Title

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**Abstract**

**Purpose:**

* TBD

**Methods:**

* TBD

**Results:**

* TBD

**Conclusion:**

* TBD

**Keywords:** list

# INTRODUCTION

Paragraph 1

* Intro to qMT & F.
  + (What) is qMT? Cite ([1](#_ENREF_1_1),[2](#_ENREF_1_2))
  + (Why) is qMT important?
  + (Which) qMT parameter is important? Cite Schmierer ([3](#_ENREF_1_3),[4](#_ENREF_1_4)) for histology. Cite Yarnykh ([5](#_ENREF_1_5),[6](#_ENREF_1_6)) for single-param F.
    - (How) is qMT measured? E.g. ancillary measurements like B1, T1.

Paragraph 2

* Transition into where current litt is incomplete
  + In particular, previous MRM paper investigated what is the ideal T1 mapping method to minimize B1-sensitivitiy of qMT, considering a fixed protocol.
  + The optimal qMT protocol conditions to minimize B1-sensitivity have yet to be explored.

Paragraph 3

* Research question(s)

# THEORY

In the presence of a small inaccuracy of a measurement parameter, such as B1 in qMT, a portion of the error will propagate to the fitting parameters of the model. The behavior of this error propagation can be explored through a sensitivity analysis, by expanding the fitted signal in the presence of a ΔB1 with a Taylor expansion ([7](#_ENREF_1_7)). Assuming a small ΔB1 and a good fit (*M*(*B1*+ ΔB1) ≈ *M*(*B1*) ≈ *M*meas, where *M* is the signal generated by the fit), a first-order approximation of the Taylor expansion of the fitted signal results in the following matrix equation ([8](#_ENREF_1_8)):

|  |  |  |
| --- | --- | --- |
|  |  | **[1]** |

where *p* are the model fitting parameters (e.g. for the Sled and Pike model of qMT ([9](#_ENREF_1_9)): F, kf, T2,f, T2,r), is the column vector of errors in fitted parameters [ΔF, Δkf, ΔT2,f, ΔT2,r]ʹ, and are matrices where the elements are sensitivities values , the partial derivatives of the signal *M* relative to each fitting parameters *pi* or *B*1 (columns) for each measurement *n* (rows). can also be described as being the Jacobian of the measurement for the fitting parameters.

Given a ΔB1 value and knowing the Jacobians for *p* and B1, the errors in fitted parameters can be estimated by solving Eq. 1. However, since Eq. 1 is (typically) an overdetermined system of linear equations (), the optimal solution is found by minimizing the 2-norm:

|  |  |  |
| --- | --- | --- |
|  |  | **[2]** |

for .

Although Eq. 2 provides an estimate of the error propagated to the fitting parameters by an error in B1 got a given measurement protocol, it is insufficient in itself for optimal protocol design. qMT protocols must also be designed for robustness again random noise, which is present in measured signals. For this purpose, the Cramér-Rao lower bound (CRLB) as been shown to be an adequate and sufficient estimate to minimize the variance in fitted parameters due to experimental noise ([10](#_ENREF_1_10)).

Consider the Fisher information matrix (FIM) **J**, which has elements:

|  |  |  |
| --- | --- | --- |
|  |  | **[3]** |

where σ is the standard deviation of the noise, and **x***n* is the acquisition protocol for the *n*th measurement out of N unique measurements. The CRLB is defined as the inverse of the FIM, however to take into account the varying weights due to the different order of magnitudes of the fitting parameters, the parameter-normalized CRLB (*V*) is defined ([10](#_ENREF_1_10)):

|  |  |  |
| --- | --- | --- |
|  |  | **[4]** |

In this work, we propose a regularization approach to minimizing both for noise (Eq. 4) and B1-error propagation (Eq. 2), using an iterative optimization approach for the acquisition protocol design ([11](#_ENREF_1_11)). Particularly, we are interested in minimizing the propagation of B1-error to the pool-size ratio *F* (Δ*F*). Thus, to optimally reduce an acquisition protocol of N unique measurements to N-1 measurements, at each iteration we solve for:

|  |  |  |
| --- | --- | --- |
|  |  | **[5]** |

where λ is the regularization parameter constant, and **x**N-1 is the N-1 optimal qMT subset protocol of **x**N for a given iteration. The regularization parameter controls the tradeoff between CRLB (noise) and *F* sensitivity to B1-inaccuracies during the optimization, and its value is determined prior to evaluating the protocol optimization.

