# INTRODUCTION

Quantitative Magnetization Transfer (qMT) imaging is a powerful MRI technique used to investigate macromolecular content not typically detectable with conventional MRI. MR properties of macromolecular hydrogen are measured with qMT by indirect means: the magnetization of the macromolecular pool is saturated, and energy is exchanged with nearby water molecules via cross-relaxation processes and chemical exchange (1,2). In imaging brain white matter (WM), the pool-size ratio (F), the ratio between the equilibrium magnetization of hydrogen in macromolecules versus hydrogen in water, has been shown to be a good marker of myelin density (3,4). In particular, the pool-size ratio has been used to study multiple sclerosis lesions (5-7). Several methods have been developed to estimate qMT parameters from the mathematical model that describes the exchange processes (8-12).

Commonly, off-resonance qMT imaging uses an MT-prepared spoiled gradient (SPGR) echo pulse sequence (13). It is a standard SPGR sequence preceded by an off-resonance RF pulse that varies in amplitude and frequency offset between measurements; 10 measurements or more are generally required to fit this Z-spectrum (normalized MT signal vs. off-resonance frequencies) (14), and one additional measurement without the MT-preparation for signal normalization. These qMT techniques also require three additional measurements: B0, B1 and T1. In post-processing, B0 maps calibrate the off-resonance frequency of the MT pulse in each voxel. B1 maps are used to scale the SPGR excitation flip angle and MT-pulse saturation power. A T1 map is necessary to constrain certain fitting parameters of the two-pool MT fitting model (2). For a given voxel, the measured T1 (T1,meas) is a function of the T1 of the water molecules (T1,f, “f” is for “free pool”) and of the T1 of the macromolecules (T1,r, “r” is for “restricted pool”), and two other parameters (F, ratio of the two pool sizes in the voxel, and kf, the exchange rate constant). The large number of measurements required to sample the Z-spectrum and additional quantitative maps make qMT a time-costly technique.

Increasingly, whole-brain qMT imaging has been achieved via a reduction in qMT measurements (15,16) and new rapid techniques to measure the required quantitative calibration maps (17-19). However, integrating new methods into quantitative imaging studies can introduce unintended effects. For example, transitioning from single-slice T1 mapping techniques (i.e. Inversion Recovery - IR) to 3D techniques (i.e. Variable Flip Angle - VFA) also results in transitioning from B1-insensitive (20,21) to B1-sensitive (22) T1 mapping. If VFA is used in the qMT imaging protocol, inaccuracies in B1 will propagate into fitted qMT parameters through two pathways instead of just one (Figure 1): from errors induced in T1, used to restrict the fitting parameters, and from errors in scaling the MT saturation powers with the B1 maps. The potential effect of B1-uncorrected qMT on the fitted parameters has been noted in previous work (23,24), however these were limited in scope to B1-insensitive T1 techniques. To our knowledge no comprehensive characterization of the B1-sensitivity of qMT (and notably, comparing different T1 mapping methods) has previously been performed.

This work focuses on answering the following three questions: 1 - how sensitive is each qMT parameter to B1-inaccuracies?; 2 - how does the B1-sensitivity of qMT parameters differ between protocols using B1-independent (IR) and B1-dependent (VFA) T1 mapping methods?; and, 3 - which T1 mapping method results in the most robust measure of the pool-size ratio in the presence of B1-inaccuracies? To explore these questions, we first focused on simulations under ideal measurement conditions for a single tissue type, and then used this framework to perform a sensitivity analysis of the signal curves. We then measured qMT maps in healthy human volunteers using both T1 mapping methods (IR and VFA), and compared measured B1 maps with fictitious maps generated to have a large range of potential inaccuracies. Finally, we compared the relative agreement of qMT fits between three different B1 mapping methods (Double Angle, Actual Flip angle Imaging, Bloch-Siegert) using both T1 mapping methods (IR and VFA).

# METHODS

All measurements were performed with a 3.0 T whole-body MRI scanner (Magnetom TIM TRIO, Siemens, Erlangen, Germany) using a 32-channel phased-array receive-only head coil and whole-body transmit coil. Healthy volunteers were scanned after providing informed consent, in compliance with and approved by the institutional ethics committee. The total scan time for the entire acquisition protocol described in Sections C and D was 28 minutes and 58 seconds.

