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Propagation of Error from Parameter Constraints in Quantitative MRI: Example Application of Multiple Spin Echo T_2 Mapping

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Abstract

Purpose—Quantitative MRI may require correcting for nuisance parameters which can or must be constrained to independently measured or assumed values. The noise and/or bias in these constraints propagates to fitted parameters. For example, the case of refocusing pulse flip angle constraint in multiple spin echo T_2 mapping is explored.

Methods—An analytical expression for the mean-squared error of a parameter of interest was derived as a function of the accuracy and precision of an independent estimate of a nuisance parameter. The expression was validated by simulations and then used to evaluate the effects of flip angle (θ)-constraint on the accuracy and precision of $\hat{T}_2$ for a variety of multi-echo T_2 mapping protocols.

Results—Constraining θ improved $\hat{T}_2$ precision when the θ -map signal-to-noise ratio was greater than approximately one-half that of the first spin echo image. For many practical scenarios, constrained fitting was calculated to reduce not just the variance but the full mean-squared error of $\hat{T}_2$, for bias in $\hat{\theta} \lesssim 6\%$.

Conclusion—The analytical expression derived in this work can be applied to inform experimental design in quantitative MRI. The example application to T_2 mapping provided specific cases, depending on $\hat{\theta}$ accuracy and precision, in which θ measurement and constraint would be beneficial to $\hat{T}_2$ variance or mean-squared error.

Keywords

MRI; precision; accuracy; T_2 ; B_1

Introduction

Accurate parameter mapping with MRI often requires consideration of nuisance parameters that affect acquired signals. For example, the signal from a multiple spin echo sequence will depend on both T_2 (a tissue parameter of interest) and the refocusing pulse flip angle (a nuisance parameter). A similar situation involving field variations in B_1^+ and/or B_0 exists for various T_1 mapping protocols (1–3), quantitative magnetization transfer methods (4, 5), dynamic contrast enhanced MRI (6), water/fat imaging (7) and MR fingerprinting (8). Also, some methods are specifically designed as a multi-stage protocol; for example, DESPOT1/2 (9) involves the measurement of T_1 which then serves as a nuisance parameter for the measurement of T_2 . In these and other situations, it may be possible to jointly fit the nuisance parameter(s) along with the parameter(s) of interest, but it may also be possible or even necessary to independently measure one or more of the nuisance parameters and fit the remaining signal model parameters while using the independent measurements as constraints. Some such evaluations exist in the literature for specific cases (10–12), but to our knowledge no general framework for analyzing the propagation of error from independently measured nuisance parameters has been reported.

It is well-known that constraining parameters in a joint fit will generally improve the precision of the remaining fitted parameters and will simplify the fitting processes, thereby reducing the likelihood of convergence to a local minimum. The cost of parametric constraint is the imparting of bias in remaining parameters, although these biases may be small compared to their respective variances. This tradeoff is captured in a parameter's mean-squared error—the sum of its variance and squared bias—which may actually decrease as a result of parametric constraint (13). The objective of this work is to provide a theoretical framework for analyzing the effect of nuisance parameter constraint on the precision and accuracy of fitted model parameters, for the purpose of guiding quantitative MRI experiment design.

As an example, this framework is applied to the case of multiple spin echo-based T_2 mapping. Accurate T_2 mapping with a multiple spin echo imaging sequence requires accounting of echoes from indirect signal pathways (14–17), which can be done by joint fitting of T_2 and refocusing flip angle (18). Useful signal models for such analysis include the extended phase graph model (EPG) (16, 18–23), the echo generating function (24, 25), and the Bloch equations (12, 26, 27). For an appropriate multiple spin echo sequence, each of these models can determine echo magnitudes given four parameters: equilibrium magnetization (M_0), the relaxation time constants T_1 and T_2 , and the refocusing pulse flip angle (θ). Due to the relatively weak T_1 -dependence of multiple spin-echo signals, T_1 can be fixed to an approximate value and subsequently ignored (18). The remaining three unknown parameters can be jointly fitted from the measured echo magnitudes; alternatively, one can independently measure θ from a B_1^+ mapping method (28–32) and then fit only M_0 and T_2 . To date, there is no complete analysis of the advantages/disadvantages of these two options. The unanswered questions regarding these methods are therefore an ideal example application for the statistical analysis proposed in this work.

Theory

When simultaneously estimating a vector of tissue parameters, $\boldsymbol{\beta}$, from a Gauss-distributed signal vector, $\mathbf{s}$, one can use the Cramér-Rao Bound (CRB) to estimate the covariance matrix of $\hat{\boldsymbol{\beta}}$,

$$\Sigma_{\hat{\boldsymbol{\beta}}} = (\mathbf{J}^T \Sigma_s^{-1} \mathbf{J})^{-1}, \quad [1]$$

where the ‘hat’ notation ($\hat{\cdot}$) indicates an estimated parameter, $\mathbf{J}$ is the signal model Jacobian matrix populated by values of $\partial \mathbf{s} / \partial \boldsymbol{\beta}$, and Σ_s is the covariance matrix of the signal noise. In most cases, Σ_s is an identity matrix scaled by the noise variance of the measured signal (σ_s^2).

The variance of a particular fitted parameter (e.g., $\sigma_{T_2}^2$) can be extracted from the relevant diagonal element of $\Sigma_{\hat{\boldsymbol{\beta}}}$.

