k, \alpha) + S(k, \alpha) \right) \right] + R(\alpha),
\]

(13)
where $k$ is the index of the relaxation set of interest; and $\alpha$ is a vector containing the FA train. The FA train may be the same for all TSLs as in MAPSS (in this case of size $VPS \times 1$), or it may be different for each TSL as in MPGRE-WR and MNGRE, of size $T_{TSL} \times VPS \times 1$.

The first term, $A(k, \alpha)$, is chosen to improve accuracy, particularly at the beginning of each shot of the SE where the components are related to the acquisition of the central area of the $k$-space. This term counters the $T_1$ contamination caused by the delay $\tau$ in the pulse sequence as well as the differences in $M_{\text{prep}}(s)$ in the MNGRE sequence or MNGRE-WR with imperfect Mz reset pulse as modeled in Eq. (12).

In this work, we used

$$A(k, \alpha) = -\lambda A \|Am_k(\alpha)\|_2^2,$$

where $m_k(\alpha)$ is a vector of size $T_{TSL} \cdot (S + D) \cdot VPS \times 1$ with the normalized SE of the $k$th component of the relaxation parameter set. The SE is stacked in a vector for all TSLs, shots, and pulses. The $m$th component of the vector is defined as $[m_k(\alpha)]_m = M_{xy}(k, q, s, n)/e^{-t_{T1} \rho / \omega_k}$, where $m = (q - 1) \times (S + D) \times VPS + (s - 1) \times VPS + n$. Figure S1 shows an illustrative example of how $m_k(\alpha)$ is constructed. The SE is normalized by the effect of the $T1\rho(k)$ relaxation, $e^{-t_{T1} \rho / \omega_k}$, which is different for each TSL. The matrix $A$ computes the finite difference between all pairs of $M_{xy}(k, p, s, 1)/e^{-t_{T1} \rho / \omega_k}$ and $M_{xy}(k, q, s, 1)/e^{-t_{T1} \rho / \omega_k}$, where $t_p$ and $t_q$ are two different TSLs. This is done for the first elements for all $S$ acquired shots (not for the dummy shots). An illustration of how the matrix $A$ is constructed is shown in Figure S2. The idea behind this term is that if this difference is minimized, the accuracy of $T_1\rho$ mapping is improved in the low-frequency components, as illustrated by Figure 3, because, ideally, the SE of these components should differ only because of the normalization factor $e^{-t_{T1} \rho / \omega_k}$. The $\lambda A$ is the weighting factor of this term of optimization. As we will discuss later, this term is not necessary for the optimization of the MAPSS sequence, because it uses the same $\alpha$ for all TSLs. Also, in MAPSS, the $T_1$ contamination effects caused by the delay $\tau$ are solved by using phase-cycling acquisitions.

The second term, $F(k, \alpha)$, is designed to improve the flatness of the SE, consequently making the modulation transfer function (MTF), which represents the $k$-space filtering, as constant as possible. This term counters the FE caused by the change in the magnitude of the measured signal that happens during SE within a shot. In this work,
we used
\[ F(k, \alpha) = -\lambda_F \|Fm_k(\alpha)\|_2^2, \quad (15) \]

where \( m_k(\alpha) \) is the same as before. The matrix \( F \) computes
the finite difference on the SE inside each shot, for \( 1 \leq n \leq VPS \),
and it is repeated for all TSLs and all \( S \) acquired shots (except dummy
shots). An illustration of how the matrix \( F \) is constructed is shown in Figure S3.
This term enforces \( SE \) to be as smooth as possible, preferably constant,
as illustrated by Figure 3, removing the FE of the images as done by
MAPSS \(^{28} \) and tailored VFA \(^{26} \) approaches. The \( \lambda_F \) is the weighting factor of this term of the
optimization.

The third term, \( S(k, \alpha) \), is designed to improve the signal strength
at the beginning of the SE. This term focuses on improving SNR by forcing
the components of the SE related to low-frequency k-space components
to be close to the desired signal intensity. In this work, we used
\[ S(k, \alpha) = -\lambda_S \|S(m_k(\alpha) - m_{ref})\|_2^2, \quad (16) \]

where \( m_k(\alpha) \) is the same as before; \( m_{ref} \) is the reference
signal; and the matrix \( S \) has ones in the positions where we want \( m_k(\alpha) \) to be close to \( m_{ref} \), and zeros on the others,
as illustrated by Figure S4. In this work, \( S \) has ones on the positions related to \( M_{xy}(k, 1, s, 1)e^{-\frac{t_2}{T_1}}, \) the first element
of the first TSL, for all \( S \) acquired shots except the dummy shots.
An illustration of how the matrix \( S \) is constructed is shown in Figure S4.
In this work, \( m_{ref} \) is a constant SE; combined with matrix \( S \), it adjusts the SE related to the
first FA of the train, possibly increasing the signal strength corresponding
to the central area of the k-space. The \( \lambda_S \) is the weighting factor of this term of optimization.