## Simulations

The coupled Bloch-McConnell differential equations describing two-pool magnetization exchange were solved numerically (MATLAB2011a, The Mathworks Inc.) for a pulsed MT-prepared SPGR pulse sequence using the Sled and Pike model (23,25). The pulse sequence was decomposed into event blocks of instantaneous saturation of the free pool, constant irradiation of the restricted pool, and free precession. Prior to simulating exchange, the fractional saturation of the longitudinal magnetization induced by direct saturation was computed numerically in the absence of exchange and T1 recovery. The steady-state solution was approximated analytically using the assumption that the magnetization at an arbitrary time *t* should be equal to that of time *t*+TR, as described in detail in the appendix of Ref. 10. The signal was simulated with the following pulse sequence parameters (14,15): repetition time (TR) = 25 ms, excitation flip angle (FA) = 7°, MT pulse flip angle (FAMT) = 142° and 426°, MT pulse duration = 10 ms, 10 off-resonance frequencies ranging between 423.9 Hz and 17.2354 kHz in logarithmic steps. The envelope of the MT-preparation RF pulse was a Gaussian-Hanning function, and a super-Lorentzian lineshape function was used for the transition rate of the restricted pool to approximate the behavior observed in tissues (25). qMT tissue parameters for all simulations were set to healthy white matter values measured in a previous scan: pool-size ratio (F) = 0.122 n.u. (normalized units), magnetization exchange rate (kf) = 3.97-1, free-pool longitudinal relaxation rate (R1,f 1/T1,f) = 1.12 s-1, restricted-pool longitudinal relaxation rate (R1,r 1/T1,r) = 1.00 s-1, free-pool transverse relaxation time (T2,f) = 27.2 ms, restricted-pool transverse relaxation time (T2,r) = 10.96 μs.

SPGR qMT experiments require three additional quantitative measures: B0, B1, and T1. B0 measurement methods typically don’t require B1 or T1 calibration, thus ideal B0 homogeneity was used in the simulations. MT signal values were simulated using B1 (to scale the MT saturation powers and excitation flip angles) and T1,meas (to constrain the fitting parameters) that were fixed to their ideal values (1 n.u. and 0.9 s respectively). The MT signal was subsequently fitted using the Sled and Pike method (23). As per convention, R1,r was fixed to 1 s-1. R1,f was calculated during the fitting algorithm from an analytical expression of F, kf, R1,r and T1,meas. To investigate the effect of inaccuracies in B1 and T1,meas on the fitted qMT parameters, the simulated MT signal values were fitted using a large range of B1 and T1,meas values. Four qMT parameters (F, kf, T2,f, T2,r) were explicitly fitted for each pair of 100 B1 and 100 T1,meas values (10,000 combinations). The set of B1 values varied linearly from 0.5 to 2 n.u., and T1,meas varied from 0.1 s to 4 s. For this stage, B1 and T1,meas varied independently of each other.

We investigated the qMT parameter sensitivities due to B1 inaccuracies for two T1 mapping techniques: IR, approximately B1 independent (21), and VFA, inherently B1-dependent (22). The IR case was interpreted to be a linear subset of the B1-T1 combination discussed above by a fixed T1 (T1,IR = 0.9 s = constant). The VFA signals from a two flip angle experiment were calculated for T1 = T1,true = 0.9 s from the analytical steady-state SPGR equation (TR = 25 ms, FA = 3° and 20°). T1,VFA values were subsequently estimated by linear least-square fitting of the VFA data with flip angle calibration (26) using the set of 100 B1 values (0.5 to 2 n.u.). The fitted VFA T1,meas values were then used in conjunction with their respective B1 values to fit the qMT parameters to the simulated MT signal.

## Sensitivity Analysis

To provide further insight into the behavior of fitted parameters in the presence of B1 inaccuracy, a sensitivity analysis of the qMT signal was performed (27). For each qMT parameter, the following definition of sensitivity was used (cf. Appendix A):

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

where the index *i* describes a specific qMT acquisition point, *Mi* is the normalized signal of the *ith* qMT measurement, and *Sp,i* is the sensitivity of the MT signal with respect to *p* for the *ith* qMT acquisition. The sensitivity *Sp,i* represents the change in normalized MT signal induced by a slight change in fitting parameter value or model input value (e.g. B1). A large absolute *Sp,i* value signifies that, to a linear approximation, a large change in MT signal will occur (at that Z-spectrum value) for a small variation of *p*. In the context of fitting data to measurements using an inaccurate B1 value, the following relationship can be shown (cf. Appendix A):