For an unbiased estimate, the mean squared error (ϵ^2) of a given parameter is equal simply to its variance (i.e., $\epsilon^2 = \sigma^2$). However, when some nonempty subset of $\boldsymbol{\beta}$, $\boldsymbol{\beta}_c \subset \boldsymbol{\beta}$, is constrained to an independently measured value, the mean-squared error of each of the remaining fitted parameters includes more than its variance. Defining $\boldsymbol{\beta}_f$ as the freely-fitted, non-constrained complement to $\boldsymbol{\beta}_c$, the mean-squared error of the parameters in $\hat{\boldsymbol{\beta}}_f$ are the diagonal elements of the matrix $\epsilon_{\hat{\boldsymbol{\beta}}_f}^2$,

$$\epsilon_{\hat{\boldsymbol{\beta}}_f}^2 \approx \sigma_s^2 (\mathbf{J}_{\boldsymbol{\beta}_f}^T \mathbf{J}_{\boldsymbol{\beta}_f})^{-1} + \frac{\partial \bar{\boldsymbol{\beta}}_f(\bar{\boldsymbol{\beta}}_c)}{\partial \bar{\boldsymbol{\beta}}_c} \Sigma_{\hat{\boldsymbol{\beta}}_c} \frac{\partial \bar{\boldsymbol{\beta}}_f(\bar{\boldsymbol{\beta}}_c)^T}{\partial \bar{\boldsymbol{\beta}}_c} + (\bar{\boldsymbol{\beta}}_f(\bar{\boldsymbol{\beta}}_c) - \boldsymbol{\beta}_f)(\bar{\boldsymbol{\beta}}_f(\bar{\boldsymbol{\beta}}_c) - \boldsymbol{\beta}_f)^T. \quad [2]$$

The bar notation denotes the average estimate of a parameter, and the subscripts of $\mathbf{J}$ in the leftmost term imply a selection of only the columns corresponding to the given parameters. The leftmost term in Eq [2] is the CRB of the variance of an unbiased estimate $\hat{\boldsymbol{\beta}}_f$, given an exactly correct constraint. The middle term is the propagation of noise from the independent measure $\hat{\boldsymbol{\beta}}_c$ to the estimate $\hat{\boldsymbol{\beta}}_f$ and is formulated as a simple first-order propagation of error from the covariance matrix, $\Sigma_{\hat{\boldsymbol{\beta}}_c}$. (Note that this covariance matrix is not generally diagonal, and can be estimated using Eq [1] where the Jacobian matrix is that of the independent measure.) The rightmost term, which is a diagonal matrix, represents the squared bias in the estimate $\hat{\boldsymbol{\beta}}_f$ caused by bias in $\hat{\boldsymbol{\beta}}_c$. In general, constraint of $\boldsymbol{\beta}_c$ will decrease the value of the leftmost term relative to the comparable term in Eq. [1], but will result in nonzero values of the middle and rightmost terms depending on the precision and accuracy of $\hat{\boldsymbol{\beta}}_c$, respectively.

Thus, to reduce the value of $\epsilon_{\hat{\beta}_f}^2$ by constraining $\beta_c = \hat{\beta}_c$, $\hat{\beta}_c$ must be sufficiently precise and accurate. A derivation of Eq [2] is presented in the Appendix.

For example, consider the mean squared error of an estimate, $\hat{T}_2$, which results from a multiple spin echo measurement. The signal model includes three parameters, $\beta = [M_0, T_2, \theta]^T$, which can be jointly fit. Alternatively, a B_1^+ mapping method can provide an estimate of the flip angle, $\hat{\theta}$, which can then be used as a constraint in the fit of M_0 and T_2 . In terms of the formalism above, $\beta_c = \theta$ and $\beta_f = [M_0, T_2]^T$, and considering only the error in $\hat{T}_2$, Eq [2] reduces to

$$\epsilon_{\hat{T}_2}^2 \approx \sigma_s^2 \left(\mathbf{J}_{M_0, T_2}^T \mathbf{J}_{M_0, T_2} \right)_{T_2, T_2}^{-1} + \sigma_{\hat{\theta}}^2 \left(\frac{\partial \bar{T}_2}{\partial \theta} \right)^2 + (\bar{T}_2(\bar{\theta}) - T_2)^2. \quad [3]$$

Because Eq [3] evaluates a scalar value and involves only a scalar constraint, the second and third terms are reduced in notation compared to Eq [2].

Methods

The application of Eqs [1] and [2] was demonstrated for the case of indirect echo-compensated, multiple spin-echo T_2 mapping. In order to evaluate the effects of using independent measures of refocusing pulse flip angle, θ , in T_2 fitting, Eqs [1] and [3] were evaluated for a variety of different T_2 values, pulse sequence parameters, and signal-to-noise ratios. In all cases, signal calculations were performed using the EPG algorithm, with T_1 constrained to the true value of 1000 ms. To evaluate the partial derivative terms in the Jacobian matrix, a forward difference approximation was used with a step size 1×10^{-6} times the parameter value. The partial derivative $\partial \bar{T}_2 / \partial \hat{\theta}$ was estimated by fitting T_2 without added image noise and performing a center-difference approximation across θ , taking $\hat{\theta} = \theta \pm 1^\circ$.

Two different echo train lengths were investigated, corresponding to the extremes of common T_2 -mapping protocols. The first was a 32-echo protocol with echo spacing (ESP) = 10 ms, and the second was a 4-echo protocol with ESP = 30 ms. (The echo spacing of the 4-echo protocol was extended relative to the 32-echo protocol to provide comparable regimes of maximal T_2 sensitivity. However, the exact ESP values are arbitrary, as only the ESP/ T_2 ratio and the number of echoes are relevant.) For the 32-echo protocol, T_2 values from 20ms to 200ms were considered; for the 4-echo protocol, T_2 was kept within the smaller range of 30ms to 120 ms. In each case, two refocusing schemes were evaluated: i) a nonselective, rectangular refocusing pulse, and ii) a five-lobed sinc-shaped slice-selective pulse with full-width half-max $2 \times$ that of the excitation pulse. For the simulations of slice-selective refocusing, the flip angle profile of the pulse was calculated through numerical solution of the Bloch equations for each nominal flip angle θ , and evaluations were made for the case

that this known profile was used in the fitting (profile corrected) and for the case that it was not (uncorrected).