Optionally, one may consider specific constraints to apply desired behavior in the FA, such as in MAPSS, \(^{28} \) where the last FA is constrained to be 90°.
\[ R(\alpha) = -\lambda_R \|R(\alpha - \alpha_{ref})\|_2^2, \quad (17) \]

The matrix \( R \) has ones to force the elements of \( \alpha \) we want to be close or equal to the reference, letting the others be defined by the optimization. The \( \lambda_R \) is the weighting factor of this term of optimization.

We can also write Eq. (13) as
\[ \hat{\alpha} = \arg\min_\alpha \left[ \sum_{k=1}^{K} \omega_k \left( \lambda_A \|Am_k(\alpha)\|_2^2 + \lambda_F \|Fm_k(\alpha)\|_2^2 + \lambda_S \|S(m_k(\alpha) - m_{ref})\|_2^2 \right) \right] + \lambda_R \|R(\alpha - \alpha_{ref})\|_2^2, \quad (18) \]

where \( \omega_k \) is a weight that is given to each particular relaxation parameter
according to its importance in the set. In this work we used \( \omega_k = |T1\rho(k)|^2/\sum_{k=1}^{K}|T1\rho(k)|^2 \), as it produced results with more uniform errors across different sets of parameters.

Ideally, the optimization searches for FA \( \alpha \) that produce normalized SEs, \( m_k(\alpha) \), as constant as possible and close to \( m_{ref} \), prioritizing the desired properties of the SE related to low-frequency k-space components. If that happens, the SE will have all undesirable factors that affect
accuracy, such as \( T_1 \) contamination and FE, removed or minimized, whereas \( T_1\rho \) contrast will be preserved. At the same time, the signal should have the desired strength, defined by \( m_{ref} \), which can be chosen to improve SNR and, consequently, the precision of \( T_1\rho \) mapping. Equation (18) is a nonlinear least-squares problem and was solved using the trust region conjugate gradient method. \(^{33} \)

2.4 | Synthetic profile evaluation

We evaluated the theoretical performance of the optimized VFA using simulated signals, as seen in Figure 4A, assuming a profile as shown in Figure 4C. The ideal profile undergoes signal modulation in the frequency domain (Figure 4B) according to the SE of the specific pulse sequence with all the relaxation parameters tested. This will apply the desired \( T_1\rho \) contrast, but will also apply imperfections of the SE, such as \( T_1 \) contamination and FE. White Gaussian noise, with a SD equivalent to the estimated from real acquisitions, is also added to simulate the noise effects to evaluate SNR improvements, as shown in Figure 4E. The \( T_1\rho \) mapping is evaluated using artificially distorted profiles, as shown in Figure 4F,G.
FIGURE 4 Simulated evaluation of the sequences using the effects of the signal evolution (SE) on the idealized profile, as shown in (C), with spectrum produced by fast Fourier transform (FFT) as shown in (D). The SEs are different for different spin-lock times (TSLs) and relaxation parameters, as shown in (A), leading to different modulation transfer functions, as shown in (B). The resulting modulated and noisy profiles are shown in (E). After $T_1$ fitting, as shown in (F), three types of errors are seen in the estimated $T_1$ values, as shown in (G). The $e_a$ is the error in accuracy, usually related to the error in the first echoes of the echo train, related to the central k-space; the $e_f$ is the error due to the filtering effect (FE), which is usually larger in the discontinuities of the profile; and $e_s$ is the error due to noise, which is larger when the SNR is small.

Note that three kinds of errors are noted in the $T_1$ values, as seen in Figure 4:

$$
\varepsilon(n) = p(n) - p_{\text{ref}}(n),
$$

$$
\varepsilon(n) = e_a(n) + e_f(n) + e_s(n),
$$

$$
\varepsilon(n) = \left[ \bar{p}_{\text{nl}} - \bar{p}_{\text{ref}} \right] + \left[ (p_{\text{nl}}(n) - \bar{p}_{\text{nl}})(p_{\text{ref}}(n) - \bar{p}_{\text{ref}}) \right] + \left[ (p(n) - p_{\text{nl}}(n)) - (p_{\text{ref}}(n) - \bar{p}_{\text{ref}}) \right].
$$

where the error $\varepsilon(n)$ between the measured $T_1$ values, $p(n)$, and the reference values, $p_{\text{ref}}(n)$, consist of three components: $e_a$, $e_f$, and $e_s$. The $e_a$ are the inaccuracies error due to $T_1$ contamination that affect the first echoes, corresponding to the center of the k-space, biasing the estimated values (visible as a shift of the estimated value from the measurements). The $e_a$ is defined as the difference between the mean value of the noiseless $T_1$ values, $\bar{p}_{\text{nl}}$, and the mean value of the reference, $\bar{p}_{\text{ref}}$. The $e_f$ is the error due to FE, caused by the lack of flatness in the SE (visible as peaks of large error that happen around the edges of the difference between the k-space-filtered noiseless profile $p_{\text{nl}}(n)$ and the reference profile $p_{\text{ref}}(n)$); and $e_s$ is the error caused by noise, due to the limited signal strength produced by the sequence (visible as a random oscillation of the measured $T_1$ values, $p(n)$, around the k-space filtered noiseless $T_1$ values, $p_{\text{nl}}(n)$). In the optimization of Eq. (13), $e_a$ is countered by the first term (Eq. [14]); $e_f$ is reduced by the second term (Eq. [15]); and $e_s$ is reduced by the third term (Eq. [16]). These errors are different for each set of relaxation values.