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|  |  | **[2]** |

Thus, the sensitivity values can provide an insight as to why certain fitting parameters are more likely to have large errors due to inaccurate B1 values. When comparing two measurement protocols, the following metrics can be expected to provide insight into which fitting parameters *p* are more/less sensitive to *B*1 inaccuracies (cf. Appendix A):

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| --- | --- | --- |
|  |  | **[3]** |
|  |  | **[4]** |

where is the vector of sensitivity values for a set of N measurements, is its norm, and is its unit vector. If the sensitivity values of a parameter *p* and B1 have very similar curves (Eq. [3] ≈ 1), then *p* is likely to be most sensitive to B1 inaccuracies compared to other parameters. The relative error of *p* will then be proportional to the ratio in Eq. [4].

The qMT measurement protocol and tissue parameters from Section A were used to simulate normalized MT signal values. Partial derivatives with respect to qMT parameters (and B1) of the MT signal were evaluated at each point of the Z-spectrum (28). B1 sensitivity values were calculated for two cases: T1,meas independent of B1 (which for consistency with the other sections, we denote as IR), and T1,meas with VFA B1-dependency. As T1,meas is primarily used to constrain R1,f, R1,f was modified in addition to B1 accordingly for the VFA case. The derivative steps were fixed to a 10-5 % relative increase of the parameter denominator value, sufficient for the convergence of the partial derivative at each Z-spectrum point of our qMT protocol.

## B1-Sensitivity of qMT in Healthy Subjects

Three healthy adult volunteers were scanned (two males, one female, 30 ± 4 years old). All quantitative imaging sequences were acquired at a resolution of 2x2 mm2 in-plane x 5 mm slice thickness. Single slices were acquired parallel to the AC-PC line, superior to the corpus callosum.

### T1 maps

VFA T1 maps were acquired using a spoiled 3D gradient echo sequence (19): echo time (TE) = 2.89 ms, TR = 15 ms, FA = 3° and 20°, spoiler gradient moment (AG) = 280 mT•ms/m, RF phase increment (φ) = 169°, 1m28s scan time. Prior to fitting the data for T1, the nominal flip angles were scaled voxel-wise with each B1 map. The VFA T1 values were then estimated from linear least square fitting. Inversion recovery T1 data was collected from a four inversion-time (TI) spin echo sequence (21): TE/TR = 11/1550 ms, TI = 30, 530, 1030, 1530 ms, 9m16s scan time. An open-source software package for robust inversion recovery fitting was used to fit the IR T1 maps (20).

### qMT maps

qMT data were acquired according to the 10-point MT-prepared SPGR acquisition protocol described in the simulations methods (Section A), which for our single slice has a 2m38s scan time. B0 maps were acquired for off-resonance frequency correction using a two-point phase-difference gradient measurement (29): TE1/TE2/TR = 4/8.48/25 ms, FA = 7°, 30s scan time. qMT parameter maps were produced by fitting the normalized qMT data voxel-wise using the Sled and Pike fitting model (30).

### B1 maps

Two categories of B1 maps were compared: (1) in vivo measured B1 maps, and (2) B1 maps that had a single value assigned to all voxels (B1,Flat). B1,Flat maps were used to investigate the sensitivity of qMT to B1 inaccuracies for in vivo conditions (noise, tissue partial volume, a broad range of qMT tissue parameter values, etc.). Single-slice double angle (DA) B1 maps (B1,DA) were acquired using a spin echo readout: TE/TR 12/1550 ms, FA = 60°/120°, with slice-selective excitation and 180° refocusing pulses, 4m28s scan time. A set of B1,Flat maps were generated for a range of values (B1,Flat = 0.5, 0.75, 0.9, 1, 1.1, 1.25, 1.5, 2 n.u.), where B1,Flat = 1 n.u. represents the nominal flip angle case. Prior to fitting the qMT data, each B1 map (B1,DA and the set of B1,Flat) was used as a corrective factor for the VFA nominal flip angles, MT excitation flip angles, and MT saturation powers.

