Published in final edited form as:

Magn Reson Med. 2018 June ; 79(6): 2978–2985. doi:10.1002/mrm.26964.

Fast Quantitative Parameter Maps without Fitting: Integration Yields Accurate Mono-exponential Signal Decay Rates

Ruitian Song¹, Ralf B. Loeffler¹, Joseph L. Holtrop¹, Mary B. McCarville¹, Jane S. Hankins², and Claudia M. Hillenbrand¹

¹Department of Diagnostic Imaging, St. Jude Children's Research Hospital, Memphis, TN, USA

²Department of Hematology, St. Jude Children's Research Hospital, Memphis, TN, USA

Abstract

Purpose—To develop a computationally fast and accurate algorithm for mono-exponential signal modelling and validate the new technique in the context of R_2^* mapping for iron overload assessment.

Methods—An algorithm is introduced that directly calculates R_2^* values from a series of images based on integration of the mono-exponential signal decay curve. The algorithm is fast, because fitting is avoided and only arithmetic computations without iterations are applied. Precision and accuracy of the method is determined in comparison to the conventional log-linear (LL), least-squares-based Levenberg–Marquardt (NLM), and squared nonlinear Levenberg–Marquardt (SQNLM) methods, which rely on iterative curve fitting.

Results—In simulations, the signal integration based method consistently had the same or better accuracy than the LL, NLM, and SQNLM algorithms for R_2^* values ranging from 50 s⁻¹ to 1200 s⁻¹. In phantoms and *in vivo* (12 participants), this method was robust over a wide range of R_2^* values and SNRs. Computation times were about 100, 1460, and 930 times faster than those of the LL, NLM, and SQNLM methods, respectively.

Conclusions—The fast signal integration method accurately calculates R_2^* maps. It has the potential to replace conventional, mono-exponential fitting methods for quantitative MRI such as R_2^* parameter mapping.

Keywords

Fast R_2^*/T_2^* mapping; relaxivity fitting; apparent transverse relaxation rate; gradient echoes (GRE); iron overload

Introduction

Non-invasive quantification of MR tissue and material properties (e.g., via T_1 , $T_{1\rho}$, T_2 , T_2^* , and diffusion) requires robust mono-exponential signal decay fitting. Over the past decade,

Correspondence to: Claudia M. Hillenbrand, PhD, Department of Diagnostic Imaging, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105-3678, USA, Phone: (901) 595-4118, claudia.hillenbrand@stjude.org.

Conflict of Interest: The authors have no conflict of interest to declare.

quantitative parameter mapping has been increasingly applied to modern diagnostic imaging. For example, measurement of apparent transverse relaxation rate R_2^* (often expressed as its reciprocal, the relaxation time T_2^*) has been reliably used for quantitative assessment and clinical interpretation of iron deposition in the liver (1–4), heart (5,6), brain (7), and spleen (8). R_2^* maps are usually obtained from rapid imaging sequences such as multi-echo gradient-recalled echo (mGRE), which can be acquired within a single breath-hold.

Because R_2^* based iron quantification became such an active field of research, numerous approaches have been proposed to quantify R_2^* maps thereby focusing on improving fitting accuracy and computational speed. Traditionally, R_2^* maps are obtained by fitting exponential curves, most commonly using the non-linear least-square-based Levenberg–Marquardt (NLM) method(1,9), or log-linear (LL) method (2,5,10). Miller and Joseph (11) proposed the fitting of squared signals to overcome the effect of non-central chi noise for images with low signal-to-noise ratios (SNRs), and Feng et al. more recently used this approach in NLM (SQNLM) specifically for R_2^* fitting in iron overloaded organs (12). Non-fitting approaches have also been used to quantify R_2^* maps: an autoregressive moving average (ARMA) approach has been evaluated to generate quantitative R_2^* maps of the liver and heart (13,14), and auto-regression on linear operations (ARLO) has been proposed to increase the computational speed of T_2^* estimations (15). Further, truncation models have been proposed to mitigate another shortcoming of R_2^* mapping: for high R_2^* values the magnitude signal rapidly decays and reaches a positive mean value for the later echoes; this non-zero mean value of the noise can cause a bias in R_2^* estimation. To avoid this bias truncation models discard echoes below a certain SNR threshold (9,15–17).