2.5 T1 in model agarose phantoms and human knee joint

We use five agarose tubes with concentrations of 3%, 4%, 5%, 6%, and 8% as phantoms. The MRI scans have a voxel size of $0.8 \times 0.8 \times 4$ mm (HR uses $0.4 \times 0.4 \times 4$ mm), with a FOV of $200 \times 200 \times 96$ mm. We repeated the agarose gel model phantom measurements 4 times on 4 different days to evaluate repeatability and stability. We scanned 5 healthy volunteers, with a mean age of 35 and SD = 6.4 years old. The MRI scans have a voxel size of $0.7 \times 0.7 \times 4$ mm (HR uses $0.35 \times 0.35 \times 4$ mm), with FOV of $180 \times 180 \times 96$ mm. This study was approved by the institutional review board of New York University Langone Health and was compliant with the health insurance portability and accountability act. All volunteers provided their consent before MRI scanning.
2.6 Image reconstruction, fitting, and evaluation

The image reconstruction is performed when k-space data are acquired from the MRI scanner. The 3D volume for each TSL is separated into 2D slices by applying fast Fourier transform in the readout direction; each slice is reconstructed with SENSE, which minimizes

$$\hat{\mathbf{q}} = \arg\min_{\mathbf{x}_q} \| \mathbf{y}_q - \mathbf{E} \mathbf{B} \mathbf{x}_q \|_2^2,$$  

(20)

where $\mathbf{x}_q$ is a complex-valued vector that represents an image with TSL $t_q$, with size $N_x \times N_z$, with $N_y$ being the image size in the y-axis and $N_c$ the size in the z-axis. The vector $\mathbf{y}_q$ represents the captured k-space with size $N_y \times N_z$, where $N_c = 15$ is the number of coils. Matrix $\mathbf{B}$ contains the coil sensitivities and phase compensation; and $\mathbf{E}$ is the Fourier that transforms of all sensitivity-weighted images. The $\| \mathbf{e} \|_2^2$ is the squared $l_2$-norm or Euclidean norm of $\mathbf{e} = \mathbf{y}_q - \mathbf{E} \mathbf{B} \mathbf{x}_q$.

The $T_{1p}$ fitting is performed using mono-exponential models given by

$$f(q, n) = a(n) \exp \left(-\frac{t_q}{p(n)}\right),$$  

(21)

where $a(n)$ is the complex-valued amplitude at the voxel $n$, and $p(n)$ corresponds to the $T_{1p}$ values. For the fitting, we used a shallow neural network, previously used in Zibetti et al. This neural network performed similarly to nonlinear least-squared fitting (the details of the architecture and training of the neural network can be found in Zibetti et al.). To estimate the SD of the noise and the respective SNR or acquired images, we use the Marchenko–Pastur Principal Component Analysis method from Veraart et al. for in the entire volume with all TSLs.

The quality of $T_{1p}$ mapping is evaluated in terms of the mean of normalized absolute difference (MNAD), denoted as

$$\text{MNAD(ROI)} = \frac{\text{mean}_{n \in \text{ROI}} \left( \frac{|p(n) - p_{\text{ref}}(n)|}{|p_{\text{ref}}(n)|} \right)}{\text{mean}_{n \in \text{ROI}} \left( |p_{\text{ref}}(n)| \right)},$$  

(22)

In the simulated performance tests, the reference, $p_{\text{ref}}$, are the ground-truth values. For model agarose phantoms and healthy volunteers, the ground truth is unknown: we used a MAPSS sequence, named MAPSS REF, with VPS = 64 (instead of 128 or 256 as the other comparing sequences) and larger Trec (2428 ms instead of 1110 or 340 ms) as a reference method. The reference is an 18-min scan with the highest SNR and minimal filtering effects when compared with any other scans in this study. We also computed the histograms to observe the distribution of the measured $T_{1p}$ values. Independent histograms for each agarose gel concentration are shown in Figures S6 to S10.

Note that the MTFs cause FE, which is different for each TSL and each different relaxation parameter set. We computed the predicted full-width at half maximum (FWHM) of their corresponding point spread functions to evaluate numerically (shown in voxel numbers) the loss of detail caused by the FE.