### Data analysis

qMT parameter maps (F, kf, T2,f, T2,r) were fitted voxel-wise using four sets of B1 and T1 combinations: B1,DA and B1,Flat used with IR and VFA T1 maps (Figure 1). Voxel data of each qMT parameter map were pooled (across all subjects) for each B1 and T1 set, and linear regression analysis was performed (comparing B1,DA and each B1,Flat).

## B1 Method Comparison

Several techniques exist to measure B1 maps, and each method can be prone to unique sources of systemic biases or local artifacts (31). To probe the robustness of the B1-sensitivity of qMT between different B1 measurement techniques, two additional B1 maps were acquired and compared against the DA B1 maps in all three subjects from Section C. Actual Flip angle Imaging (AFI) (17), a two-TR steady-state SPGR-based pulse sequence, was applied to produce B1 maps with a 2x2x5 mm3 whole-brain 3D spoiled acquisition (19): TE/TR1/TR2 3.53/20/100 ms, FA = 60°, AG = 450 mT•ms/m, φ = 39°, 5m38s scan time. Bloch-Siegert shift (BS) B1 mapping (18), an SPGR-based method with an off-resonance RF preparation pulse, produced B1 maps using a single-slice 2x2x5 mm3 acquisition: TE/TR 15/100 ms, α = 25°, 8 ms Fermi Pulse of 500° at ±4kHz off-resonance, phase-shift constant (KBS) = 74.01 rad/G2, 19s scan time.

At the resolution of our data (2x2x5 mm3), partial volume effects near cortical grey matter (GM) and adjacent to ventricles can be significant. The partial volume effects can make the analysis of in GM challenging. Preliminary data (not shown) suggested that an insufficient number voxels exist containing only GM, for a reliable analysis to be performed, and including all voxels containing at least some GM would include a significant bias in the qMT parameters from cerebrospinal fluid. As such, the images were masked solely for white matter (WM). Whole-brain T1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE) 3D volumes (1x1x1 mm3) were acquired: TE/TR/TI = 3.32/2300/900 ms, iPAT factor = 2 (GRAPPA), BW = 230 Hz/Px, 5m30s scan time. Tissue classification maps (WM, GM, CSF) were estimated via Intensity Normalized Stereotaxic Environment for the Classification of Tissue (INSECT) (32) using the MP-RAGE data with the ICBM-152 atlas. WM tissue masks were resampled to match the AC-PC 2x2x5 mm3 single-slices using a majority voting analysis (75% threshold). The histograms of WM qMT parameters were calculated for all three B1 maps, using both VFA and IR T1 maps in the processing pipeline. Chi-square of the histogram differences was calculated to quantify how well the histograms matched between the DA case versus AFI and BS.

# RESULTS

## Simulations

The error (%) in the pool-size ratio (F) calculated after fitting the simulated qMT signal using each B1 and T1 value-pair is displayed in Figure 2. T1 curves as a function of B1 inaccuracies are superimposed with solid (IR) and dotted (VFA) lines. The error in F (%) is a smooth nonlinear function of B1 and T1, with some speckling in values occurring far from the true B1 and T1 intersection (where they are both grossly inaccurate). IR T1 is set to be constant, resulting in a wide range of errors in F (<-100% to 50%) for the B1 inaccuracy range evaluated. B1 underestimation resulted in an overestimation of VFA T1, and the error in F for this case overlaps near the 0% error contour line (green).

At 3T, the B1 amplitude varies approximately ±30% in the brain. The errors in the four qMT fitted parameters are shown for this range of B1 inaccuracy in Figure 3, for both the IR and VFA T1 cases. Note that Figure 3a corresponds to the values superimposed by the IR and VFA T1 lines in Figure 2. Relative to IR, errors in F due to B1 inaccuracies are substantially reduced using VFA. For VFA, the errors in F ranged between -3% and 7% (blue line) for ± 30% B1 inaccuracy; for IR, the errors ranged between -40% and >100% (red line). kf exhibits the inverse trend; errors in kf are larger for VFA relative to IR (Figure 3b) for all B1 values. No advantage in either T1 method is identified for T2,f; the slopes of the curves flip between both T1 methods with approximately the same magnitude. T2,r is insensitive to B1 inaccuracies for both T1 mapping method (Figure 3d).