All established fitting methods require substantial calculation time and the fit may fail in some instances. In this study, we propose the fast calculation of R_2^* maps from a series of mGRE images based on signal integration. To evaluate the proposed signal integration method, we tested its robustness and accuracy specifically for R_2^* mapping in hepatic iron overload, and compared its performance with those of the conventional LL, NLM, and SQNLM algorithms in simulations, phantoms, and patients with hepatic iron overload.

Methods

Mono-exponential Signal Integration Algorithm

In mGRE, the true signal $s(t)$, acquired at echo time t , can be modeled by using the mono-exponential function

$$s(t) = s_0 e^{-R_2^* t}, \quad [1]$$

where s_0 represents the signal at the start of decay, which is a function of sequence parameters such as the flip angle, T_f , and repetition time. In mGRE, $s(t)$ is acquired discretely at certain time points TE_n ($n = 1, 2, 3, \dots, N$). Using Eq. [1], the integral a of $s(t)$ over t from TE_1 to TE_N can be derived by(15)

$$a = \int_{TE_1}^{TE_N} s(t) dt = [s(TE_1) - s(TE_N)]/R_2^*, \quad [2]$$

and thus R_2^* can be calculated as

$$R_2^* = [s(TE_1) - s(TE_N)]/a. \quad [3]$$

However, the measured signal $m(t)$ is always compromised by noise $n(t)$. This can be expressed as

$$m(t) = s(t) + n(t) = [s_R(t) + n_R(t)] + i[s_I(t) + n_I(t)]. \quad [4]$$

where $s(t)$ and $n(t)$ are complex data, and subscripts R and I represent the real and imaginary parts of the data. $n_R(t)$ and $n_I(t)$ represent random Gaussian distributed noise with standard deviation σ . However, noise in a magnitude image follows a Rician distribution causing $n(t)$ to have a non-zero mean bias (18,19). This bias accumulates during integration and leads to substantial overestimation of a and consequent underestimation of R_2^* when Eq. [3] is used. The so-called power image P introduced by Miller and Joseph (11) can be used to address this issue:

$$P(t) = m(t)^2 = [s_R(t) + n_R(t)]^2 + [s_I(t) + n_I(t)]^2. \quad [5]$$

The average of the power signal is therefore(12):

$$\bar{P}(t) = s_0^2 e^{-2R_2^* t} + 2\sigma^2, \quad [6]$$

$2\sigma^2$ is the average value of P over a region of interest (ROI) that is known to have no signal (i.e. the background). Equation [6] is basically the square form of Eq. [1] with noise contribution. Therefore, by using the same steps to derive Eq. [3], we obtain

$$R_2^* = \frac{P(TE_1) - P(TE_N)}{2A - 2\sigma^2(TE_N - TE_1)} \quad [8]$$

where A is the integral of the power signal $P(t)$ over t from TE_1 to TE_N .

The signal integral A can be obtained by numerical integration over the measured signal. However, the signal is acquired discretely at certain TE_n values with given echo spacing. Because the echo spacing cannot be infinitely small, integral A carries an error. Still, A can be accurately determined by using the information that the true signal follows an exponential decay. If M new interpolated points are inserted to generate a total of $M+2$ points (interpolated and original) between TE_n and TE_{n+1} , the m th ($m = 0, 1, 2, \dots, M+1$) point can be represented by

$$P(TE_{n,m}) = P(TE_n)^{\frac{M-m+1}{M+1}} P(TE_{n+1})^{\frac{m}{M+1}}. \quad [9]$$

Signal integration between $TE_{n,m}$ and $TE_{n,m+1}$ can be approximated as (20)

$$A_{n,m} = \frac{\Delta TE_n}{M+1} P(TE_{n,m}), \quad [10]$$

where $TE_n = TE_{n+1} - TE_n$. In case of equidistant echo spacing, $TE_n = TE$. Summing $A_{n,m}$ over n and m , we obtain the signal integral from TE_1 to TE_N as

$$A = \sum_{n=1}^{N-1} \frac{\Delta TE_n}{M+1} \sum_{m=0}^M P(TE_n)^{\frac{M-m+1}{M+1}} P(TE_{n+1})^{\frac{m}{M+1}}. \quad [11]$$

By using this interpolation integration technique, all interpolated points will be exactly on the signal decay curve between 2 measured points. Therefore, true integration can be achieved if sufficient interpolated points are used without increasing the number of measured points. We used exponential interpolation in this study as indicated by Eq. [9]. However, the interpolation could also be performed by using a curve generated by a two-point exponential fit, but the computation cost is higher. In contrast, using numerical integration methods without proper interpolation yields only an approximation of the integral between 2 measured points.