The effect of θ constraint on $\hat{T}_2$ precision

The propagation of noise from an unbiased measure of the flip angle to the estimate $\hat{T}_2$ was evaluated for all tested protocols (4- and 32-echo, non- and slice-selective refocusing, with and without profile correction) and with various actual flip angles and T_2 s. Equation [1] was used to calculate $\epsilon_{\hat{T}_2}^2$ when jointly fitting T_2 , M_0 , and θ , and Eq [3] was used for the same purpose when θ was constrained to an unbiased estimate, $\hat{\theta}$. (Note that the third term of Eq [3] was equal to zero in this scenario, because $\hat{\theta}$ and, therefore, $\hat{T}_2$ were unbiased.) The standard deviation of noise added to the signal was set as $\sigma = 0.01 \times M_0$; thus, the image signal-to-noise ratio was $SNR_s \triangleq M_0/\sigma = 100$. Calculations were repeated for θ values over the range 90° to 180° and with $SNR_{\hat{\theta}} = 25, 50, 100$, and ∞ . The resulting $\hat{T}_2$ precision, reported as $SNR_{\hat{T}_2}$, scales linearly with SNR_s as long as the ratio $SNR_{\hat{\theta}}/SNR_s$ is constant, and thus the chosen SNR_s value is arbitrary within the regime of the approximation.

The effect of θ constraint on $\hat{T}_2$ accuracy

If the independent measure of flip angle is biased, then the resulting estimate of T_2 will also be biased, and this effect is captured by the third term of Eqs [2] and [3]. Values of $\bar{T}_2(\bar{\theta})$ were calculated by estimating T_2 using $\bar{\theta} = 90^\circ$ to 180° for four different values of θ : 90° , 120° , 150° and 175° . As above, this was repeated for all tested protocols (4- and 32-echo, non- and slice-selective refocusing, with and without profile correction). Also, the level of θ -bias was determined at which independently-measured and jointly-fitted θ resulted in the same $\epsilon_{\hat{T}_2}^2$. This evaluation was performed with nonselective refocusing pulses only; including slice selective refocusing would add an independent and predictable bias to $\hat{T}_2$ related to the definition of the flip angle as the peak θ rather than average (across the slice) θ .

Monte Carlo simulations

In order to validate calculations of $\epsilon_{\hat{T}_2}^2$ using Eqs [1] and, in particular, [3], Monte Carlo simulations were performed in which T_2 was fitted from noisy multiple spin echo data and, where relevant, constrained to a noisy and/or biased $\hat{\theta}$. Simulated signals were generated using $T_2 = 80\text{ms}$ and $\theta = 150^\circ$. Gaussian noise was added to the simulated signals and flip angle estimates at levels corresponding to $SNR_s = 100$ and $SNR_{\hat{\theta}} = 100$, respectively. Both unbiased ($\bar{\theta} = \theta = 150^\circ$) and biased ($\bar{\theta} = 155^\circ$; $\theta = 150^\circ$) scenarios were tested. The 32-echo, nonselective refocusing protocol was used. Each calculation was repeated 10000 times with independent realizations of noise, and the root mean squared errors of $\hat{T}_2$ were compared to those predicted by Eqs [1] and [3].

Results

The results of the Monte-Carlo simulations, presented in Table 1, demonstrate close agreement between the simulated and predicted fitting errors. Across all simulations, the root mean squared errors of $\hat{T}_2$ predicted by Eq [1] or [3] matched those from the simulations to within $< 1.5\%$. Figure 1 shows example multiple-spin echo signals calculated for the 4- and 32-echo protocols, using $\theta = 120^\circ$ and $T_2 = 80$ ms. The effect of imperfect refocusing is apparent in the signal oscillations relative to a smooth exponential decay. These signal oscillations enable the joint fitting of T_2 and θ .

Effect of θ constraint on $\hat{T}_2$ precision

Figure 2 shows the $SNR_{\hat{T}_2}$ resulting from various constrained and jointly-fitted protocols for $SNR_s = 100$ and $T_2 = 80$ ms, as calculated by the proposed method. For the 32-echo protocol, the predicted improvement in $SNR_{\hat{T}_2}$ through θ constraint was more pronounced when slice-selective refocusing pulses were assumed. In fact, for nonselective refocusing protocols with well-calibrated transmit fields ($\theta > 165^\circ$), as might be the case for single-slice experiments, Fig 2a shows that the benefit of θ constraint was minimal even in the presence of a noiseless flip angle estimate. In contrast, for a slice-selective protocol, Figs 2c and 2e demonstrate an increase in $SNR_{\hat{T}_2}$ by up to $\approx 30\%$ can be attained through θ constraint. In the extreme case of a 4-echo protocol, poorly calibrated refocusing ($\theta = 90^\circ$), and $SNR_{\hat{\theta}} = SNR_s$, $SNR_{\hat{T}_2}$ was predicted to triple by constraining θ . The results for the other tested values of T_2 were qualitatively similar, and can be found in the supporting figures, S1 and S2. For any of the tested scenarios, constraining θ increased $SNR_{\hat{T}_2}$ as long as $SNR_{\hat{\theta}} \gtrsim \frac{1}{2} \times SNR_s$, and $SNR_{\hat{T}_2}$ increased with increasing values of $SNR_{\hat{\theta}}$. For the shortest T_2 s used, this limit relaxed to lower than $\gtrsim \frac{1}{4} \times SNR_s$.

Other observations from Fig 2 include that the optimal refocusing flip angle for multiple spin echo T_2 measurement was at or near 180° , for both jointly fitted and independently measured θ . However, for the 4-echo, joint-fitted protocol, the $SNR_{\hat{T}_2}$ was roughly independent of θ for $\theta \gtrsim 150^\circ$. Also, while slice-selective refocusing imposed a modest penalty on $SNR_{\hat{T}_2}$, correcting for the known slice profile had little effect on $SNR_{\hat{T}_2}$.