# METHODS

The core qMT functions and routines used in the simulations and fitting of this work are from qMRLab (http://github.com/neuropoly/qMRLab), an open-sourced quantitative MRI software packaged which evolved from qMTLab ([12](#_ENREF_1_12)) written in MATLAB (MATLAB 2017a; MathWorks Inc., Natick, MA). The source code developed in this work, particularly for numerically estimating the Jacobians of the system, the protocol optimization algorithms, and the Monte Carlo simulations, is released as its own open-source package (http://github.com/mathieuboudreau/qMTLab\_Tabs). This source code, also written in MATLAB, was developed to wrap around the qMRLab code, to be easily adaptable with other qMT software packages or in-house code.

## Uniform Protocols

The regularization term in Eq. 5 proposed for optimization against B1 was derived as a result of a first-order approximation of a Taylor series. To ensure that this approximation is valid for ΔB1 values used in the optimization routines, **Δ*p*** values (ΔF, Δkf, ΔT2,f, ΔT2,r) were calculated from Eq. 2 for a range of ΔB1 typically observed in vivo (±30%, assuming B1 = 1.0 n.u.), and compared to error parameter values estimated by fitting the signal to the Bloch-McConnell equations. A “uniform” qMT protocols was used, which means a protocol with logarithmically uniform off-resonance frequencies for each MT flip-angle (αMT) preparation pulse (see Table 2). Jacobian calculations for Eq. 2 (and) were estimated from numerical partial derivatives (10-2 % relative increase in parameter values). Two different qMT cases were considered for : B1-independent T1 measurements (IR) and B1-dependent T1 measurements (VFA). Signal simulation details (protocol and tissue parameters) are described in detail in a recent study ([11](#_ENREF_1_11)).

We were also interested in investigating the dependence of values estimated from Eq. 2 on the number of MT flip angles and off-resonance values for “uniform” qMT protocols. MT-prepared SPGR (TR = 25 ms, α = 7°) pulse sequence protocols using every combination of three αMT values (150°, 400°, 650°) were used (each unique αMT, each combination of two αMT values, and all three). Logarithmically-uniform offset frequencies for each αMT values ranged between 300 Hz and 20 kHz. To fairly assess all “uniform” protocols, the total number of acquisitions were limited between 8 and 30 by varying the number of logarithmically uniform offset values per αMT case. For example, a single-αMT 10-point protocol would have 10 off-resonance frequencies, and a two-αMT 10-point protocol would have the same 5 off-resonance frequencies for each αMT. qMT signals were generated for tissue values within the typical white matter range (Table 1). A 5% overestimation in B1 value (ΔB1 = +0.05 n.u.) relative to the expected value (B1 = 1 n.u.) was used for all protocols to solve Eq. 2 for .

## Protocol Optimization

qMT protocol were iteratively optimized ([11](#_ENREF_1_11)) from a large search-space set of potential protocol values of effective MT-preparation pulse flip-angles (αMT) and off-resonance frequencies (Δ), while other sequence parameters remained fixed (TR = 25 ms, α = 7°). The optimization search-space consisted of 312 points; each combination of 12 αMT values (ranging between 150° to 700°, in 50° increments) and 26 Δ values (ranging between 300 Hz and 20 kHz, with logarithmically uniform steps). A few (<5%) protocol points resulted in outlier partial derivative values (non-smooth Jacobian sensitivity curve at those points), which were likely due to rounding errors in the signal simulation of the open-source software used. Those protocol points were replaced with the nearest-neighbor points in a higher-resolution 2929-point search-space (29 αMT and 101 Δ values). Simulated signals were generated for white matter tissue values (Table 1).