Substituting Eq. [11] into Eq. [8], we obtain

$$R_2^* = \frac{P(TE_1) - P(TE_N)}{2 \sum_{n=1}^{N-1} \frac{\Delta TE_n}{M+1} \sum_{m=0}^M P(TE_n)^{\frac{M-m+1}{M+1}} P(TE_{n+1})^{\frac{m}{M+1}} - 2\sigma^2(TE_N - TE_1)} \quad [12]$$

Equation [12] is valid for both, equidistant and non-equidistant echo spacing situations.

It should be noted that the integral of Eq. [2] was approximated by the Riemann sum for a simplified presentation of Eqs. [10] - [12]. Other methods, such as the midpoint integral interpolation, approximate the integral more accurately for smaller values of M . All

experimental results in the manuscript were obtained by using the midpoint integral interpolation and respective Eqs. [10*] - [12*]:

$$A_{n,m} = \frac{\Delta TE_n}{M+1} [P(TE_{n,m})P(TE_{n,m+1})]^{1/2}, \quad [10*]$$

$$A = \sum_{n=1}^{N-1} \frac{\Delta TE_n}{M+1} \sum_{m=0}^M P(TE_n)^{\frac{2M-2m+1}{2M+2}} P(TE_{n+1})^{\frac{2m+1}{2M+2}}. \quad [11*]$$

$$R_2^* = \frac{P(TE_1) - P(TE_N)}{2 \sum_{n=1}^{N-1} \frac{\Delta TE_n}{M+1} \sum_{m=0}^M P(TE_n)^{\frac{2M-2m+1}{2M+2}} P(TE_{n+1})^{\frac{2m+1}{2M+2}} - 2\sigma^2(TE_N - TE_1)}. \quad [12*]$$

Algorithm Implementation

The proposed technique, in the following for simplicity referred to as *Calculation of Relaxivities by Signal Integration* (CRSI), was implemented and used on mGRE data as described above. CRSI was compared with the LL, NLM, and SQNLM algorithms for R_2^* estimation. Additionally, all algorithms were implemented with noise truncation. Results compiled from complete data sets were labeled as CRSI, LL, NLM, and SQNLM, while results from incomplete, truncated data sets were denoted as tCRSI, tLL, tNLM, and tSQNLM. The noise ($2\sigma^2$) was determined based on Eq. [6] in background regions of power images on ROIs of size 5×5 voxels located on the 4 corners of all images (total of 2000 voxels for $N=20$) where no signal was present. By using this noise measurement, SNR was estimated for each voxel at each TE, and only the initial consecutive time points with $SNR > 3$ were included (15,18); however, independent of SNR the first two time points were always kept. An interpolation factor of $M = 3$ was used in this study to balance accuracy and computation speed. All simulations and images were processed in Matlab 8.6 (Mathworks, Natick, MA) on a Windows 7 (64 bit) desktop computer (Intel Xeon® CPU E5-1650 3.5GHz, 40 GB memory).

Simulation Study

Simulations were conducted to compare the accuracy of the proposed method with those of the LL, NLM, and SQNLM methods for different R_2^* values. The raw MRI signal, obtained by quadrature detection, consists of real and imaginary parts corrupted by uncorrelated Gaussian-distributed noise. The noise in magnitude images is characterized by a Rician distribution after Fourier transformation. To replicate this process, Gaussian noise was added to k-space data simulated at different TEs. Digital phantom images were created as follows:

- 1) Digital phantoms resembling cylindrical vials with true R_2^* values (true R_2^*) ranging from 50 s^{-1} to 1200 s^{-1} were created with a matrix size of 256×256 (Figure 1).

2) Using Eq. [1], images were created at different TE s (1.07–18.17 ms with an echo spacing of 0.90 ms for a total of 20 echoes) on the basis of R_2^* maps.

3) Images were Fourier-transformed into k-space, and then complex noise was added to the k-space data.

4) Final images with noise used for R_2^* estimation were obtained by inverse Fourier transformation of k-space data.

R_2^* maps were obtained from time series images with noise by using the CRSI, LL, NLM, and SQLNM methods and compared to the true R_2^* map. The accuracy of each method was assessed by the relative R_2^* error, given as $\eta = \frac{\text{mean}(R_2^* - \text{true}R_2^*)}{\text{true}R_2^*}$. The precision was evaluated

by calculating the coefficient of variation (CV) which is the standard deviation of R_2^* divided by true R_2^* .