Effect of θ constraint on $\hat{T}_2$ accuracy

Figure 3 shows the biased estimator $\bar{T}_2(\bar{\theta})$ for a true T_2 value of 80 ms. The curves have a generally logarithmic shape, indicating that overestimation of θ —i.e., constraint to a value that is higher than the true flip angle—was found to generate less bias in $\hat{T}_2$ than underestimation of θ . Nonselective refocusing or profile correction provided an unbiased $\hat{T}_2$

when $\hat{\theta}$ was unbiased, as expected. Assuming a uniform slice profile when in fact a slice-selective refocusing pulse was employed resulted in a biased $\hat{T}_2$, but this was primarily due to the definition θ as the peak flip angle rather than the average flip angle across the slice. For example, with $\theta_{\text{peak}} = 175^\circ$, the average flip angle over the slice was $\theta_{\text{ave}} \approx 154^\circ$. Constraining the fit with the average flip angle (not shown) provided an approximately accurate value for $\hat{T}_2$.

The effects of θ -constraint on variance, bias, and mean-squared error of $\hat{T}_2$ are summarized in Fig 4 for an example scenario of selectively-refocused protocols with $\theta = 150^\circ$ and $T_2 = 80$ ms. (The results for the other tested values of T_2 were qualitatively similar, and can be found in the supporting figures, S3 and S4.) The standard deviation, $\sigma_{\hat{T}_2}$, whether θ was

constrained or jointly fitted, is assumed independent of bias in $\hat{\theta}$, and is thus constant between the two panels. Panel a) shows that constraining θ with high accuracy (e.g., 1° error) and sufficient precision ($SNR_{\hat{\theta}} \gtrsim \frac{1}{2} \times SNR_s$) resulted in a similar reduction of variance and mean-squared error of $\hat{T}_2$. However, with a less accurate independent estimate of θ , (e.g., 5° error), panel b) shows that when bias dominates variance as the source of mean squared error, θ -constraint can reduce variance in $\hat{T}_2$, but has little effect on the net error.

The maximum permissible θ bias at which constraining θ results in a lower mean-squared error than achievable through joint-fitting is presented in Fig 5 as a two-dimensional function of $SNR_{\hat{\theta}}$ and SNR_s . The results presented are for nonselective refocusing pulses, $\theta = 150^\circ$ and $T_2 = 80$ ms. Note that the maximum permissible bias is largely a function of SNR_s but goes to zero when $SNR_{\hat{\theta}} \lesssim \frac{1}{2} \times SNR_s$, in agreement with results in Fig 2. There is also little difference in this threshold between the 4- and 32-echo protocols, despite the difference in the biases between these two protocols (Fig 3).

Discussion

The theory and results demonstrate how to evaluate the statistical effect of using independent measurement of nuisance parameters in quantitative MRI parameter mapping. In the demonstrated application, multiple spin echo-based T_2 mapping, refocusing pulse flip angle (θ) can be measured through B_1^+ mapping and then constrained in the fit of T_2 . The statistical analysis revealed that θ constraint is beneficial only under specific circumstances which depend on a number of factors, including the SNR of both the multiple spin echo images and the B_1^+ map, whether slice-selective or non-selective refocussing is used, and to what extent the accuracy (and not merely precision) of $\hat{T}_2$ is important.

In order to improve $\hat{T}_2$ precision by measuring rather than jointly fitting θ , the independent estimate $\hat{\theta}$ will typically require an SNR $\gtrsim 50\%$ as high as that of the spin echo image at TE = 0 (compare red and dash-dot lines in Fig 2). For the 32-echo non-selective refocusing case,

with $SNR_{\hat{\theta}} = SNR_s$ (dashed line in 2a) and $\theta = 150^\circ$, constraining $\theta = \hat{\theta}$ results in $\approx 22\%$ increase in $SNR_{\hat{T}_2}$. However, the estimate $\hat{\theta}$ comes at a cost of acquisition time, which could also be used to increase the $SNR_{\hat{T}_2}$ through signal averaging. From data presented by Park et al. (33), using the Bloch-Siegert shift method of B_1^+ -mapping, $SNR_{\hat{\theta}} \geq SNR_s$ can be obtained in the same scan time as the multiple spin echo measurement (conservatively estimated from Fig 4 in ref (33)). In this case, it would be better to simply double the number of averaged excitations of the spin echo acquisition, which would increase $SNR_{\hat{T}_2}$ by $\sqrt{2}$. However, B_1^+ maps are typically smooth functions, and so in practice a low-resolution (and, consequently, higher SNR) map is probably sufficient. For example, using a B_1^+ map acquired in 1/4 the scan time of the multiple spin echo acquisition would result in $\approx 30\%$ increase in $SNR_{\hat{T}_2}$ (see Fig 2a) at the cost of only a 25% longer scanning time.

For low flip angle refocusing pulses ($\theta = 140^\circ$) the benefits in $\hat{T}_2$ precision from constraining θ are similar for non-selective and selective refocusing schemes; they are also indifferent to whether the slice profile was corrected (compare different rows of Fig 2). However, for larger flip angles ($140^\circ < \theta < 180^\circ$), the benefit diminishes substantially for the 32-echo, non-selective refocusing case. The reason for this effect is that as θ increases toward 180° , the covariance between $\hat{\theta}$ and $\hat{T}_2$ decreases toward zero for nonselective protocols, making joint-fitting more effective. For a slice-selective protocol, the variation in θ across the slice mitigates this effect—in other words, stimulated echoes are never removed entirely from the signal—and some benefit in constraining θ remains. Thus, for a single-slice protocol, which is amenable to good flip angle calibration, there may be little benefit to independently measuring θ . However, for multi-slice protocols or even 3D protocols where a sizable variation in θ over the volume is unavoidable, acquiring a low resolution B_1^+ map may be beneficial for the precision of $\hat{T}_2$.