2.7 Compared sequences

We applied the optimization of the VFA with three different sequences: MAPSS, MPGRE-WR, and standard MPGRE. For MPGRE-WR, the model with imperfect Mz reset pulse from Eq. (12), using $c = 0.05$ was considered in this work. We noticed that our implemented Mz reset pulse was leaving a residual Mz magnetization close to 5%. Because the original MPGRE-WR corrects $T_1$ contamination by using postprocessing, we modified it to also account for imperfect Mz reset pulse, named MPGRE-WR C2 (see comparisons regarding MPGRE-WR postprocessing correction in Tables S5 and S6 and Figure S10). However, synthetic evaluations of MPGRE-WR assumed a perfect Mz reset pulse. The optimization of the variable flip angles (OVFA) offers flexibility regarding the optimization purpose, weighting it according to our desired purpose. The purpose of each tested OVFA method is listed in Table S1, as well as their weighting parameters ($\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5$) and $\mathbf{m}_{\text{ref}}$ and $\mathbf{a}_{\text{ref}}$ values used for optimization.

The faster OVFA setups, as shown in Table 1 (with name FAST), use a smaller Trec and higher VPS, which usually leads to more loss of quality. In this case, OVFA should minimize these problems.

The MPGRE is the only sequence that can use Trec equal to zero. This new configuration, denoted as MPGRE-OVFA ZRT, is achievable only because MPGRE does not use an Mz reset pulse, so it can exploit the remaining Mz of previous shots. In this case, we use OVFA for three different purposes: (1) to improve SNR, (2) to improve flatness as in Johnson et al. and Li et al., and (3) to improve speed, using an undersampling factor (R) of 2. This sequence uses an undersampling pattern learned with BASS for SENSE reconstructions.

We also use the MPGRE-OVFA ZRT to obtain $T_{1p}$ mapping with improved spatial resolution, using 4 times the in-plane resolution (2-times horizontal and 2-times vertical). This sequence is denominated as MPGRE-OVFA ZRT HR, and it is used to illustrate the potential of optimized VFA for HR $T_{1p}$ mapping.
| Sequence FA       | Parameters for Each TSL or PC | VPS | S | Trec (ms) | D | Time (min) | Total Time (min) | FWHM | Evaluation | Sim. Phantom | Phantom | Sim. Volunteer | Volunteer |
|-------------------|-------------------------------|-----|---|-----------|---|------------|------------------|------|------------|-------------|---------|----------------|-----------|
| MAPSS REF         |                               | 64  | 96| 2428      | 0 | 4.5        | 18               | 1.0  | 1.0        | 34.1        | 35.9    | 15.9           | 17.2      |
| MAPSS             |                               | 128 | 48| 1110      | 0 | 1.5        | 6                | 1.0  | 1.0        | 14.2        | 12.7    | 6.5            | 7.0       |
| MAPSS-OVFA        |                               | 128 | 48| 1110      | 0 | 1.5        | 6                | 1.3  | 1.3        | 25.0        | 22.7    | 11.5           | 12.2      |
| FAST MAPSS-OVFA   |                               | 256 | 24| 340       | 0 | 0.75       | 3                | 2.0  | 2.0        | 8.8         | 6.7     | 4.0            | 4.5       |
| MPGRE-WR C2       |                               | 128 | 48| 1110      | 0 | 1.5        | 3                | 1.0  | 1.0        | 18.1        | 17.1    | 8.4            | 9.6       |
| MPGRE-WR-OVFA     |                               | 128 | 48| 1110      | 0 | 1.5        | 3                | 1.3  | 1.0        | 28.9        | 27.7    | 13.5           | 15.8      |
| FAST               |                               | 256 | 24| 340       | 0 | 0.75       | 1.5              | 1.3  | 1.0        | 14.0        | 14.6    | 7.4            | 10.6      |
| MPGRE-WR-OVFA     |                               | 128 | 48| 1024      | 3 | 1.5        | 3                | 1.2  | 1.0        | 27.3        | 28.0    | 12.9           | 14.8      |
| MPGRE-CFA         |                               | 128 | 48| 1024      | 3 | 1.5        | 3                | 1.3  | 1.0        | 31.5        | 32.2    | 14.9           | 16.9      |
| MPGRE-OVFA        |                               | 128 | 48| 1024      | 3 | 1.5        | 3                | 1.3  | 1.0        | 23.0        | 23.6    | 10.6           | 12.5      |
| FAST MPGRE-OVFA   |                               | 256 | 24| 180       | 3 | 0.75       | 1.5              | 1.3  | 1.0        | 15.4        | 14.3    | 7.4            | 9.6       |
| MPGRE-OVFA ZRT FLAT |                           | 128 | 48| 0         | 7 | 0.7        | 1.4              | 1.0  | 1.0        | 15.4        | 14.3    | 7.4            | 9.6       |
| MPGRE-OVFA ZRT SNR |                             | 128 | 48| 0         | 7 | 0.7        | 1.4              | 1.3  | 1.0        | 19.5        | 17.4    | 9.0            | 11.3      |
| MPGRE-OVFA ZRT FAST |                            | 128 | 24 R = 2 | 0 | 7 | 0.35      | 0.7              | 1.3  | 1.0        | 13.6        | 11.2    | 6.4            | 7.1       |
| MPGRE-OVFA ZRT HR  |                               | 128 | 96| 0         | 7 | 1.8        | 3.6              | 1.3  | 1.0        | 9.1         | 8.9     | 5.3            | 5.3       |