Phantom Study

Eight cylindrical 1-L polystyrene bottles were filled with a 2% solution of agar (Sigma–Aldrich, St. Louis, MO) in water and doped with various amounts of Bionized NanoFerrite starch particles (micromod Partikeltechnologie GmbH, Rostock, Germany) to obtain a wide range of R_2^* values. Phantoms were scanned at the iso-center of a clinical 1.5T whole-body MAGNETOM Avanto MRI scanner (Siemens Medical Solutions, Malvern, PA). A single slice was acquired with field of view (FOV) = $300 \times 300 \text{ mm}^2$; matrix size = 128×128 ; slice thickness (SL) = 5 mm; and $TR = 200$ ms. TE ranged from 1.20 ms to 27.86 ms with an echo spacing of 0.86 ms, which yielded 32 echoes. To obtain images with different SNR levels, image series were acquired with different FAs (4° , 8° , and 35°) with a single average. Reference R_2^* maps were obtained by using the NLM fit on a set of images with very high SNR obtained by collecting a dataset with 320 averages, 64 echoes with TE ranging from 1.20 ms to 55.38 ms with an echo spacing of 0.86 ms, and all other parameters identical to those given above. Circular ROIs were drawn on each phantom bottle. Mean R_2^* values from each ROI were obtained for the different algorithms and compared to the phantom “reference” dataset.

In Vivo Study

MRI imaging was performed on 12 participants (2 with sickle cell anemia, 4 with thalassemia major, and 4 with acute myelocytic leukemia, all with transfusional iron overload, and 2 healthy volunteers; 8 female and 4 male, age 25.4 ± 11.9 years) by using the clinical 1.5T scanner. Informed consent was obtained from all participants. The study was approved by the institutional review board. Axial mGRE images with fat saturation were obtained in a single breath-hold. Images were acquired with the participant in a supine position, using anterior array and spine array coils with the following sequence parameters: $TR = 200$ ms; TE ranging from 1.07 ms to 18.17 ms in increments of 0.9 ms (total of 20 echoes); single transverse slice of 10 mm thickness; matrix size $128 \times (96\text{--}128)$; and FOV $280 \text{ mm} \times (285\text{--}380 \text{ mm})$, depending on the participant’s habitus. To test the robustness of each method, images were acquired with different SNRs by changing the flip angle (3° , 8° ,

15°, and 35°). ROIs were drawn to cover the whole liver, excluding major hepatic vessels (21). The same ROI was employed for all analysis techniques within individual participants.

Obtaining a reference R_2^* map for human participants is challenging, because acquiring an image set with extremely high SNR, as done in the phantoms, is not practical due to limited scan time. Reference R_2^* values are therefore taken from the image with the highest SNR (FA = 35°). Because our simulation study showed that the accuracy of R_2^* estimation methods depends on SNR_0 and R_2^* , choice of the best algorithm to obtain R_2^* reference values will depend on the SNR_0 and R_2^* for each participant. Based on simulations, a contour plot showing the best algorithm was created for a range of relevant SNR_0 and R_2^* values. Consulting the contour plot, the reference method can be selected for each participant by using the calculated SNR_0 and a preliminary R_2^* value (obtained with NLM).

Results

Simulation Study

Figure 1 shows R_2^* maps of the digital phantom obtained with the LL, NLM, SQNLM, and CRSI methods, along with the true R_2^* map that was used as input to generate the images with noise. All methods were applied without (top row) and with (bottom row) noise truncation. Figure 2 shows the corresponding error maps of Figure 1. Compared with the true R_2^* , the LL method without truncation was unsuccessful (mean error > 60%) at estimating high R_2^* values whereas the truncated tSQNLM method was inaccurate for high R_2^* values (mean error > 60%). The tCRSI method and the SQNLM method had the best overall accuracy, with mean errors of 0.74% and 0.26%, respectively, whereas the mean errors for the tLL method and the NLM method were 55.63% and 3.43%, respectively. The tCRSI and the tLL method had the best overall precision, with CVs of 2.48% and 1.82%, respectively, whereas tNLM and SQNLM had CVs of 2.72% and 4.58%, respectively.