An additional factor in determining whether to measure or jointly fit θ relates to bias. Given an unbiased estimate of θ , the above analysis of precision tells the whole story. However, if the B_1^+ mapping is inaccurate, then the bias in $\hat{\theta}$ will result in bias in $\hat{T}_2$. Figure 3 demonstrates that this effect is greater with fewer echoes and lower refocusing pulse flip angles. A more complete characterization of measurement error then is the mean squared error, $\epsilon_{\hat{T}_2}^2$. As apparent from Fig 5, for $SNR_s \approx 40$ (a typical level for in vivo quantitative MRI), $\hat{\theta}$ must be accurate to within $\approx 6\%$ for its use in T_2 fitting to lower $\epsilon_{\hat{T}_2}^2$, and this requirement becomes more demanding as SNR_s increases. While numerical studies indicate the potential for several methods to map B_1^+ to within $\pm 2\%$ (33, 34), experimental evaluations of such methods to accurately measure large flip angles remain to be done. For

the case of multiple spin-echo T_2 mapping, one approach to evaluating such bias would be to compare average $\hat{\theta}$ values derived from the independent measure and joint fitting.

Even in cases where the bias in $\hat{\theta}$ is above the threshold in Fig 5, certain applications may benefit from the reduction in variance over the loss in accuracy. Note the reduction in variance that occurs in general when $SNR_{\hat{\theta}} \gtrsim \frac{1}{2} \times SNR_s$ holds under diverse circumstances, including those in which $\hat{\theta}$ is biased (see, for examples, Fig 4). Furthermore, as shown in Fig 3, constraining θ to a value greater than the true value will introduce less bias than using an underestimated θ . In fact, for a 32-echo protocols with nonselective refocusing pulses and $\theta \gtrsim 150^\circ$, simply constraining $\theta = 180^\circ$ will provide up to 30% improvement in $SNR_{\hat{T}_2}$ at the cost of < 5 ms error in T_2 (for true $T_2 = 80$ ms). This primitive approach is therefore an alternative strategy for situations in which the calibration can be assumed to be reasonably accurate. In the case of extremely accurate calibration ($\theta > 170^\circ$), constraint provides little benefit to 32-echo, nonselective protocols (Fig 2a). Interestingly, the $\theta > 150^\circ$ regime of 4-echo protocols shows little improvement in joint-fitted $SNR_{\hat{T}_2}$ as the flip angle approaches 180° . This implies that accurate calibration of B_1^+ is not important to T_2 mapping using these protocols in conjunction with stimulated echo correcting models. Contrariwise, there might be cases in which the inaccuracy caused by θ -bias is far more significant than the potential precision gain. One example is model-based reconstruction methods which use stimulated echo correcting models (22, 23, 25, 26). In these applications, model inconsistencies may result in spatial distortions, such as ghosting, which can degrade the quality of $\hat{T}_2$ maps.

McPhee and Wilman (12) recently compared different approaches to T_2 relaxometry, including simultaneous and independent fitting of T_2 and θ , and a few different signal models. They reported similar $\hat{T}_2$ accuracy and precision between joint-fitted and constrained- θ methods in vivo. Although not directly reported, it appears that these studies involved $SNR_{\hat{\theta}}/SNR_s \approx 0.5$, making their observations consistent with the analysis here (Fig 2). They also noted the importance of accurately accounting for slice profile as a function of flip angle, demonstrating that using an EPG signal model with a flip-angle invariant slice profile was less accurate than using a full Bloch equation signal model. Here, a library of profiles was computed via the Bloch equations and then used with the EPG algorithm to accurately account for the slice profile independently of flip angle. The only difference between this approach and the use of a full Bloch equation signal model (for sequences applicable to the EPG algorithm) is the effect of altered relaxation during the refocusing pulses (35). This effect will result in a small systematic inaccuracy in $\hat{T}_2$, but should not affect precision. Thus, we postulate that the results presented here should be generally applicable to T_2 relaxometry using all signal models (EPG, generating function, and Bloch equations) as long as the slice profile is accurately accounted.

Some tissues, such as white matter, experience multi-exponential transverse relaxation that cannot be well described by a single T_2 value. Equation [2] can accommodate arbitrarily complex models, sufficient, for example, to include myelin water fraction in white matter

(36, 37). However, considering the large SNR_s (100s (38)) required for such measurements and the results shown in Fig 4, it is unlikely that $\hat{\theta}$ can be measured with sufficient accuracy and precision to improve the myelin water fraction estimate. Alternatively, one may wish to fit an ‘apparent’ T_2 (T_{2app}) from a multi-compartment tissue like white matter. This case too (and other cases where the signal model is incorrect) can, in principle, be handled with Eq [2] and a subsequent propagation of error from the full signal model parameters to $\hat{T}_{2app}$.

However, to the extent that T_{2app} of white matter can be thought of as the mono-exponential, non-myelin component, the mono-exponential example analysis presented here will be sufficient, given some care in defining terms. Given T_{2app} and the corresponding θ_{app} defined as the expected values from the joint fitting of T_2 and θ when the model is incorrect, and defining SNR_s in terms of the non-myelin component amplitude, Fig 2 is predictive of $SNR_{\hat{T}_{2app}}$, where the x-axis values of θ correspond to θ_{app} . Bias of an ‘apparent’ parameter

is less meaningful, but Figs 3, 4, and 5 can be used where either the bias in $\hat{\theta}$ is defined as the difference between $\hat{\theta}$ and θ_{app} or the bias in $\hat{T}_{2app}$ is defined as the difference between $\hat{T}_{2app}$ and the T_{2app} value that results from fitting with θ constrained to its correct value.

