Title

**Mathieu Boudreau MSc1 and G. Bruce Pike PhD1,2**

1Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada

2Hotchkiss Brain Institute and Department of Radiology, University of Calgary, Calgary, Alberta, Canada

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**Corresponding author**

Mathieu Boudreau

Room WB-325, McConnell Brain Imaging Centre

Montreal Neurological Institute

McGill University, Montreal

Quebec, Canada

H3A 2B4

E-mail: mathieu.boudreau2@mail.mcgill.ca

Phone: (438) 822-8747

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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

The simulated errors in each fitting parameter (ΔF, Δkf, ΔT2,f, ΔT2,r) estimated from the first-order approximation of the Taylor expansion in Eq. 2 (solid lines) and from the relative error in fitting to the Sled and Pike model (dash line) in the presence of B1 errors (±30%) are presented in Figure 1. A B1-independent T1 measure (IR, red) and a B1-dependent T1 measure (VFA, blue) where simulated separately. The overall trends in the error curves produced by fitting the model replicate well the results presented previously ([8](#_ENREF_1_8)) (Boudreau et al 2017, Figure 3), which share the same sequence protocol and tissue parameters, but differed in core qMT simulation and fitting software. Replication of these results justified the use of the open-source qMTLab software ([12](#_ENREF_1_12)) in this study.

The parameter errors estimated from Eq. 2 approximated well the ones resulting from fitting for all parameters for B1 errors within ±5%. For VFA T1 and ΔB1 = 0.05 n.u. (+5 %), the Δ*p* values (Eq. 2, Fit) are: ΔF = (-0.94 %, -1.06 %), Δkf = (14.77 %, 16.88 %), ΔT2,f = (-2.56 %, -1.97 %), and ΔT2,r = (-0.51 %, -0.65%). Both ΔF (for VFA) and ΔT2,r had the most linear trends for the “Fit” case, which resulted in better agreement with Eq. 2 overall. Even though ΔF is very linear for a wide range of ΔB1, a ΔB1 of 0.05 n.u. was selected for the iterative optimization (Eq. 5) later on in this work.

Figure 2 shows the simulated errors in each fitting parameter in the presence of a 5% ΔB1 for a wide range of uniform qMT acquisition protocols (assuming VFA T1), varying in number of FA, number of off-resonance frequencies per FA, and overall number of acquisitions points. Most curves (sets of FA combinations) do trend asymptotically with increasing number of acquisition points, however not specifically towards 0% parameter error values (except for a few T2,r cases, the # FA > 1 cases that contain 650°). For F, the three # FA = 1 curves (dark blue, orange, yellow) result in the largest ΔF values overall, demonstrating the benefit of having at least two flip angles in your qMT protocol to give it lower B1-sensitivity. The three protocols that have # FA > 1 that contain the largest FA=650° (green, light blue, red) resulted in ΔF curves that followed each other closely, and intercepted ΔF = 0 % values for between 10 and 15 total acquisition points. However, ΔF values kept deviating from 0 for these curves for protocols with >15 acquisition points.

## Protocol Optimization

Figure 3 displays the values of the Jacobian sensitivity matrices (**a-d** are the columns of , **e** is , and f is ). Each plot may also be interpreted as the sensitivity of the Z-spectrum relative to each parameter-of-interest (i.e. the change in Z-spectrum signal value due to a small increase in a given parameter). The peak in the sensitivity curve for F occurs at an order of magnitude higher off-resonance frequencies for high FAMT (>500°) relative to the low values (~150-300°), whereas the peak sensitivity for kf remained constant near Δ = 1-2 kHz. The peak in sensitivity curve for also remained constant near Δ = 1-2 kHz, which may explain why kf has the largest errors out of all other fitting parameters due to ΔB1 (Eq. 1) for the VFA case in Figure 1. The higher sensitivity of F at high off-resonance (>10kHz) values relative to might be a contributing factor in its higher robustness against B1, as was mentioned in the previous section for Figure 2 for the uniform protocols (# FA > 1) that contained the high FAMT value (650°).

The variance-efficiency and ΔF values (for ΔB1 = 0.05) over the course of the iterative optimization of the 312-point protocol search space are shown in Figure 4 for a wide range of regularization parameter λ values. The highest variance-efficiency curve occurs for the λ=0 case (i.e. unregularized parameter-normalized CRLB, Eq. 5), as well as for the λ = 0.01 case. The magnitude of ΔF steadily increases to 1% as the protocol is iteratively reduced to ~150 acquisition points, and then proceeds to decrease to ~0.5% for N < 25. Increasing the regularization parameter by an order of magnitude (λ = 0.1) substantially reduces ΔF values for # acq. points > 25 by up to a factor of two while keeping the variance-efficiency relatively unaffected, however ΔF reconverges to ~-0.5% abruptly when the # acq. points are lower than 25. A regularization parameter of 0.5 was the lowest value tested which succeeded in ΔF converging to values near 0 for a low N; for N = 10, λ = 0.5 resulted in ΔF = -0.04% compared to -0.53 % for λ = 0, a relative improvement by a factor of 13. A slight overall reduction in variance-efficiency occurs for λ = 0.5; for N=10, the variance-efficiency reduced by 7% for λ = 0.5 relative to λ = 0. For higher λ values, the regularization term in Eq. 5 dominates early in the iterative optimization at the cost of lower variance-efficiency, which never recovers to its unregularized values. For intermediately-high λ values (λ = 1, 2), a second region where the regularization term in Eq. 5 dominates the iterative optimization is observed near N = 60 and 120 respectively, also at the expense of variance-efficiency. Overall, a λ value 0.5 appears to show the best compromise between ΔF (insensitivity of F against B1) and variance-efficiency out of the parameters evaluated.

The 10-point optimized protocols for λ = 0 (CRLB) and λ = 0.5 (CRLBλ=0.5) are shown in Figure 5, overlayed on the 312-point protocol search-space (displayed as line plots for better visibility of the optimized protocols). The details of these optimized protocols are also listed in Table 2. Overall, both optimized protocols share 7 out of 10 (Δ, FAMT) pairs, with only three acquisition points changing when the regularization term in Eq. 5 (λ = 0.5) is added. Both protocols have coverage of low, medium, and high off-resonance values, as well as low and high FAMT values.

## 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).

Figure 7. 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) fitted using a range of SNR values (25, 50, 75, 100, 150, and 200) 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 data fitted for an ideal SNR case (noiseless), and the grey region represents the region of ±1% error. Data was fitted under the assumption of ideal B1 values (B1 = 1 n.u., solid lines), and for the case of a 15% overestimation in B1 (B1 = 1.15 n.u., dotted lines). 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).



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).



Figure 7. 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) fitted using a range of SNR values (25, 50, 75, 100, 150, and 200) 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 data fitted for an ideal SNR case (noiseless), and the grey region represents the region of ±1% error. Data was fitted under the assumption of ideal B1 values (B1 = 1 n.u., solid lines), and for the case of a 15% overestimation in B1 (B1 = 1.15 n.u., dotted lines). 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).