Note: Common parameters are two TSLs (1 ms, 35 ms), and TR of 6 ms (except MPGRE-OVFA ZRT HR, which uses TR of 8.6 ms). For each sequence, it is specified as views per shot (VPS), the number of acquired shots (S), T1 recovery time (Trec), dummy shots (D), the time for each TSL (Time), which does not include phase cycling time, and the total time of the acquisition (Total Time), which include all TSLs and phase cycling acquired. Abbreviations: CFA, constant flip angle; HR, high resolution; MNAD, mean of normalized absolute difference; MAPSS, magnetization-prepared angle-modulated partitioned k-space spoiled gradient echo snapshots; MPGRE, magnetization-prepared gradient echo; MPGRE-WR, magnetization-prepared gradient echo (with magnetization reset); OVFA, optimization of the variable flip angle; REF, reference; VPS, view per shots.
2.7.1 Parameters for the optimization of the VFA

We assume our target object consists of nine sets of relaxation parameters. They are generated by a $3 \times 3$ grid of $T_1$ relaxation (900, 1200, and 3000 ms) and $T_{1p}$ relaxation (13, 32, 58 ms). We assume the following $T_2^*$ values (12, 30, and 55 ms) that are paired with the $T_{1p}$ values shown. The weighting parameters ($\lambda_A, \lambda_F, \lambda_S, \lambda_R$) used in the optimization were systematically selected to minimize the predicted MNAD in the simulated case, adjusted to obtain a maximum FWHM of 1.3. The constant values of $m_{\text{ref}}$ were also chosen with the same purpose. The used values are given in Table S1.

2.8 MRI scanning specifications

The data were acquired on a Prisma 3T scanner (Siemens Healthcare, Erlangen, Germany) with a vendor-provided 1-transmit/15-receive knee coil (QED, Mayfield, Ohio, USA). The 3D volume has 24 slices with a data matrix size of $256 \times 256$ voxels (HR uses $512 \times 512$ voxels). The linear readout (frequency encoding) direction acquires 256 samples (HR uses 512 samples), with $N = 256 \times 24$ phase-encoding positions in the fully sampled case (HR uses $N = 512 \times 24$). The number of shots (Figure 1) to acquire all data at each TSL is found in Table 1 for each sequence. We use binomial pulses for water excitation only.\(^\text{27,46}\) Also, the number of shots (S), dummy shots (D), VPS, and Trec are included in Table 1, and $\tau = TR/2$.

We acquire two TSLs of 1 and 35 ms, following Zibetti et al.\(^\text{33}\) The MAPSS sequences always use double the total acquisition time for the same configuration, due to phase-cycled acquisitions.\(^\text{28}\)

3 RESULTS

The average numerical results of all different sequences are provided in Table 1 (see results for each scanned phantom or volunteer in Tables S3 and S4, and for MPRGE-WR postprocessing correction in Tables S5 and S6). Some resulting FAs are plotted in Figure S5. Note that all
three sequences improved SNR and reduced MNAD when OVFA was used, primarily because the optimization purpose was to improve SNR. The faster versions used different parameters that halve the total acquisition time, usually causing degradation in the performance. This illustrates that OVFA can help to make a sequence faster and/or more precise.

Note that some systematic error (due to $T_1$ contamination or other factors) in MPGRE and MPGRE-WR was reduced with OVFA, which indicates that these sequences were also made more accurate with OVFA. The correction of systematic error can easily be seen in the histograms of the phantoms in Figures 6 and 7 and Figures S7, S8, and S10.

The FE, partially measured by the MTF, caused a small loss of detail. The FWHM of the point spread functions of each MTF for each relaxation parameter set was measured, and their average is given in Table 1 for the first and the second TSL, respectively. MAPSS has the same FEs for all TSLs, but MPGRE and MPGRE-WR have more FE in the first TSL. The high-frequency amplification that usually happens with long TSLs was very minor in our experiments. The sequences optimized for maximum flatness achieved lower FWHM, showing more detail in the $T_1\rho$ maps.

In Figure 5, the SNR improvements in MAPSS-OVFA can be easily seen, compared with MAPSS. The histogram of the agarose phantoms using MAPSS-OVFA shows the five peaks related to each tube with concentrations of 3%, 4%, 5%, 6%, and 8%. Figure S6 shows the histograms of the agarose gel separated for each concentration. In the ordinary MAPSS and FAST MAPSS OVFA, the noise spreads the peaks shown in the histograms; for example, the peaks related to 5%, 6%, and 8% agarose are seen as only one wider peak.