Returning to the broader use of Eq [2] in evaluating the accuracy and precision of parameter estimates, the presented formalism can be used to analyze a wide variety of quantitative MR protocols. For example, variable flip angle (VFA) T_1 mapping commonly involves an independent measure of B_1^+ . While propagation of noise from the VFA images to the precision of $\hat{T}_1$ has been presented analytically (39) and evaluated experimentally (40, 41), the method presented here could be used to evaluate the effect of both accuracy and precision of $\hat{B}_1^+$ on the mean squared error of $\hat{T}_1$. This same framework could also be used to interrogate the propagation of error in a joint-fit of $\hat{T}_1$ and $\hat{B}_1^+$ to a modified acquisition protocol (3, 42), or when assuming a known T_1 in a reference tissue in order to constrain B_1^+ in the estimate of T_1 in a region of interest (43, 44). Furthermore, the proposed framework can be applied in a nested manner to analyze the propagation of error from $\hat{B}_1^+$ to $\hat{T}_1$ and, in turn, to subsequent parameter mapping, such as has been considered for quantitative dynamic contrast enhanced MRI (45, 46). This is a particularly rich problem because it also includes an independent measure or assumption about another source of error—the arterial input function—which has been obtained in a variety of ways (47, 48) and could be explored with Eq [2].

Other examples of potential applications include pulsed quantitative magnetization transfer imaging, which involves a coupling between T_1 and macromolecular pool size that can be addressed through their joint-fit following independent measures of B_1^+ and B_0 (49).

Likewise, as recently investigated (50), the paired DESPOT1/DESPOT2 protocols (9) for T_1 and T_2 mapping represents another opportunity for uncertainty analysis given the ability to joint-fit common parameters or treat the individual imaging modes as separable. Beyond variations of relaxometry, another example is g-ratio imaging (51), which involves estimating axonal g-ratio based on independent measures of axon volume fraction and

myelin volume fraction, both of which will contribute variance and bias to the mean squared error of g-ratio. Finally, we note that while B_1^+ and B_0 are common nuisance parameters, magnetic field *gradients*, particularly when they are time varying, may not always equal assumed values and can be independently measured (52, 53) for either post-processing correction or gradient waveform optimization (54). The propagation of error from these measurements (or from using an assumed waveform) to final quantitative MRI measures may be complex but can, in principle, also be handled with the formalism present here.

Across the myriad of different potential applications, the correct use of Eq [2] will vary depending on the exact data analysis protocol being used. Constraining a nuisance parameter to an assumed value, such as the T_1 constraint of 1 s used here for multiple spin echo $\hat{T}_2$ mapping or similar constraint used in quantitative magnetization transfer analysis (55), will reduce the dimensionality and value of the leftmost term in Eq [2] and potentially introduce bias through the right term, but will not contribute to imprecision via the middle term, as $\sigma_{\hat{\beta}_c}$

will be identically zero. Jointly fitted parameters are described by expanding the Jacobian matrix in the left term by concatenating the sensitivity vectors of all measurements, as applied in (56). Constraining a parameter to an independent measurement contributes to uncertainty via the middle term of the equation, and potentially adds bias via the right term. Where necessary, estimation of $\sigma_{\hat{\beta}_c}$ can be accomplished by nested application of Eq [2]

until no pre-estimated parameters exist.

Conclusions

Quantitative MRI parameter mapping involves fitting the MRI signal to a model which is typically dependent on parameters that are not of interest to the investigator. Often, one or more of these nuisance parameters can or must be independently measured rather than remain part of the fitting. This work presents a statistical framework capable of predicting the accuracy and precision, and therefore scan time efficiency, of fitted parameters under the conditions of a) joint fitting with nuisance parameters and b) independently measuring (or assuming) and constraining nuisance parameters in the fit. The framework was applied to the example scenario of multiple spin echo-based T_2 mapping, which is contaminated by imperfect refocusing pulses. The results demonstrated that independent measurement of refocussing flip angle is potentially beneficial if this measure is accurate to within 6% and at least 50% as precise as the spin echo images.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

Consider a signal vector, $\mathbf{s}$, which is characterized by a model that is dependent on the parameter vector, $\boldsymbol{\beta}$. In general, these parameters can be sub-divided into those which are freely fitted ($\boldsymbol{\beta}_f$) and those which are constrained ($\boldsymbol{\beta}_c$) during analysis,

$$\boldsymbol{\beta} = \begin{bmatrix} \boldsymbol{\beta}_f \\ \boldsymbol{\beta}_c \end{bmatrix}. \quad [\text{A1}]$$

The mean squared error of $\hat{\beta}_f$, is then well approximated by Eq [2] in the Theory section. The derivation of this formula is presented below.

By definition, the mean squared error for an estimate of $\hat{\beta}_f$ is

$$\epsilon_{\hat{\beta}_f}^2 = \mathbb{E} \left[(\hat{\beta}_f(\mathbf{s}, \hat{\beta}_c) - \beta_f) (\hat{\beta}_f(\mathbf{s}, \hat{\beta}_c) - \beta_f)^T \right], \quad [\text{A2}]$$

where $\mathbb{E}$ is the expectation operator. Henceforth, for brevity of notation and readability, the matrix operation $\mathbf{A}\mathbf{A}^T$ is presented as $\mathbf{A}^2$, thus, $\epsilon_{\hat{\beta}_f}^2 = \mathbb{E} \left[(\hat{\beta}_f(\mathbf{s}, \hat{\beta}_c) - \beta_f)^2 \right]$. Assuming $\mathbf{s}$ and $\hat{\beta}_c$ are independent random variables (but not that the elements of $\hat{\beta}_c$ are independent of each other), the expectation operation in Eq [A2] can be separated into two stages:

$$\epsilon_{\hat{\beta}_f}^2 = \mathbb{E}_{\hat{\beta}_c} \left[\mathbb{E}_{\mathbf{s}} \left[(\hat{\beta}_f(\mathbf{s}, \hat{\beta}_c) - \beta_f)^2 \right] \right], \quad [\text{A3}]$$