Figure 3 shows the accuracy and precision of each method for an SNR_0 of 20, 50 and 100 at different R_2^* values. LL and tSQNLM performed poorly in the R_2^* estimation, as shown in Figure 1. Hence, they were not considered viable and not included for comparing the accuracies of the methods. Overall, tCRSI performed better than all other methods with lowest mean errors for all three SNR cases. tCRSI and NLM performed better than CRSI and tNLM, respectively. Therefore, tCRSI was only compared to tLL, NLM, and SQNLM in the following phantom and *in vivo* studies. NLM, tLL, and SQNLM perform differently well at different SNR and R_2^* values. Figure 4 illustrates the fit methods of choice with best accuracy in the clinically relevant range of SNR_0 and R_2^* values based on our simulations.

Phantom Study

For comparisons in phantoms, a reference R_2^* map was estimated by using the NLM method and high-SNR images (Average = 320, flip angle = 35°). Figure 5 compares the R_2^* maps obtained by tCRSI, NLM, tLL, and SQNLM methods at low SNR (FA = 4°) with the reference map. CRSI had the best overall accuracy, with a mean error of 3.88%, whereas the mean error was 6.88% for tLL, 10.10% for NLM, and 5.41% for SQNLM.

Figure 6 shows the robustness of each method, which was tested by comparing three image series acquired at flip angles of 4° , 10° and 35° to the reference R_2^* . For the flip angles of 4° and 35° , tCRSI delivered the closest results to the unity line as shown in the figure, while SQNLM performs better than tCRSI for the flip angle of 10° . tCRSI had the lowest mean errors (3.4%), whereas the mean error was 7.3% for tLL, 8.2% for NLM, and 4.4% for SQNLM.

In vivo Study

Figure 7 shows MRI R_2^* maps from a patient with iron overload, which were derived from a series of images acquired at a flip angle of 8° by using tCRSI, tLL, NLM, and SQNLM, along with a reference R_2^* map obtained from high-SNR images (flip angle = 35°) using the SQNLM method according to Figure 4. Although SQNLM had the lowest mean error, the R_2^* maps generated by the tCRSI, tLL, and SQNLM methods were all very similar to the reference R_2^* map (mean errors: 6.6% for tCRSI, 8.6% for tLL, and 3.8% for SQNLM). However, R_2^* was consistently overestimated by the NLM method with a mean error of 14.8%.

Figure 8 compares the R_2^* values estimated by using tCRSI, tLL, NLM, and SQNLM for different flip angles in all participants. The reference method for each participant was selected from Figure 4 by using the participant-specific R_2^* and SNR_0 . For flip angles of 8° , 15° , and 35° tCRSI and SQNLM yielded the more accurate R_2^* in general, although NLM was also reasonably accurate. However, for a flip angle of 3° , only tCRSI was robust enough to give reasonably accurate results. The mean relative errors of all measurements were 5.3% for tCRSI, whereas they were 13.2%, 11.3%, 11% for tLL, NLM and SQNLM respectively.

To test computation speed, four R_2^* maps was generated for one patient from four image data sets obtained with flip angles of 3° , 8° , 15° , and 35° , and each data set has 20 GRE images with a matrix size of 128×104 . The total processing times for the tLL, NLM, and SQNLM were 22.17 s, 319.26 s, and 204.47 s, respectively, versus only 0.22 s for tCRSI. For a fair comparison, parallel computing and vector optimization were not used for testing the computation speed of any method. The computation speed of tCRSI was about 100, 1460, and 930 times higher than that for tLL, NLM, and SQNLM, respectively.

Discussion

In this study, we developed a robust, mathematically simple, and computationally inexpensive method to quantify R_2^* values. Our computer simulations, phantom data, and in vivo data support that tCRSI is more robust against noise than other conventional methods for calculating R_2^* values.

R_2^* quantification has wide applications in both clinical research and practice. In patients with iron overload, liver R_2^* values can vary widely, depending on iron concentration (22). Therefore, there is a clinical need for an R_2^* quantification method that is robust and valid across the entire R_2^* range. Findings from our simulation and phantom studies showed that the accuracy and precision of different conventional methods vary with SNR and R_2^* . The tLL method performed well only for high SNRs and low R_2^* values. In contrast, the

SQNLN method performed well for low SNRs and high R_2^* values. However, it could not estimate R_2^* values and generated abnormal values for some voxels in the simulation and phantom studies. The NLM method is widely accepted to be the best conventional method to estimate R_2^* , but its accuracy and precision were not as good as that of the SQNLN method. tCRSI was very accurate and precise over a wide range of R_2^* values and SNRs, indicating that it is equivalent or outperforms the conventional NLM method for measuring R_2^* for most scenarios. The high accuracy and precision advantage can be understood by the behavior of signal and noise in the summation of images. The SNR of combined images is proportional to the square root of the number of summations. Because CRSI uses summation, or integration, to calculate R_2^* , the noise contribution is suppressed in the calculation.