In Figure 6, we can see the SNR and accuracy improvement of OVFA in MPGRE-WR, when compared with the regular MPGRE-WR version from Johnson et al. The histogram of the agarose phantoms of the MPGRE-WR-OVFA is much closer to the reference. Figure S7 shows the histograms of the agarose gel separated for each concentration. In the ordinary MPGRE-WR, there is an overestimation of the large $T_1\rho$ values that were not completely corrected by the postprocessing step. This error is caused...
**Figure 7** Illustration of the performance of the optimization of the variable flip-angles (OVFA) with the magnetization-prepared gradient-echo (MPGRE) sequence. (A,B) Histograms for the model phantom and human knee joint. (C,G) Reference $T_1\rho$ maps for model phantoms (Slice 10, Phantom 3) and human knee joints (Slice 5, Volunteer 4). (D,H) The $T_1\rho$ maps of the MPGRE-OVFA sequence. (E,I) The $T_1\rho$ maps of the ordinary MPGRE-CFA sequence. (F,J) The $T_1\rho$ maps of the FAST MPGRE-OVFA for model phantom and human knee joint. MNAD, mean of normalized absolute difference.

**Figure 8** Illustration of the performance of the optimization of the variable flip-angles (OVFA) with the magnetization-prepared gradient-echo (MPGRE) with zero recovery time (ZRT) sequences. (A,B) Histograms for model phantoms and human knee joints. (C,G) Reference $T_1\rho$ maps for model phantoms (Slice 10, Phantom 3) and human knee joints (Slice 7, Volunteer 3). (D,H) The $T_1\rho$ maps of the version with more SNR. (E,I) The $T_1\rho$ maps of the version with more flatness. (F,J) The $T_1\rho$ maps of the version with undersampling for model phantoms and human knee joints. MNAD, mean of normalized absolute difference.
by $T_1$ contamination and imperfect Mz reset pulse (see Figure S10 for histograms of the agarose gel separated for each concentration for different postprocessing corrections on MPGREG-WR). The OVFA was able to better compensate for these imperfections in the pulse sequence.

In Figure 7 we can see primarily the improvement in accuracy with OVFA in MPGREG when compared with the version with CFA. The histogram of the agarose phantoms of the MPGREG-OVFA is much closer to the reference (see Figure S8 for histograms separated for each agarose gel concentration). In the ordinary MPGREG-CFA, there is a small underestimation of the large $T_{1p}$ values, which was improved with OVFA. The MPGREG is the sequence with the best SNR of all. In all cases, the agarose gel peaks are distinct.

In Figure 8 we can see visually the quality of MPGREG-OVFA ZRT when the optimization targets are more SNR, more flatness (fewer FE), or when it is combined with undersampling ($R = 2$) for more speed (see Figure S9 for histograms separated for each agarose gel concentration).

In Figure 9, we illustrate the performance of the MPGREG-OVFA ZRT HR, comparing the HR $T_{1p}$ maps with MAPSS. The improvement in details because of the better resolution can make $T_{1p}$ mapping useful in applications such as cartilage repair, which requires investigation of smaller structures.

### 4 | DISCUSSION AND CONCLUSION

The flexibility of OVFA helped to improve the quality of all three $T_{1p}$ mapping sequences. Perhaps the important target improvement was the SNR, which is relevant in the MAPSS because of the chosen voxel size, because
this sequence is already the most accurate of all three (see Figure 5). In MPGRE and MPGRE-WR, in addition to SNR, the improvement in accuracy was also very important, correcting the overestimation of large T1, values in MPGRE-WR and underestimation in MPGRE (see Figures 6 and 7). The results show that if sources of inaccuracy such as the delay τ (Figure 1; the delay between the MP and the first FA) and imperfect Mz reset pulse are included in the SE model, then the OVFA can reduce its deteriorating effects by simply finding FAs that account for that, improving the accuracy of the pulse sequence. No postprocessing step such as the ones used in Johnson et al.26 is necessary (see Tables S5 and S6 for more on this correction). Other potential problems such as inhomogeneity in the B1 field48 can be also considered in future studies.

In this study, we are interested in the knee joint, but if the application of interest includes areas with high-frequency details and edges, such as the cartilage49,50 (see results from Table S2 for MNAD of the cartilage region and Table S8 for mean T1, values of all 5 volunteers in their cartilage regions; the cartilage regions were manually segmented in each slice of each volunteer), then it is recommended to configure the optimization weights of OVFA to find a good balance between reducing filtering effects and increasing SNR. As discussed previously, the user can adjust the optimization to improve the aspect of a particular sequence that needs improvement by changing the weighting parameters and mref in the cost function (see Table S1 for chosen values for this study). We illustrate some examples using MPGRE-OVFA ZRT sequences (see Figure 8). However, there is substantial room for improvement in all aspects of the sequence, and in the end, maximizing one aspect comes at the cost of reducing others. For example, increasing SNR may reduce the maximum flatness that can be achieved (see bold-letter results in Table 1).