where the expectation symbol's subscript defines the random variables over which integration is implied. It is conventional to separate mean-squared error into two parts: the contribution caused by an estimate's variance and that caused by its bias. In order to achieve this, the term $\bar{\beta}_f(\hat{\beta}_c)$ is introduced as

$$\bar{\beta}_f(\hat{\beta}_c) \triangleq \mathbb{E}_{\mathbf{s}} [\hat{\beta}_f(\mathbf{s}, \hat{\beta}_c)]. \quad [\text{A4}]$$

which means that $\bar{\beta}_f(\hat{\beta}_c)$ is the average estimate of β_f for a given constraint, $\beta_c = \hat{\beta}_c$, and it is not a function of noise in the signal, $\mathbf{s}$. Adding and subtracting this term within Eq. [A3] provides

$$\begin{aligned} \epsilon_{\hat{\beta}_f}^2 &= \mathbb{E}_{\hat{\beta}_c} \left[\mathbb{E}_{\mathbf{s}} \left[(\hat{\beta}_f(\mathbf{s}, \hat{\beta}_c) - \bar{\beta}_f(\hat{\beta}_c) + \bar{\beta}_f(\hat{\beta}_c) - \beta_f)^2 \right] \right] \\ &= \mathbb{E}_{\hat{\beta}_c} \left[\mathbb{E}_{\mathbf{s}} \left[(\hat{\beta}_f(\mathbf{s}, \hat{\beta}_c) - \bar{\beta}_f(\hat{\beta}_c))^2 \right] \right] + \mathbb{E}_{\hat{\beta}_c} \left[2(\mathbb{E}_{\mathbf{s}} [\hat{\beta}_f(\mathbf{s}, \hat{\beta}_c)] - \bar{\beta}_f(\hat{\beta}_c)) (\bar{\beta}_f(\hat{\beta}_c) - \beta_f)^T \right] + \mathbb{E}_{\hat{\beta}_c} \left[(\bar{\beta}_f(\hat{\beta}_c) - \beta_f)^2 \right]. \end{aligned} \quad [\text{A5}]$$

The cross-term in Eq [A5] vanishes due to the definition in Eq [A4], resulting in

$$\epsilon_{\hat{\beta}_f}^2 = \mathbb{E}_{\hat{\beta}_c} \left[\mathbb{E}_s \left[(\hat{\beta}_f(s, \hat{\beta}_c) - \bar{\beta}_f(\hat{\beta}_c))^2 \right] \right] + \mathbb{E}_{\hat{\beta}_c} \left[(\bar{\beta}_f(\hat{\beta}_c) - \beta_f)^2 \right]. \quad [A6]$$

The remaining expectation over $\mathbf{s}$ is the variance in $\hat{\beta}_f$ caused by noise in $\mathbf{s}$ for a given value of $\hat{\beta}_c$. In most practical cases, this term has only weak dependence on $\hat{\beta}_c$, and so it can be approximated by the CRB of the variance independently of $\hat{\beta}_c$ as

$$\mathbb{E}_s \left[(\hat{\beta}_f(s, \hat{\beta}_c) - \bar{\beta}_f(\hat{\beta}_c))^2 \right] \approx \sigma_s^2 \left(\mathbf{J}_{\beta_f}^T \mathbf{J}_{\beta_f} \right)^{-1}. \quad [A7]$$

For brevity, this term is defined here as $\sigma_{\hat{\beta}_{f,s}}^2$. Thus, equation [A6] reduces to the approximation,

$$\epsilon_{\hat{\beta}_f}^2 = \sigma_{\hat{\beta}_{f,s}}^2 + \mathbb{E}_{\hat{\beta}_c} \left[(\bar{\beta}_f(\hat{\beta}_c) - \beta_f)^2 \right]. \quad [A8]$$

From here, the same procedure used for expanding Eq [A2] can be applied to the second term of Eq [A8]. To do so, we define two new average parameter terms,

$$\bar{\beta}_c \triangleq \mathbb{E}_{\hat{\beta}_c} [\hat{\beta}_c], \quad [A9]$$

and then

$$\bar{\beta}_f(\bar{\beta}_c) \triangleq \mathbb{E}_s \left[\hat{\beta}_f \left(\mathbf{s}, \mathbb{E}_{\hat{\beta}_c} [\hat{\beta}_c] \right) \right] = \mathbb{E}_s [\hat{\beta}_f(\mathbf{s}, \bar{\beta}_c)]. \quad [A10]$$

Then, adding and subtracting $\bar{\beta}_f(\bar{\beta}_c)$ inside the squared term in Eq [A8] results in

$$\begin{aligned}
e_{\hat{\beta}_f}^2 &= \sigma_{\hat{\beta}_f, s}^2 + \mathbb{E}_{\hat{\beta}_c} \left[(\bar{\beta}_f(\hat{\beta}_c) - \bar{\beta}_f(\bar{\beta}_c) + \bar{\beta}_f(\bar{\beta}_c) - \beta_f)^2 \right] \quad [\text{A11}] \\
&\approx \sigma_{\hat{\beta}_f, s}^2 + \mathbb{E}_{\hat{\beta}_c} \left[(\bar{\beta}_f(\hat{\beta}_c) - \bar{\beta}_f(\bar{\beta}_c))^2 \right] \\
&\quad + 2 \left\{ \mathbb{E}_{\hat{\beta}_c} [\bar{\beta}_f(\hat{\beta}_c)] - \bar{\beta}_f(\bar{\beta}_c) \right\} (\bar{\beta}_f(\bar{\beta}_c) - \beta_f)^T \\
&\quad + (\bar{\beta}_f(\bar{\beta}_c) - \beta_f)^2.
\end{aligned}$$

Here (unlike with Eq [A5]) the cross-term is not zero in general; however, if $\bar{\beta}_f(\hat{\beta}_c)$ is smooth and monotonic over the support of $\hat{\beta}_c$, then $\left| \mathbb{E}_{\hat{\beta}_c} [\bar{\beta}_f(\hat{\beta}_c)] - \bar{\beta}_f(\bar{\beta}_c) \right|$ will be small enough to make the cross-term negligible. (That is, the average fitted parameter using the average constrained parameter is close to the average of fitted parameters across all probable constrained values).

