Evaluation of Parameter Estimation Methods for T2* Relaxometry: A Monte Carlo Approach

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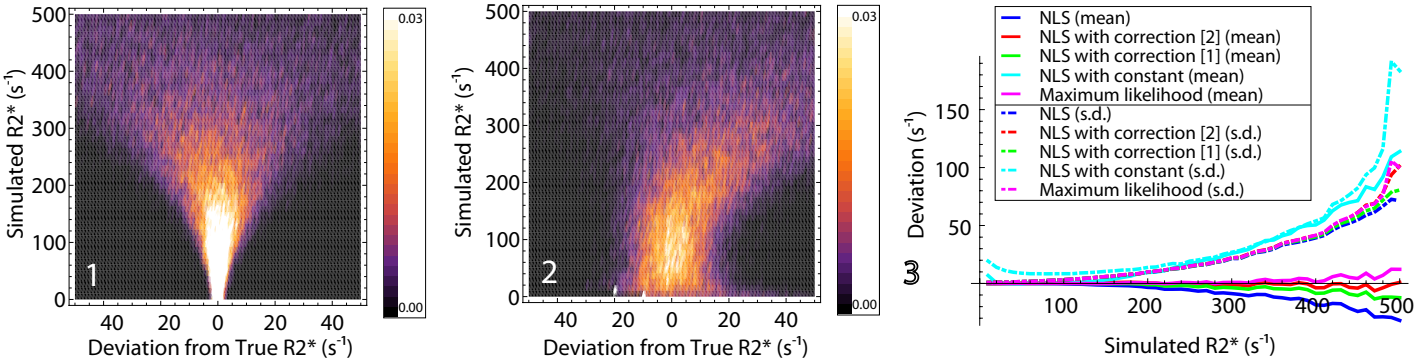
INTRODUCTION T2* relaxometry gains increasing importance with its new clinical role to measure regional organ tissue iron concentrations for managing iron overload patients with thalassemia, hemochromatosis, cardiomyopathy, chemotherapy, etc. Most T2*-based studies have estimated T2* by nonlinear least squares (NLS) fitting of multi-gradient-echo data to $S(TE)=S_0e^{-TE/T2^*}$. A recent paper recommends an additive constant, $S(TE)=S_0e^{-TE/T2}*+C$, to correct for the influence of noise bias.[1] Another recent study demonstrates the exclusion of data points that exhibit sufficiently low SNR.[2] More insightful studies apply one of two proposed Rician noise bias corrections prior to NLS fitting: [1] $S_C=\sqrt{|S^2-\sigma^2|}$ and [2] $S_C=\sqrt{|S^2-2\sigma^2|}$; σ=std. dev., see below)[3-6], or use maximum likelihood estimation (MLE; expressions too large to include) [7]. But which method(s) provides the most accurate and precise T2* quantitation and under what conditions? This project uses Monte Carlo techniques to simulate the effects of Rician noise on measured signal intensity, then characterizes the performance of the various proposed parameter estimation methods, and identifies the most accurate and appropriate methods for practical T2* relaxometry.

METHODS Simulated gradient-recalled MR data was generated with TE={2.1, 5.5, 8.9, 12.3, 15.7, 19.1, 22.5, 25.9} ms via $S(TE) = |X + iY|$ where $X \sim N(S_0e^{-R2^*\cdot TE}\ cosTE,\ \sigma^2)$ and $Y \sim N(S_0e^{-R2^*\cdot TE}\ sinTE,\ \sigma^2)$. S_0 was kept constant while σ and R2* were systematically varied, ranging from 10 to 40 and 10 to 500 s^{-1} respectively (R2* = 1/T2*). The resulting SNR at TE=0 ms ranged from 37.5 to 150. The stochastic variation of repeated measurements was modeled by simulating 1000 echo trains per combination of σ and R2*. All computations in this study operated on the same set of simulated data. Data was optionally pre-processed with one of two proposed noise bias corrections for the NLS methods[4-6] using the true σ value. MLE incorporates the noise probability distribution function into the model and thus requires no bias correction. NLS methods were applied using both $S_0e^{-R2^*\ TE}$ and $S_0e^{-R2^*\ TE}+C$ models to estimate both R2* and S_0. MLE was performed by maximizing the natural logarithm of the likelihood function. Finally, computed R2* values were compared with the simulated values to evaluate the estimation methods for accuracy and bias.



RESULTS AND DISCUSSION Figure 1 shows a color probability density plot of the NLS R2* estimates using bias correction [2] with simulated R2* on the vertical axis, deviation of the estimate on the horizontal axis, and probability represented by color for simulated data having σ = 25 and $SNR_{TE=0}$= 60. The plot's horizontal symmetry about the center shows the unbiased performance of this method, which is the best method overall. The increasing spread of the estimates with increasing R2* reflects the drop in the SNR and the number of contributing relaxing data points. This method and MLE gave nearly identical results within the usual clinical decision range, diverging slightly at high R2*. Thus, the greater computational burden of MLE is unwarranted whenever an accurate estimate of σ may be obtained by other means. Figure 2 depicts a probability density plot of the NLS estimates for the $S_0e^{-R2^*\ TE}$+C model. The marked asymmetry of the plot and horizontal dispersion of the values demonstrate the substantial mean bias and greater variability that render this model inappropriate for use in R2* relaxometry. Figure 1 shows the best method tested, while Figure 2 shows the worst.

Figure 3 presents a summary comparison of the performance of the 5 tested methods. Solid color lines plot the deviation of the mean R2* fit, and dotted lines represent the standard deviation of the bias as a function of the simulated R2*. Although NLS estimation with no correction (dark blue) clearly underestimates high R2* values but with low standard deviations, its performance was satisfactory within the range containing the applicable T2*/R2* clinical decision thresholds published in the literature, ~20-70 s^{-1}. NLS with correction [2] (red) shows the best accuracy and nearly the best precision. NLS with correction [1] (green) shows small ~3% underestimation at high R2* values and equivalent precision. NLS with a fitted constant (aqua) provides unacceptable overestimation of R2* above ~200 s-1 and much higher variance than the other methods. Our tests show that earlier literature R2* values published for clinical decision thresholds up to ~150 s-1 can still be used when based upon any of the 5 methods, however caution should be given for results of studies based upon the NLS with additive constant because of its bias and higher variance especially when number of subjects is small.

Implications for protocol optimization: The decrease of SNR as TE increases appears to be the dominant factor in the performance of all the methods. This suggests that an optimal R2* quantitation scanning protocol will have a minimized short initial TE and a small echo spacing to provide relaxation data points well above the noise floor to minimize variability and bias. For this study, the correct value of σ was assumed to be known for the fitting process. In practice, σ would either be computed from an ROI in air if SNR is spatially invariant, determined using another supporting acquisition to obtain a difference image[8], or by treating σ as an additional estimated parameter fit by MLE in the case of multi-coil or parallel imaging (presuming sufficient SNR and many echoes).

The effectiveness of excluding data points with low SNR from the estimation procedure (often called *truncation*) was not evaluated in this study because the resulting variance will be higher than the methods shown. Experimental MR results verifying these simulations will be presented. We have selected to cast this investigation in terms of R2* to encourage this usage as it simplifies the methodology and provides numerical values typical for the clinical context.

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