For IR, a 10% underestimation in B1 produced a 23% error in F, 6% error in kf, 12% error in T2,f, and 0.78% error in T2,r. For VFA, a 10% underestimation in B1 produced a 1.5% error in F, 25 % error in kf, 6.7% error in T2,f, 0.78% error in T2,r. Thus, switching from IR to VFA reduces B1-sensitivity of F by a factor of 15 for a 10% error in B1. The error in F for the IR case (23%) produced from a 10% error in B1 is consistent with the value calculated by Sled and Pike using a 60 point protocol (20%) (23).

## Sensitivity Analysis

The plots of the sensitivity values for our qMT protocol are shown in Figure 4, and the sensitivity metrics (from Eqs. 3 and 4) are calculated in Table 1. The curve similarity metric informs us of how well changing a particular fitting parameter *p* (*F*, *kf*, *T2,f*, and *T2,r*) can correct the expected signal change due to an error in B1. For a B1-independent T1 measurement (e.g. IR), we see from Table 1 that the values have the following trend: ; for VFA: . This suggests that F has a higher sensitivity to B1 inaccuracies for IR than VFA, with a reverse relationship expected for kf, both in agreement with the simulations results from Section A. Figure 4 illustrates these relationships; the sensitivity curves for (Figure 4a) have a similar pattern to those for F (Figure 4c), while the sensitivity curves for (Figure 4b) have a similar pattern to those for kf (Figure 4d). For these respective cases, is greater for kf  than F (Table 1), suggesting that larger relative errors in kf are required to compensate inaccuracies than F for , consistent with our simulation observations. Lastly, note that the minima observed in is due to a zero-crossing of , a characteristic that was also reported in a previous study (37).

## B1-Sensitivity of qMT in Healthy Subjects

Noise, partial volume effects of tissue, and a wide range of different qMT tissue parameters were not considered in the previous sections, all of which could potentially impact the B1-sensitivity of the qMT fits. In vivo data was acquired to investigate whether the B1-sensitivity features identified in our simulations hold under real-world conditions. Single-slice qMT parameter maps are shown in Figure 5, fitted using VFA (a) and IR (b), for either DA B1 maps or the nominal flip angle assumption (B1,Flat = 1). For VFA and B1,Flat, the elevated T1 at the center of the brain counteracts the underestimated B1 values, resulting in minimal errors in the qMT F maps relative to the IR F maps. At the perimeter of the brain where B1,Flat overestimates the measured values, the VFA case results in nearly no qMT F bias. Regions of very high T1, suggesting presence of CSF, do exhibit speckling of large errors in F. qMT F fitted with the combination of IR and B1,Flat resulted in large errors, where the B1 profile is clearly distinguishable in map of errors in F.

Table 2 lists the correlation and linear regression slope (B1,DA vs. B1,Flat = 1) for all fitted qMT parameters, using both T1 methods. qMT F using VFA had the best correlation (*ρ* = 0.97, slope = 0.97), as opposed to IR (*ρ* = 0.81, slope = 0.57). T2,f also demonstrated good correlations (*ρ* = 0.97), but with an underestimation of the slope (slope = 0.86). Based on our simulations, the low correlation of kf for the IR case (*ρ* = 0.26) was unexpected. Upon further investigation of the raw kf scatter plots (not shown), the linear assumption for fitting the kf scatter plot was violated. Thus, for conditions exhibited in vivo (i.e. noise, multi-tissue voxels), the kf parameter fits were not stable in the presence of large B1 errors, resulting in kf voxel values diverging substantially in the scatter plot data.

Expanding the correlation analysis of F to a larger B1,Flat set of values (ranging from 0.5 to 2 n.u.), F was more robust against B1 overestimations than underestimations (Figure 6a). The correlations break down rapidly for B1,Flat values below 0.75, yet are near unity for most values ranging between 1 and 2. The same trend is true for the fit slope for F; it is near unity slight B1 underestimations and for large B1 overestimations (Figure 6b).