Note that the methods presented in Johnson et al.26 and Li et al.30 are also optimized approaches. The proposed approach can obtain nearly the same results if we use only one set of relaxation parameters (K = 1), and the weighting parameters are adjusted to a maximum flatness of the SE. In this sense, the proposed approach increases the flexibility of the optimization target and expands the OVFA to standard MPGRE (without Mz reset).

Another interesting aspect is making the sequence faster by using a combination of parameters that reduce the scan time. These changes usually cause a reduction in SNR and accuracy, but the OVFA can minimize this loss, achieving similar performance as a slower sequence. If time is still of concern, one can still include undersampling, particularly data-driven learned undersampling18–22 and deep learning reconstructions.51–55 Assuming fully sampled data are acquired, the reduction of scan time happens here because of acquiring more data per unit of time. The SNR efficiency of each sequence can be found in Table S7, which indicates that OVFA can make the sequences in a more SNR-efficient manner.

With OVFA, one can use previously unthinkable parameters in these sequences. One example is the MPGRE ZRT (zero T1 recovery time). The MPGRE-OVFA ZRT is very efficient because it does not have any idle time, as the others. Fully sampled data for T1, mapping can be acquired in just 1.4 min with the tested configuration (compared to 6 min with MAPSS, which is more than 4 times faster) with good SNR. As an illustration of the possibilities of OVFA with this sequence, we were able to produce T1, maps with a voxel size 4-times smaller with MPGRE-OVFA ZRT HR, obtaining fully sampled HR T1, maps in less than 4 min.

The proposed OVFA approach was tested with TSLs of 1 ms and 35 ms, with a range of T1, values between 10 ms and 75 ms as found in the knee joint. Other applications with different anatomies, TSLs, and T1, values may benefit from the proposed approach. However, the improvement in accuracy, precision, and speed that can be obtained will depend on the particular application.

There are several aspects to be investigated and improved in the proposed optimization approach. Here the weighting parameters were chosen manually by a systematic search that reduces MNAD in the simulated case. However, the automated procedure can perhaps obtain better choices, such as in Refs. 56–58. The matrices used here were relatively simple (see Figures S1–S4). Other choices could potentially obtain better results.

Finally, we believe that this optimization approach can be extended to other similar sequences, such as balanced SSFP,25,59,60 other kinds of contrast like T1 and T2 mapping,61,62 and different magnetic field strengths.63 The OVFA can make MP sequences with VFA more efficient, opening the possibility to achieve more accuracy, precision, speed, or improved spatial resolution in quantitative MRI.

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CONFLICT OF INTEREST
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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher’s website.

TABLE S1. Comparison of different magnetization-prepared $T_1$ pulse sequences with their weighting parameters ($\lambda_A, \lambda_F, \lambda_S, \lambda_R$), and $m_{\text{ref}}$ and $\alpha_{\text{ref}}$ values, used for optimization.

TABLE S2. Tested sequences with human volunteers comparing mean of normalized absolute difference results at the entire knee joint and the cartilage region. Cartilage was manually segmented in all slices of volunteers, including patellar, medial, and lateral cartilage.

TABLE S3. Summary of results from repeated model agarose gel phantom scans. Model phantoms were manually segmented in all slices of volunteers, including patellar, medial, and lateral cartilage.

TABLE S4. Summary of results for knee joint for 5 different healthy subjects.

TABLE S5. Comparing different postprocessing corrections for magnetization-prepared gradient-echo with magnetization reset (MPGRE-WR) on agarose gel phantoms. MPRGE-WR C1 accounts for $e_r$ and $(1 - e_r)$ in Eqs. (3) and (4). MPRGE-WR C2 accounts for $T_1$ contamination and imperfect Mz reset, using Eq. (12). The corrections follow the same postprocessing as proposed in Johnson et al.26

TABLE S6. Comparison of different postprocessing corrections for magnetization-prepared gradient-echo with magnetization reset (MPGRE-WR) on 5 healthy volunteers.

TABLE S7. SNR versus SNR efficiency (SNR/sqrt(min)) of each tested method.

TABLE S8. Mean $T_1$ values of all 5 healthy volunteers in the manually segmented cartilage regions and its difference concerning the reference method. The last column shows the minimum and maximum differences.