Each estimation method performs differently for different scenarios of SNR and R_2^* . SQNLN and CRSI are overall the two most robust methods observed in this study. CRSI was especially robust in estimating R_2^* for low SNRs and high R_2^* values, as shown in the simulation, phantom, and *in vivo* studies. For low FA (3°) images (SNR₀ values were approximately 3 to 10), the LL, NLM, and SQNLN methods could not generate accurate R_2^* values for datasets with such low SNRs, but CRSI produced satisfactory results.

In the LL method, a logarithm is applied to the signal, which amplifies the noise contribution for low-SNR images. This explains why LL could not perform satisfactorily for low-SNR images. NLM and SQNLN solve the least-square curve fitting problem by minimizing the cost function (sum of the squares of deviations) by using iterative methods. False results or divergence may result from a poor choice of initial guess, damping parameter, or boundary condition (20). CRSI provides a direct solution for R_2^* in a simple arithmetic form and does not need an initial guess, other supporting parameters, or a boundary condition. This property makes the method more robust, because it is unaffected by the convergence problems commonly associated with NLM and SQNLN.

While ARMA (13,14) and ARLO (15) require equidistant echo spacing, CRSI has no such limitation. R_2^* simply depends only on the signal integral and the signal intensities at the first and last echoes in CRSI, which are readily obtained in the case of non-equidistant echo spacing (22). Another advantage of CRSI over conventional methods is computation speed. CRSI was over 1000 times faster than NLM and SQNLN and about 100 times faster than the tLL method. Thus, CRSI yielded accurate R_2^* maps at a faster speed, which is an important consideration in real-time MRI. LM fitting, which is generally adopted in algorithms that measure relaxation rate, usually requires a long computation time because it involves Jacobian matrix calculations and iterative searches (20). In contrast, CRSI uses simple arithmetic calculations, which greatly improve computation speed.

CRSI was tested to quantify R_2^* in this study, but it can also be used to quantify $R_2(T_2)$ and diffusion coefficients. R_2 is generally estimated with the LL or NLM method by fitting the signal decay of a series of images acquired with a turbo spin echo sequence at different TEs (23). However, CRSI can be used to measure R_2 in the same manner as it was used to measure R_2^* in this study. With some modification, CRSI can also possibly be employed for T_1 quantification.

One limitation of our technique is that it assumes mono-exponential decay. In its current form, it cannot handle images that include relaxation times of multiple species. However, this limitation also occurred in the other techniques that were used for comparison. Nevertheless, mono-exponential decay is used in almost all clinical applications.

CRSI's greatest benefit results from its treatment of noise, which allows to take advantage of "signal averaging". MRI noise is generally characterized by a Rician distribution in a magnitude image (18). Rician noise is signal dependent and not additive. It is generally not a zero-mean noise, especially at low SNRs, where the noise approximates the Rayleigh distribution with a non-zero mean. However, in power images the noise is a simple addition to the signal, and can be subtracted.

In conclusion, CRSI provides a robust way to accurately and quickly estimate R_2^* maps. Because the algorithm uses arithmetic calculation instead of fitting, it has a high computation speed. Summation of the images enables CRSI to take advantage of "signal averaging" and to achieve high accuracy. The potential of CRSI for fast calculation of relaxivities and diffusion coefficients needs to be further explored. Because of its convincing speed, accuracy, and precision this method may be extremely helpful e.g. for real-time parameter fitting on clinical scanners.

Acknowledgments

The authors would like to acknowledge Gail Fortner, RN for patient enrollment. Aaryani Tipirneni-Sajja, PhD, and Chris Goode, RT for MRI data collection. The authors would also like to thank Dr. Vani Shanker for scientific editing.

Funding: This study was supported by NIH grant 5 R01 DK088988 from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and by ALSAC.