The other expectation in Eq [A11] (second term) is by definition the variance of a random vector function and can be approximated by linear propagation of error as

$$\mathbb{E}_{\hat{\beta}_c} \left[(\bar{\beta}_f(\hat{\beta}_c) - \bar{\beta}_f(\bar{\beta}_c))^2 \right] \approx \frac{\partial \bar{\beta}_f(\bar{\beta}_c)}{\partial \bar{\beta}_c} \Sigma_{\hat{\beta}_c} \frac{\partial \bar{\beta}_f(\bar{\beta}_c)^T}{\partial \bar{\beta}_c}, \quad [\text{A12}]$$

where $\Sigma_{\hat{\beta}_c}$ is the covariance matrix of $\hat{\beta}_c$ and can in turn be estimated by the CRB of the independent measurement. This term represents the propagation of noise from the independent measure, $\hat{\beta}_c$, to the fitted parameters of interest, $\hat{\beta}_f$. Finally, the last term in Eq [A11] is the squared-bias of the average β_f estimate, which results from bias in the measurement $\hat{\beta}_c$.

Thus, in summary, the mean squared error in $\hat{\beta}_f$ when using an independent measure, $\hat{\beta}_c$, of the complementary parameters, is approximated as the sum of three terms,

$$e_{\hat{\beta}_f}^2 \approx \sigma_s^2 \left(\mathbf{J}_{\beta_f}^T \mathbf{J}_{\beta_f} \right)^{-1} + \frac{\partial \bar{\beta}_f(\bar{\beta}_c)}{\partial \bar{\beta}_c} \Sigma_{\hat{\beta}_c} \frac{\partial \bar{\beta}_f(\bar{\beta}_c)^T}{\partial \bar{\beta}_c} + (\bar{\beta}_f(\bar{\beta}_c) - \beta_f) (\bar{\beta}_f(\bar{\beta}_c) - \beta_f)^T. \quad [\text{A13}]$$

This includes the propagation of noise from measured signal (first term), the propagation of noise from the independently measured parameters (second term), and the squared bias resulting from bias in the independently measured parameters (third term). In the special case of a single constrained parameter, this approximation takes on a simpler form,

$$\epsilon_{\hat{\beta}_f}^2 \approx \sigma_s^2 \left(\mathbf{J}_{\beta_f}^T \mathbf{J}_{\beta_f} \right)^{-1} + \sigma_{\hat{\beta}_c}^2 \left(\frac{\partial \bar{\beta}_f(\bar{\beta}_c)}{\partial \bar{\beta}_c} \right)^2 + (\bar{\beta}_f(\bar{\beta}_c) - \beta_f)^2, \quad [\text{A14}]$$

where, again, the superscripts ‘-1’ and ‘2’ represent the matrix inverse and the matrix operation $\mathbf{A}\mathbf{A}^T$, respectively. Equation [A14] is employed in this manuscript for the particular case of T_2 mapping with independent measurement of refocusing pulse flip angle.

Figure 1.

Example multiple spin echo signals resulting from imperfect refocusing. This example used $T_2 = 80$ ms, hard pulse refocusing, and $\theta = 120^\circ$.

Figure 2.

The effect of θ -constraint on $\hat{T}_2$ precision. In general, constraining θ when $SNR_{\hat{\theta}} \gtrsim \frac{1}{2} \times SNR_s$, resulted in higher $SNR_{\hat{T}_2}$ compared that from joint fitting of T_2 and θ (red lines). All calculations for this figure used $SNR_s = 100$.

Figure 3.

$\bar{T}_2(\bar{\theta})$ as a function of $\bar{\theta}$ for four values of θ , demonstrates how bias in the flip angle estimate propagates to bias in the T_2 estimate. The true T_2 value was 80 ms, indicated by the solid gray line.

Figure 4.

Examples of the contributions of standard deviation (SD, blue) and bias (green) to total root-mean-square-error (RMSE, red) of $\hat{T}_2$. When θ is constrained to $\hat{\theta}$, the standard deviation in $\hat{T}_2$ (blue) decreases as $SNR_{\hat{\theta}}$ increases. A small bias in $\hat{\theta}$ (panel a) allows θ -constraint with sufficient $SNR_{\hat{\theta}}$ to decrease the SD of $\hat{T}_2$ below that attained when jointly fitting θ (orange). With a larger bias in $\hat{\theta}$ (panel b), SD of $\hat{T}_2$ can be reduced but the RMSE remains above that for the joint fitted case. All calculations for this figure used $SNR_s = 100$.

Figure 5.

θ bias at which θ -constraint results in a greater $\hat{T}_2$ mean-squared error than joint fitting.

Greater fractional bias ($|\theta - \bar{\theta}|/\theta$) is permitted when $\hat{\theta}$ is more precise and when the multi-echo signal, s , is less precise, conditions which favor constraint. Contrariwise, when s is significantly more precise than $\hat{\theta}$, little or no bias is permitted before constraint penalizes $\hat{\theta}$ mean-squared error.

Table 1

Monte-Carlo simulation results

Fit Type	Analytic [*]	Monte Carlo
	$\varepsilon_{\hat{T}_2}$ (ms)	$\varepsilon_{\hat{T}_2}$ (ms)
Joint Fit	1.13	1.14
Constrained, Unbiased[†]	0.94	0.95
Constrained, Biased[‡]	1.37	1.37

^{*} Equation [1] was used for the joint fit and Eq [3] was used for the constrained- θ fits.

[†] Unbiased fits used $\bar{\theta} = \theta = 150^\circ$.

[‡] Biased fits used $\bar{\theta} = 155^\circ; \theta = 150^\circ$.