The most time-intensive part of the optimization algorithm is computing the Jacobian sensitivities ( and ). The Jacobian sensitivities were precomputed using parallel processing (4 cores), and cached for rapid access during the optimization algorithm. Note that both terms in Eq. 5 require element values from the Jacobian sensitivity matrices (through Eq. 4 and 3).

Prior to protocol optimization, an optimal value for the regularization parameter λ had to be determined. The iterative optimization algorithm evaluating Eq. 5 was executed for a range of λ values (λ = 0, 0.01, 0.1, 0.5, 1, 2, 5), assuming ΔB1 = 0.05 and a B1-dependent T1 mapping method, VFA (TR = 15ms, α = 3° and 15°). Since TR, TE, and α were fixed for all protocol points, the standard deviation of the noise in Eq. 3 (σ) was arbitrarily set to 1 for all calculations. The ΔF values and variance-efficiency ((variance × # acq. points)-1/2, where the variance is interpreted to be the parameter-normalized CRLB) curves versus the # of acq. points of the iterative optimization procedure were compared, and λ = 0.5 was determined to minimize ΔF while having the least overall reduction in variance-efficiency.

Two sets of 10-point protocols were optimized by iteratively finding the N-1 protocol subset which minimized Eq. 5 for ΔB1 = 0.05 (and assuming the VFA as above) and two cases of λ (λ = 0, noted CRLB, and λ = 0.5, noted CRLBλ=0.5). The optimal 10-point protocol for each case were determined, to be compared with the uniform 10-point protocol evaluated in the first part of the previous section.

## Monte Carlo Simulations

Ideal (noiseless) MT-prepared signals were generated through simulations for three 10-point protocols (Table 2: Uniform, CRLB, and CRLBλ=0.5) and two tissue types (Table 1: white matter, grey matter). Rician noise was added to each simulated MT signal, as well as a no-MT signal (typically measured for signal normalization), followed by followed by the typical normalization of the MT-weighted signal from the no-MT signal (*M*MT/*M*no-MT). Six different SNR levels were considered (SNR = 25, 50, 75, 100, 150, 200). Sets of 10,000 noisy MT signals were independently generated and compared for each combination of protocol, tissue, and SNR level. Each set were subsequently fitted for the fitting parameters (F, kf , T2,f, and T2,r) for a range of B1 errors (±30% in increments of 5%), and considering a two-FA VFA T1 mapping method (TR = 15ms, α = 3° and 15°).

# RESULTS

## Uniform Protocols

* Figure 1 remarks
  + First order approximation of Taylor expansion (Eq.1 & 2) seems to be valid for all qMT parameters for ΔB1 = ±5%, as the results from minimizing Eq. 2 match the results from fitting the data within this range.
    - F particularly matches well between Eq. 2 and fitting the data.
  + Fig 1 reproduces well the analysis from Boudreau’s MRM 2017 paper (Fig. 3), validating the use of the qMRLab toolbox in this work.
* Figure 2 remarks
  + Increasing the # of FA or offsets don’t offer a clear advantage regarding minimizing the qMT parameter error due to B1. Some combinations do cross the 0% error, but increasing the number of acq points overshoots this, so it’s likely coincidental and not a reliable way to optimize for B1 error minimization.
  + Single-FA surely not appropriate for F however, as these provided the highest error due to B1. Increasing FA beyond 1FA definitely minimized the B1 error.

## Protocol Optimization

* Figure 3 remarks
  + Jacobian plot, not too much to comment on.
* Figure 4 remarks
  + Optimization of the regularization term.
  + Curves clearly shows the domination of the ΔF term of the regularization for high lamda values, and it’s effect on reducing the variance-efficiency, which is undesirable.
  + Low lamda values provided the best variance efficiency, but ΔF was never minimized (varied arbitrarily far from 0%).
  + Lamda of 0.5 appears to be the best compromise, very small reduction of variance-efficiency relative to lamda = 0, however the ΔF was greatly minimized (reaching close 0 for # acq points of around 30 and below).
* Figure 5 remarks
  + Plots of CRLB and CRLBλ=0.5 iteratively optimized 10 point protocols. Only 3 protocol points differ between the two (7 out of 10 are the same).