## B1 Mapping Method Comparison

Three B1 maps (DA, AFI, BS) are shown for one subject in Figure 7. The DA B1 map, which was used in the previous section, was set as the reference measurement that the two other methods are compared against. AFI and BS displayed heterogeneous inaccuracy patterns relative to DA; voxelwise relative errors ranged between ±10%. In this subject, B1 in the frontal lobe was overestimated by both methods, while the left and right posterior regions showed different bias patterns for both techniques. Relative to DA, the voxelwise Pearson correlation and linear regression coefficients for all three subjects were *ρ* = 0.904 (y = 1.035 x – 0.034) for BS and *ρ* = 0.912 (y = 0.960 x + 0.038) for AFI. Despite variations in voxelwise accuracy between B1 methods, the histograms of WM qMT F matched very well for the VFA case (Figure 8b, same subject as Figure 7). The excellent overlap of histogram curves for this case resulted in low chi-square values for this subject ( = 1.24, = 1.41), unlike to the IR case for F ( = 5.45, = 6.40). Consistent with our simulations, the inverse relationship was true for kf in WM (Figure 8c and d). The mean chi-square values of F for all subjects also had low standard deviations for VFA ( = 1.24 ± 0.33, = 1.41 ± 0.12) relative to IR ( = 9.25 ± 5.81, = 9.17 ± 3.94; Figure 8a). For kf, the means for all subject for VFA were = 6.10 ± 1.81, = 9.00 ± 3.45, and for IR were = 1.44 ± 0.42, = 2.44 ± 1.21. These results demonstrate the robustness of VFA for qMT F even in the presence local inaccuracies acquired in similar B1 maps, and that B1 maps containing minor artifacts can be used without degradation in quantitative F value precision.

# DISCUSSION

Our findings demonstrate that the B1-sensitivity of off-resonance MT-prepared SPGR qMT parameters is strongly influenced by the T1 mapping method used. We showed that the robustness of the fitted qMT parameters is impacted by the choice between a B1-independent and a B1-dependent T1 mapping method impacts. Overall, the pool-size ratio F was shown to be most robust against B1 errors when VFA T1 mapping is used. Using simulations, we found that a 10% overestimation in B1 results in a 1.5% error in F if VFA is used for T1 mapping. This B1-induced error in F was 15 times less than for B1-independent methods such as IR (23% error in F). While possibly a counter-intuitive prediction, the increased robustness in F against errors in B1 for a B1-dependent T1 method is made possible due to other fitting parameters (particularly kf) are more compatible to compensate the expected signal errors for this case. In vivo measurements were in agreement with our simulations; the F maps fitted using the nominal flip angle assumption (B1 inaccuracy ranging between -10% and 25%) and VFA T1-mapping correlated strongly with the case using a measured B1 map (*ρ* = 0.97). Histogram comparisons of WM qMT F between three different B1 mapping methods showed that VFA could result in 4 to 5 times better histogram matching (chi-squared values) in the presence of B1 inaccuracies compared to IR.

Although most B1 mapping methods are designed to be robust to common sources of potential artifacts (i.e. tissues with long T1), there is no well-accepted gold standard method for accurately imaging B1. Our comparison between three well-accepted B1 imaging methods showed that ±10% in voxelwise differences between B1 maps can be reasonably expected, resulting in inevitable B1 inaccuracies regardless of which technique is chosen. In addition, B1 maps are typically filtered with large blurring kernels (~10 mm3) (17,33,34), because B1 maps are expected to have a smoothly varying profile (35). In the presence of local highly inaccurate voxels, blurring filters can have the unintended effect of biasing nearby voxels. Blurring filters can also be less effective in cortical grey matter due to edge effects, an area that is already sensitive to inaccuracies due to partial volume effects with CSF. Resampling low-resolution B1 maps for higher resolution qMT applications means that some inaccurate B1 information will inevitably be used in qMT post-processing. Overall, some inaccuracies in B1 maps must be considered when planning the qMT acquisition protocol in order to minimize the sensitivity of the qMT parameter(s)-of-interest to this source of error.

The B1-sensitivity characteristics reported here are limited to the qMT imaging method and model that were used. Several other qMT techniques could benefit from a similar analysis; well-established pulsed SPGR qMT alternatives include the Ramani (12) and the Yarnykh (11) models. A key difference between these three MT models is in how they approximate the MT pulse power (25). As B1 is primarily used as a corrective factor for the MT pulse power, B1-sensitivity will likely vary between these methods and could be explored in future work. Our sensitivity analysis results may also suggest that the B1-sensitivity will vary depending on certain key Z-spectrum acquisition choices, particularly dependent on how many MT powers are used. The number of MT powers is conventionally limited to two, however optimized acquisition schemes have used anywhere between one (36,37) and eight MT pulse powers(14).