References

1. Wood JC, Enriquez C, Ghugre N, Tyzka JM, Carson S, Nelson MD, Coates TD. MRI R2 and R2* mapping accurately estimates hepatic iron concentration in transfusion-dependent thalassemia and sickle cell disease patients. *Blood*. 2005; 106(4):1460–1465. [PubMed: 15860670]
2. Hankins JS, McCarville MB, Loeffler RB, Smeltzer MP, Onciu M, Hoffer FA, Li CS, Wang WC, Ware RE, Hillenbrand CM. R2* magnetic resonance imaging of the liver in patients with iron overload. *Blood*. 2009; 113(20):4853–4855. [PubMed: 19264677]
3. Henninger B, Zoller H, Rauch S, Finkenstedt A, Schocke M, Jaschke W, Kremser C. R2* relaxometry for the quantification of hepatic iron overload: biopsy-based calibration and comparison with the literature. *Rofo*. 2015; 187(6):472–479. [PubMed: 25877992]
4. Hernando D, Levin YS, Sirlin CB, Reeder SB. Quantification of Liver Iron With MRI: State of the Art and Remaining Challenges. *J Magn Reson Imaging*. 2014; 40(5):1003–1021. [PubMed: 24585403]
5. Anderson LJ, Holden S, Davis B, Prescott E, Charrier CC, Bunce NH, Firmin DN, Wonke B, Porter J, Walker JM, Pennell DJ. Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. *Eur Heart J*. 2001; 22(23):2171–2179. [PubMed: 11913479]
6. Song R, Cohen AR, Song HK. Improved transverse relaxation rate measurement techniques for the assessment of hepatic and myocardial iron content. *J Magn Reson Imaging*. 2007; 26(1):208–214. [PubMed: 17659538]
7. Gelman N, Gorell JM, Barker PB, Savage RM, Spickler EM, Windham JP, Knight RA. MR Imaging of Human Brain at 3.0 T: Preliminary Report on Transverse Relaxation Rates and Relation to Estimated Iron Content. *Radiology*. 1999; 210(3):759–767. [PubMed: 10207479]

8. Brewer CJ, Coates TD, Wood JC. Spleen R2 and R2* in iron-overloaded patients with sickle cell disease and thalassemia major. *J Magn Reson Imaging*. 2009; 29(2):357–364. [PubMed: 19161188]
9. He T, Gatehouse PD, Smith GC, Mohiaddin RH, Pennell DJ, Firmin DN. Myocardial T2* measurements in iron-overloaded thalassemia: An in vivo study to investigate optimal methods of quantification. *Magn Reson Med*. 2008; 60(5):1082–1089. [PubMed: 18956471]
10. Hoppe S, Quirbach S, Mamisch TC, Krause FG, Werlen S, Benneker LM. Axial T2 mapping in intervertebral discs: a new technique for assessment of intervertebral disc degeneration. *Eur Radiol*. 2012; 22(9):2013–2019. [PubMed: 22544293]
11. Miller AJ, Joseph PM. The use of power images to perform quantitative analysis on low SNR MR images. *Magn Reson Imaging*. 1993; 11(7):1051–1056. [PubMed: 8231670]
12. Feng Y, He T, Gatehouse PD, Li X, Harith Alam M, Pennell DJ, Chen W, Firmin DN. Improved MRIR2* relaxometry of iron-loaded liver with noise correction. *Magn Reson Med*. 2013; 70(6): 1765–1774. [PubMed: 23359410]
13. Taylor BA, Loeffler RB, Song R, McCarville MB, Hankins JS, Hillenbrand CM. Simultaneous field and R2* mapping to quantify liver iron content using autoregressive moving average modeling. *J Magn Reson Imaging*. 2012; 35(5):1125–1132. [PubMed: 22180325]
14. Taylor BA, Loeffler RB, Song R, McCarville ME, Hankins JS, Hillenbrand CM. Automated T2* measurements using supplementary field mapping to assess cardiac iron content. *J Magn Reson Imaging*. 2013; 38(2):441–447. [PubMed: 23292658]
15. Pei M, Nguyen TD, Thimmappa ND, Salustri C, Dong F, Cooper MA, Li J, Prince MR, Wang Y. Algorithm for fast monoexponential fitting based on Auto-Regression on Linear Operations (ARLO) of data. *Magn Reson Med*. 2015; 73(2):843–850. [PubMed: 24664497]
16. Bonny JM, Zanca M, Boire JY, Veyre A. T2 maximum likelihood estimation from multiple spin-echo magnitude images. *Magn Reson Med*. 1996; 36(2):287–293. [PubMed: 8843383]
17. Beaumont M, Odame I, Babyn PS, Vidarsson L, Kirby-Allen M, Cheng H-LM. Accurate liver T2* measurement of iron overload: A simulations investigation and in vivo study. *J Magn Reson Imaging*. 2009; 30(2):313–320. [PubMed: 19629985]
18. Gudbjartsson H, Patz S. The Rician distribution of noisy MRI data. *Magn Reson Med*. 1995; 34(6): 910–914. [PubMed: 8598820]
19. Henkelman RM. Measurement of signal intensities in the presence of noise in MR images. *Med Phys*. 1985; 12(2):232–233. [PubMed: 4000083]
20. Press W, Teukolsky S, Vetterling W, Flannery B. *Numerical Recipes*. Cambridge University Press; 2007. 801–806.
21. McCarville MB, Hillenbrand CM, Loeffler RB, Smeltzer MP, Song R, Li CS, Hankins JS. Comparison of whole liver and small region-of-interest measurements of MRI liver R2* in children with iron overload. *Pediatr Radiol*. 2010; 40(8):1360–1367. [PubMed: 20335111]
22. Krafft AJ, Loeffler RB, Song R, Tipirneni-Sajja A, McCarville MB, Robson MD, Hankins JS, Hillenbrand CM. Quantitative ultrashort echo time imaging for assessment of massive iron overload at 1.5 and 3 Tesla. *Magn Reson Med*. 2017
23. Hardy PA, Yue G. Measurement of magnetic resonance T2 for physiological experiments. *J Appl Physiol*. 1997; 83(3):904–911. [PubMed: 9292479]