## Monte Carlo Simulations

* Figure 6 remarks
  + Errors of meanF were less than 1% for -10% < ΔB1 < 20% when using CRLBλ=0.5 for both WM and GM, yet only true for -5% < ΔB1 < 10% when using CRLB and -5% < ΔB1 < 5% when using the Uniform protocol.
  + The standard deviation of the F distributions between CRLB and CRLBλ=0.5 matched well, and were both much lower than for the Uniform protocol.
* Figure 7 remarks
  + For 0% B1 error: Errors of meanF were less than 1% for SNR greater than 75 (CRLB and CRLBλ=0.5) for bot hWM and GM, and for SNR greater than 100 for the Uniform protocol.
  + For 15% overestimation of B1: No change in the meanF curve for CRLBλ=0.5 for WM, unlike the two other protocols. For GM, slight increase in meanF % different, however still within 1% for SNRs greater than 100.
    - meanF error exceeds 1% for even high SNR for CRLB and Uniform protocol.
  + deltaB1 doesn’t appear to have substantial effect on the standard deviation of the F distribution vs SNR.

# DISCUSSION

* Paragraph 1
  + Summary of results
* Paragraph 2(+?)
  + Compare and contrast to previous studies
    - Our current (and previous) work suggests that optimization for measurement-insensitivity may work better for qMT model designs that fit for most qMT parameters. Single-parameter qMT methods (such as Underhill/Yarnykh ([5](#_ENREF_1_5),[6](#_ENREF_1_6))) may not be well suited for this treatment, as our current (and previous) work shows that the B1 error propagates more to kf when optimizing for F. This is evident from Eq 2, where if F was the sole fitting parameter, B1 error would be entirely propagated to it (proportional to the ratio of sensitivity values between B1 and F).
    - Cite recent work by Lankford et al ([13](#_ENREF_1_13)) et al, which demonstrates a formal derivation of the CRLB/error propagation equations for T2 mapping taking into account B1 error propagation. We only regularized the CRLB by our metric, which is still useful due to its flexibility to being quickly adaptable to other measurements/methods. Future work could be done to derive the formal CRLB equations for qMT (considering that both qMT and the T1 mapping depend on B1), and compared with the regularized equations we presented in this work. However, since we compared very few # of acquisition points (10 pts), and considering that only 3 pts were different between the CRLB and regularized, we don’t expect that a formal derivation of the CRLB /w error propagation could lead to a substantially improved protocol design relative to the work presented here.
* Paragraph 3
  + Limits of study
    - Iterative optimization could lead to local minima. A simulated annealing approach ([10](#_ENREF_1_10)) could improve the overall minimization, at the cost of longer processing time to result in a fixed # of acq. point optimized protocol.
    - Single tissue per voxels were assumed in Monte Carlo and Fitting.
      * For fitting, Cercignani et al 2006 proposed a way to consider multiple tissue types during optimization. Our work could be improved by adapting the code a similar technique.
    - Only evaluated one fitting model, however which has been shown in the past to have the best robustness.
* Paragraph 4
  + Conclusions

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Table 1. Tissue parameters

|  |  |  |
| --- | --- | --- |
| Parameter | White Matter | Grey Matter |
| F | 0.15 n.u. | 0.075 n.u. |
| kf | 4.0 s-1 | 2.5 s-1 |
| T1,f | 0.9 s | 1.3 s |
| T1,r | 1.0 s | 1.0 s |
| T2,f | 30 ms | 55 ms |
| T2,r | 12 μs | 11 μs |