Despite the fact that VFA T1 mapping benefits qMT by improving robustness of F, even for the extreme case of no B1 correction at all, certain limitations must be carefully taken into consideration prior to integration into a protocol. As shown with simulations and in vivo, the increase in robustness of one qMT parameter for a certain choice of T1 method (e.g. IR or VFA) results in a reduction in robustness of the other fitted parameters. For instance, a study whose aim is to compare all the qMT parameters should refrain from omitting B1 mapping even if VFA is used, as kf will be inaccurate in several regions. Accurate T1 maps, which are valuable to many studies because they correlate with disease characteristics, would also be compromised if measuring B1 is omitted in a qMT protocol that uses VFA. However, for circumstances where the certain qMT parameters have been well-characterized for the disease-of-interest (e.g. multiple sclerosis), choosing to improve the accuracy and robustness of one parameter (e.g. F) at the expense of others may be justified. Reducing the number of measurements to benefit one qMT parameter at the expense of others has been reported previously; for example, constraining multiple fitting parameters was used to achieve a single off-resonance qMT measurement technique of the pool-size ratio (36,37).

In summary, our work revealed the strong dependency of qMT B1-sensitivity on the choice of T1 mapping. Choosing carefully between a B1-independent and B1-dependent T1 mapping method can greatly improve the precision of certain qMT parameters. Our results showed that, for a pulsed SPGR qMT sequence with uniform Z-spectrum sampling, using VFA T1 mapping is preferable if the parameter-of-interest is the pool-size ratio F parameter. The robustness against B1 inaccuracy is so strong for this case that B1 mapping could be omitted altogether without resulting in large differences in fitted qMT F maps. Omitting this measurement could help accelerate lengthy qMT acquisition protocols, at the expense of losing quantitative T1 information. B1-sensitivity of qMT could be further improved by optimizing the Z-spectrum sampling scheme, similar to how qMT acquisition schemes have been optimized for noise performance (14).

# APPENDIX A – SENSITIVITY ANALYSIS EQUATIONS

Let’s assume an experiment consisting of N measurements *M*i,meas (i = 1, 2 ..., N). Fitting the data to a mathematical model, the algorithm is expected converge to a state where |*Mi,meas - Mi,fi*t| is minimized at each point, such that ideally:

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| --- | --- | --- |
|  |  | **[A1]** |

*Mi,fit* depends on a set model parameters (k = 1, 2, .., L). For a small error in an measured model parameter (i.e. a calibration measurement, such as B1 in qMT), the change in each *Mi,fit* is approximated by a Taylor expansion:

|  |  |
| --- | --- |
|  | **[A2]** |

The fitting algorithm will nonetheless aim at producing a good fit (Eq. [A1]), thus the following approximations are expected:

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| --- | --- | --- |
|  |  | **[A3]** |
|  |  | **[A4]** |

A first order approximation of the Taylor series for small and substituting for *Mi* condenses Eq. [A2] to:

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| --- | --- | --- |
|  |  | **[A5]** |

The *Mi* terms cancel, thus any error caused by must be compensated by errors propagated to the remaining fitting parameters for k ≠ j:

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| --- | --- | --- |
|  |  | **[A6]** |

For the Sled & Pike model of qMT, the calibration measurement we are interested in as a possible source of error in this work is B1, and the explicitly fitted parameters are F, kf, T2f and T2r:

|  |  |
| --- | --- |
|  | **[A7]** |

The sensitivity of a measurement *Mi* relative to a model parameter *pk* is defined as (27):

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| --- | --- | --- |
|  |  | **[A8]** |

For a set of N measurements, Eqs. [A7] and [A8] simplifies to matrix form:

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| --- | --- | --- |
|  |  | **[A10]** |

For a given error in B1 (), Eq. [A10] could be minimized to estimate the errors in each fitting parameter (, , , ) having known sensitivity values, which can be calculated analytically or through numerical simulations. However, to simplify the analysis, we chose to compare each fitting parameter *pk* independently to find possible easy to understand metrics to compare fitting parameter sensitivity to B1 inaccuracies. For each fitting parameter-of-interest (, we set all other values to 0. Eq. [A10] now simplifies to a vector equation:

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| --- | --- | --- |
|  |  | **[A11]** |

where is the column vector for the parameter-of-interest *p* in Eq. [A10], similar to . This equation is solved for by doing the scalar product of on both sides of the equation, and separating the norm of the vectors ( and their unit vectors (. Also, since and are absolute errors, they are scaled by the parameter values (, where is the relative error). To better compare each parameter, the relative error is preferred:

|  |  |  |
| --- | --- | --- |
|  |  | **[A12]** |

Thus, for a given relative error in B1 , the parameter *p* which maximizes for a given measurement protocol will likely have larger inaccuracies than the other fitting parameters. This can be visualized easily, since ≈ 1 means that the sensitivity curves for B1 and *p* nearly match, and any change in the Z-spectrum expected by an inaccurate B1 can be nearly completely compensated solely by adjusting that fitting parameter. The error induced () will then proportional to the ratio of overall sensitivities .