FIGURE S1. Illustration of the composition of $m_k(\alpha)$ for a signal evolution (SE) with the triplet ($T_1[k] = 3000 \text{ ms}$, $T_2'[k] = 50 \text{ ms}$, $T_1[p][k] = 58 \text{ ms}$). This example has VPS = 128, $D = 2$ (dummy shots), $S = 4$ (acquired shots), $S + D = 6$ (total shots), and $T_{\text{TLS}} = 2$. The matrix $A$ computes the finite difference between all pairs of $M_{xy}(k, p, s, 1)/e^{-\frac{\alpha}{T_{\text{TLS}}}}$ and $M_{xy}(k, q, s, 1)/e^{-\frac{\alpha}{T_{\text{TLS}}}}$, where $t_p$ and $t_q$ are two different spin-lock times (TSLs). This is done for the first elements for all S acquired shots (not for the dummy shots). This leads to several columns that are $S$ times the number of combinations of $T_{\text{TLS}}$ items (2 at a time).

FIGURE S2. Illustration of the composition of the matrix $F$ and how it performs on $m_k(\alpha)$. Example of a signal evolution (SE) with the triplet ($T_1[k] = 3000 \text{ ms}$, $T_2'[k] = 50 \text{ ms}$, $T_1[p][k] = 58 \text{ ms}$). This example has VPS = 128, $D = 2$ (dummy shots), $S = 4$ (acquired shots), $S + D = 6$ (total shots), and $T_{\text{TLS}} = 2$. The matrix $F$ computes the finite difference on the SE inside the shot, for $1 \leq ns \leq VPS$, and it is repeated for all TSLs and all S acquired shots (except dummy shots). This leads to a block matrix, consisting of finite differences blocks.

FIGURE S3. Illustration of the composition of the matrix $S$ and how it performs on $m_k(\alpha)$. Example of a signal evolution (SE) with the triplet ($T_1[k] = 3000 \text{ ms}$, $T_2'[k] = 50 \text{ ms}$, $T_1[p][k] = 58 \text{ ms}$). This example has VPS = 128, $D = 2$ (dummy shots), $S = 4$ (acquired shots), $S + D = 6$ (total shots), and $T_{\text{TLS}} = 2$. In this work, $S$ has ones on the positions related to $M_{xy}(k, 1, s, 1)/e^{-\frac{\alpha}{T_{\text{TLS}}}}$, the first element of the first spin-lock time (TSL), for all $S$ acquired segments, except the dummy segments.

FIGURE S4. Illustration of the composition of the matrix $S$ and how it performs on $m_k(\alpha)$. Example of a signal evolution (SE) with the triplet ($T_1[k] = 3000 \text{ ms}$, $T_2'[k] = 50 \text{ ms}$, $T_1[p][k] = 58 \text{ ms}$). This example has VPS = 128, $D = 2$ (dummy shots), $S = 4$ (acquired shots), $S + D = 6$ (total shots), and $T_{\text{TLS}} = 2$. In this work, $S$ has ones on the positions related to $M_{xy}(k, 1, s, 1)/e^{-\frac{\alpha}{T_{\text{TLS}}}}$, the first element of the first spin-lock time (TSL), for all $S$ acquired segments, except the dummy segments.

FIGURE S5. Some of the flip angles (FAs) used in the experiments reported in Table 1, comparing optimization of the variable flip angles (OVFA) and standard choices for MAPSS (magnetization-prepared angle-modulated partitioned k-space spoiled gradient-echo snapshots),28 MPRGE-WR (magnetization-prepared gradient-echo with magnetization reset),26 or the constant FA for magnetization-prepared gradient echo (MPGRE). The FAs for the MPRGE-WR OVFA with the perfect Mz reset model (Eq. 2) and with the imperfect Mz reset model (Eq. 12, with $c = 0.05$) can be compared in this figure. The FAs for the MPRGE OVFA with zero recovery time (ZRT) sequences are also shown, comparing the choice for more SNR (MPGRE OVFA ZRT SNR) against the choice of less filtering effects (MPGRE OVFA ZRT FLAT).

FIGURE S6. Individualized histograms of the agarose gel phantoms (3%, 4%, 5%, 6%, and 8%) for the MAPSS methods reported in Table 1.

FIGURE S7. Individualized histograms of the agarose gel phantoms (3%, 4%, 5%, 6%, and 8%) for the MPRGE-WR methods reported in Table 1.

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FIGURE S8 Individualized histograms of the agarose gel phantoms (3%, 4%, 5%, 6%, and 8%) for the MPGRE methods reported in Table 1.

FIGURE S9. Individualized histograms of the agarose gel phantoms (3%, 4%, 5%, 6%, and 8%) for the MPGRE ZRT methods reported in Table 1.

FIGURE S10. Individualized histograms of the agarose gel phantoms (3%, 4%, 5%, 6%, and 8%) for the MPGRE-WR with different corrections. MPGRE-WR C1 accounts for $e_\tau$ and $(1 - e_\tau)$ in Eqs. (3) and (4). MPGRE-WR C2 accounts for $T_1$ contamination and imperfect Mz reset, using Eq. (12). The corrections follow the same postprocessing as proposed in Johnson et al.,\textsuperscript{26} using an expected $T_1$ value of 1200 ms, the same used in the FA optimization proposed by Johnson et al.\textsuperscript{26}

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