Table 2. qMT protocols

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Uniform | | | CRLB | | | CRLB0.5 | | |
| Acq. # | TR/α | αMT | Δ (Hz) | TR/α | αMT | Δ (Hz) | TR/α | αMT | Δ (Hz) |
| 1 | 25ms/7° | 142° | 432.9 | 25ms/7° | 200.0 | 300.0 | 25ms/7° | 200.0 | 300.0 |
| 2 | 1 087.5 | 250.0 | 1 903.9 | 250.0 | 1609.5 |
| 3 | 2 731.6 | 700.0 | 1 609.5 | 700.0 | 1609.5 |
| 4 | 6 861.6 | 700.0 | 12 083.6 | 700.0 | 12 083.6 |
| 5 | 17 235.5 | 700.0 | 1 903.9 | 700.0 | 2 252.2 |
| 6 | 426° | 432.9 | 250.0 | 2 252.2 | 200.0 | 1 903.9 |
| 7 | 1 087.5 | 150.0 | 300.0 | 650.0 | 300.0 |
| 8 | 2 731.6 | 700.0 | 1 360.6 | 200.0 | 1 360.6 |
| 9 | 6 861.6 | 200.0 | 1 609.5 | 700.0 | 1 903.9 |
| 10 | 17 235.5 | 700.0 | 2 252.2 | 150.0 | 300.0 |

# FIGURE LEGEND

Figure 1. Simulated qMT parameter (F, kf, T2,f, T2,r) errors due to a range (±30%) of B1-inaccuracies (ΔB1), and comparing between a B1-independent T1 measurement (red: IR – inversion recovery) and a B1-dependent T1-measurement (blue: VFA – variable flip andle). Solid lines are parameter errors calculated from minimizing Eq. [2] (first-order approximation of the Taylor expansion), and dotted lines are parameter errors calculated from fitting the qMT signal the Sled & Pike model. The tissue parameters and qMT protocol values were matched to those presented in Boudreau et al. 2017 (see Fig. 3 of the paper).

Figure 2. Simulated qMT parameter (F, kf, T2,f, T2,r) errors estimated from Eq. [2] for ΔB1=0.05, comparing logarithmically-uniform (offsets) qMT protocols between different MT flip-angle combinations. Single (blue, orange, yellow), dual (purple, green, light blue), and triple (red) flip angle combinations of 150°, 400°, and 600° were compared. The number of offset frequencies were uniformly distributed between 300 Hz and 20 kHz, and matched for the total number of acquisition points (# offsets × # flip angles).

Figure 3. Sensitivity values for each qMT fitting parameters (F, kf, T2,f, T2,r) and B1 measurement values considering a B1-independent T1 measure (IR – inversion recovery) and a B1-dependent T1 measure (VFA – variable flip angle). The 312 point protocol (12 flip angles, 26 offset frequencies) shown represents the full search-space for the protocol optimization. The sets of sensitivity values for each fitting parameter (a–d) consists of the matrix columns of the sensitivity Jacobian (S*p* – Eq. 2).

Figure 4. Variance-efficiency (a) and ΔF (Eq. 2, ΔB1 = 5%) values over the course of the iterative optimization of the parameter-regularized Cramer-Rao Lower-Bound (CRLBλ) equation (Eq. 5). variance-efficiency is defined here as (variance × # acq. points)-1/2, where the variance is interpreted to be the parameter-normalized Cramer-Rao Lower Bound (Eq. 3).

Figure 5. Comparison between the 10-point protocol iteratively optimized from a 312 point search space using solely CRLB (λ = 0) and regularized CRLBλ=0.5. The different flip angle z-spectrums of the full search space are all displayed in blue to better display the 10 point protocols. The flip angle z-spectrums (150° to 700°, in 50° increments) range from the highest normalized MT signal values line (150°) to lowest values line (700°).

Figure 6. Mean (a, b) and standard deviations (c, d) of the distribution of pool-size ratio values (F) for sets of Monte Carlo simulations (10,000 runs, SNR = 100) fitted using a range of B1 errors (ΔB1 = ±30%, B1,nominal = 1 n.u.) and for two sets of qMT parameter values representing different tissue types (white matter – a,c; grey matter – b, d). Mean F values (% error) shown here were compared relative to the accurate B1 value case (ΔB1 = 0), and the grey region represents the region of ±1% error. Simulated signal values were generated and fitted for three different 10 point qMT protocols: Uniform (blue) – two-FA protocol with logarithmically-uniform off-resonance frequency values, CRLB (red) – protocol optimized by iteratively minimizing the increase in the parameter-normalized Cramer-Rao Lower-Bound of the system, CRLBλ=0.5 (yellow) – protocol optimized similar to CRLB, regularized by the estimated error of F (ΔF) in the presence of a B1 error (Eq. 5).

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