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Table 1. qMT Z-spectra sensitivity comparison metrics for B1 (accounting for the B1-sensitivity of each T1 method, IR and VFA) and each fitted qMT parameter. corresponds to the qMT sensitivity values relative to B1 assuming a B1-independent measure of T1, while considers a qMT protocol using a VFA T1 measurement which inherently is B1-dependent.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | |  | |
|  |  |  |  |  |
|  | **0.975** | 0.754 | **2.05** | 1.07 |
|  | 0.815 | **0.951** | 6.02 | **3.12** |
|  | 0.704 | 0.776 | 4.67 | 2.43 |
|  | 0.482 | 0.552 | 3.08 | 1.61 |

Table 2. Pooled (all subjects) Pearson correlation coefficients and linear regression slopes for qMT values comparing measured DA B1 maps and fictitious B1,Flat = 1 mapsa.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **(B1,DA) vs. (B1,Flat = 1)** | | | |
|  | **T1,VFA** | | **T1,IR** | |
| **qMT** | **Pearson *ρ*** | **Slope** | **Pearson *ρ*** | **Slope** |
| F | **0.97** | **0.97** | 0.81 | 0.57 |
| kf | 0.27 | 0.24 | 0.26 | 0.25 |
| T2,f | 0.97 | 0.86 | 0.93 | 0.90 |
| T2,r | 0.81 | 0.78 | 0.89 | 0.82 |

a B1,Flat = 1 is equivalent to the nominal flip angle assumption.

# FIGURE LEGEND

Figure 1. Quantitative measurements used in our MT-prepared SPGR qMT study. Solid arrows are used for required measurements; dotted arrows are used for specific methods of a particular measurement. DA (double angle method) is an explicitly measured B1 map. B1,Flat maps are generated using a single value in all voxels. Variable Flip Angle (VFA) is a T1 mapping methods that also requires B1 as a support measurement, unlike inversion recovery (IR).

Figure 2. Simulated differences (%) in fitted qMT F values in the presence of a wide range of B1 and T1 errors (B1,true = 1 n.u., T1,true = 0.9 s). The superimposed lines plot the T1 distribution for a B1-independent T1 mapping method (IR, solid line) and VFA (dashed line). “n.u.” is the abbreviation for normalized units.

Figure 3. Simulated errors (%) in fitted qMT parameters for ±30% B1 errors (a – pool size ratio (F), b – magnetization exchange rate (kf), c – free pool T2 (T2,f), d – restricted pool T2 (T2,r)). Fits using a B1-independent T1 measure (IR) are shown in red, and those using VFA T1 mapping are shown in blue. Note: the solid and dashed lines in Figure 2 to show the dependence of IR and VFA T1 on B1.

Figure 4. Sensitivity analysis of the MT signal relative to B1 (a,b) and fitting variables (c-f). The plots (note scale changes) show the magnitudes of the sensitivity values (Eq. [2]).

Figure 5. Single-subject comparison of qMT parameter maps fitted using DA and B1,Flat = 1 maps using (a) VFA T1 maps corrected using the corresponding B1 map and (b) IR T1 maps independent of B1.

Figure 6. Pooled (all subjects, voxel-wise) whole brain Pearson correlation coefficients (a) and linear regression slopes (b) for qMT F values between the measured DA B1 maps and generated B1,Flat maps.

Figure 7. B1 map comparison in a single subject using three different acquisition techniques: Double Angle method (DA), Actual Flip angle Imaging (AFI), and Bloch-Siegert shift (BS).

Figure 8. Single-subject WM pool-size ratio (F) (a, b) and MT exchange coefficient (kf) (c, d) distributions for three B1 mapping methods, using IR T1 mapping (a, c) or VFA T1 mapping (b, d). Chi-square values of the AFI and BS histograms were calculated relative to DA.