FIG 1.

R_2^* maps of digital phantoms obtained by using different methods from $\text{SNR}_0 = 50$ data set along with the true R_2^* map. As labeled, maps shown in the top and bottom row are from complete and truncated data sets, respectively.

FIG 2.

Corresponding R_2^* error maps to Fig. 1. tCRSI and SQNLM had the best overall accuracy, with mean absolute errors of 0.58% and 0.94%, respectively.

FIG 3.

Comparison of relative errors η , and coefficients of variation (CV) as a function of true R_2^* at different values of SNR_0 for tLL, tNLM, NLM, SQNLM, tCRSI, and CRSI. The mean η and CV over all R_2^* are also shown.

FIG. 4. Contour plot of the best fitting method with different SNR_0 and R_2^* based on numerical simulations. The SQNLM algorithm displays the highest accuracy for $R_2^* > 200 \text{ s}^{-1}$ over a wide range of SNR_0 .

FIG 5.

Comparison of R_2^* maps obtained by NLM for 320 averages (reference), tCRSI, tLL, NLM, and SQNLM for low SNRs data acquired with $FA = 4^\circ$. tCRSI had the best overall accuracy, with a mean error of 3.88%, whereas the mean error was 6.88% for tLL, 10.10% for NLM, and 5.41% for SQNLM.

FIG. 6.

Comparison of phantom R_2^* values (see Figure 5) obtained from mGRE data sets acquired at flip angles 4° (top), 10° (middle), 35° (bottom) and by applying tCRSI and the fitting methods tLL, NLM, and SQNLM. The reference R_2^* measurement was obtained with 320 averages, flip angle 35°, and NLM fitting. tCRSI exceeds SQNLM in very low SNR conditions.

FIG. 7.

MRI R_2^* maps (top row) and error maps (bottom row) of a patient obtained from a series of GRE images acquired at a flip angle of 8° and calculated by tLL, NLM, SQNLM, and tCRSI. The reference R_2^* map was estimated from high-SNR images acquired at a flip angle of 35° by using SQNLM. Only liver parenchyma is shown in the error maps. Compared with the reference R_2^* map, tCRSI, tLL, and SQNLM yielded accurate R_2^* values whereas the NLM method overestimated the R_2^* values. The R_2^* maps generated by the tCRSI, tLL, and SQNLM had lower mean errors: 6.6% for tCRSI, 8.6% for tLL and 3.8% for SQNLM, but R_2^* was overestimated by the NLM method with a mean error of 14.8%.

FIG. 8.

Comparison of R_2^* maps obtained by tCRSI, tLL, NLM, and SQNLM, with the reference R_2^* derived from high-SNR images (flip angle = 35°) and by applying the respective best fitting method according to Figure 4. Only tCRSI was robust enough to give reasonably accurate results for the case of extremely low SNR (flip angle = 3°).