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

**In submission to: Magnetic Resonance in Medicine**

**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

**Grant support:** Funding for M.B. was provided by the National Sciences and Engineering Research Council of Canada with the Alexander Graham Bell Canada Graduate Scholarships-Doctoral program. Funding to GBP from the Canadian Institutes of Health Research also supported this research.

**Running title:** Title

**Word count: # words**

**Title: TBD**

**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, the errors in fitted parameters can be estimated by minimizing Eq. 1, solving:

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

* Cite Cercignani ([10](#_ENREF_1_10)), parameter-normalized Cramer-Rao Lower Bound

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

* Fisher Information Matrix

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

* *M* 🡪 signal, **x**n 🡪 acquisition protocol for a single measurement, **N** 🡪total number of unique measurements.
* Introduce iterative optimization concept, cite Levesque ([11](#_ENREF_1_11)).

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

* λ – regularization parameter, determines tradeoff between CRLB optimization (noise) and optimization against B1-error sensitivity.
* Iteratively solve Eq. 5 for the subset protocol xN-1 at each iteration, where N is the number of acquisition points solved for in the previous iteration.
* First term minimizes the relative increase in CRLB, second term minimizes for in the presence of a B1 inaccuracy.

# METHODS

* Core qMT signal generation and fitting function used were from the open-source software qMRLab (http://github.com/neuropoly/qMRLab ([12](#_ENREF_1_12)))
* Code developed in this work (Jacobian/sensitivity qMT caching, protocol optimization, Monte Carlo simulations), which wrapped around qMRLab, is also released as an open-sourced package (http://github.com/mathieuboudreau/qMTLab\_Tabs).

## Uniform Protocols

* (Fig 1): Investigate limit of first order Taylor series approximation of Eq. 2.
  + Same protocol (2FA, 10 pt uniform) and tissue parameters as Boudreau 2017 MRM paper. Tissue parameters differ slightly than those used in the remaining paper (still WM though).
* (Fig 2): Explore the approximated errors of each parameters through solving Eq. 2 in the presence of a 5% B1 error for “uniform” protocols (logarithmically-uniform offset frequencies) having a range of flip angles and offsets / # acq. points, to see if can simply be minimized by increasing the # of FAs or offsets in uniform protocols.
  + WM tissue values (F: 0.15, kf: 4.0, T1f: 900 ms, T2f: 30 ms, T2r: 12 microsec.
  + Protocols were all 1, 2, and 3 FA combinations of 150 deg, 400 deg, and 650 deg.
  + Total number of acquisition points ranged from 8 to 30, with the number of offsets (uniformly between 300 Hz to 20 KHz) on the number of FAs (e.g. the 2FA 20 points protocols would have 10 offsets for each FA).

## Protocol Optimization

* Optimizations assume a single tissue type (WM)
* Full protocol search space was 312 points; 12 FAs (150 to 700 deg in 50 deg increments) and 26 offsets (300Hz to 20 kHz).
* (Fig. 3): Jacobian/Sensitivity values most time-intensive calculations (numerical derivatives through signal simulations), so were cached prior to use in optimization. Also helpful to pre-calculate these since this matrix is used in both the CRLB/Fisher Information term and deltaF term of Eq. 5.
* (Fig. 4): Determine the optimal regularization term consisted of comparing the variance-efficiency (interpreting the CRLB as the (lower bound) variance) and ΔF values (solving Eq. 2 for ΔB1 = 5%) during the iterative optimization considering a range of regularization term values (from 0 to 5).
* (Fig. 5): With an optimal regularization term value determined for our system and assumptions (0.5, for optimizing ΔF), optimized 10 point protocols were found through iterative optimization of Eq. 5 using λ = 0 and λ = 0.5. Both protocols (and the full search space) are plotted.

## Monte Carlo Simulations

* Ideal signal generated for two tissue types: WM (same as above in part A) and GM (F: 0.075, kf: 2.5, T1f: 1300 ms, T2f: 55 ms, T2r: 11 microsec)
* Rician noise was added to the MT signal, as well as the no-MT signal, followed by the typical normalization of the MT-weighted signal from the no-MT signal (MT/no-MT).
* Sets of 10,000 noisy signals were generated for each combination of 1- protocol (10 pt Uniform, 10 pt CRLBλ=0, 10 pt CRLBλ=0.5), 2- tissue value (WM & GM), 3- SNR (values: 25, 50 , 75, 100, 150, 200), and were subsequently fitted for a range of B1 errors (±30% in increments of 5%).

# 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 \_\_? et al, which demonstrates a formal derivation of the CRLB 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

# REFERENCES

1. Wolff SD, Balaban RS. Magnetization transfer contrast (MTC) and tissue water proton relaxation in vivo. Magn Reson Med 1989;10(1):135-144.

2. Henkelman RM, Huang X, Xiang QS, Stanisz GJ, Swanson SD, Bronskill MJ. Quantitative interpretation of magnetization transfer. Magn Reson Med 1993;29(6):759-766.

3. Schmierer K, Tozer DJ, Scaravilli F, Altmann DR, Barker GJ, Tofts PS, Miller DH. Quantitative magnetization transfer imaging in postmortem multiple sclerosis brain. J Magn Reson Imaging 2007;26(1):41-51.

4. Schmierer K, Wheeler-Kingshott CAM, Tozer DJ, Boulby PA, Parkes HG, Yousry TA, Scaravilli F, Barker GJ, Tofts PS, Miller DH. Quantitative magnetic resonance of postmortem multiple sclerosis brain before and after fixation. Magnetic Resonance in Medicine 2008;59(2):268-277.

5. Underhill HR, Rostomily RC, Mikheev AM, Yuan C, Yarnykh VL. Fast bound pool fraction imaging of the in vivo rat brain: association with myelin content and validation in the C6 glioma model. NeuroImage 2011;54(3):2052-2065.

6. Yarnykh VL. Fast macromolecular proton fraction mapping from a single off-resonance magnetization transfer measurement. Magn Reson Med 2012;68(1):166-178.

7. Cruz JB. System sensitivity analysis: Dowden, Hutchinson & Ross; 1973.

8. Boudreau M, Stikov N, Pike GB. B1 -sensitivity analysis of quantitative magnetization transfer imaging. Magn Reson Med 2017.

9. Sled JG, Pike GB. Quantitative interpretation of magnetization transfer in spoiled gradient echo MRI sequences. Journal of Magnetic Resonance 2000;145(1):24-36.

10. Cercignani M, Alexander DC. Optimal acquisition schemes for in vivo quantitative magnetization transfer MRI. Magn Reson Med 2006;56(4):803-810.

11. Levesque IR, Sled JG, Pike GB. Iterative optimization method for design of quantitative magnetization transfer imaging experiments. Magn Reson Med 2011;66(3):635-643.

12. Cabana J-F, Gu Y, Boudreau M, Levesque IR, Atchia Y, Sled JG, Narayanan S, Arnold DL, Pike GB, Cohen-Adad J, Duval T, Vuong M-T, Stikov N. Quantitative magnetization transfer imaging made easy with qMTLab: Software for data simulation, analysis, and visualization. Concepts in Magnetic Resonance Part A 2016:n/a-n/a.

# 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 . 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 . 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 . 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 . 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 . 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 . 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 . 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).