To mask or not to mask? Improving QSM quality by accounting for spatial frequency distributions and susceptibility sources

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Keywords

1) Magnetic susceptibility, 2) Larmor frequency, 3) Fitting, 4) Inverse problem, 5) Quantitative susceptibility mapping.
Purpose

Estimating magnetic susceptibility using MRI depends on inverting a forward relationship between the susceptibility and measured Larmor frequency. However, an often-overlooked constraint in susceptibility fitting is that the Larmor frequency is only measured inside the sample, and after background field removal, susceptibility sources should only reside inside the same sample. Here we test the impact of accounting for such effects in susceptibility fitting.

Methods

A digital brain phantom with scalar susceptibility was used, and the Larmor frequency was calculated with various levels of noise. Using openly-available susceptibility fitting algorithms, we estimated accuracy by comparing fitting results to ground truth. Next, we implemented the constraints that the Larmor frequency is only measured inside the brain, and susceptibility sources reside in the same volume. The outcome was compared to the standard approach.

We also tested the effect on ex-vivo gradient-echo images of a mouse brain, using the susceptibility fitting algorithms with and without constraints.

Results

Including the spatial distribution of frequencies and susceptibility sources decreased the root-mean-square-error (RMSE) substantially and removed a sign-dependent bias in susceptibility values compared to the standard approach. The relative gain in RMSE increased for increasing SNR. Fitting susceptibility from ex-vivo data revealed a large change in susceptibility estimations, with a relative difference up to 100%.

Conclusion

Informing QSM algorithms about the location of susceptibility sources and where Larmor frequency was measured improved susceptibility fitting for realistic SNR levels and demonstrates that such effects should not be ignored.
**Introduction**

Magnetic susceptibility \( \chi(\mathbf{r}) \) can vary greatly across different tissue types\(^1\), making it a highly desirable contrast mechanism reflecting chemical composition in biological tissues. A method for mapping \( \chi(\mathbf{r}) \) with MRI is dubbed quantitative susceptibility mapping\(^2-8\) (QSM), which aims to determine a voxel-specific scalar magnetic susceptibility, with promising results\(^9-11\). In QSM, the sample is effectively assumed to be isotropic with slowly varying magnetic susceptibility. This assumption allows the Larmor frequency, \( \Omega(\mathbf{r}) \), to be written as a convolution of the susceptibility \( \chi(\mathbf{r}) \) with a Lorentz-corrected dipole kernel\(^12\). Extensions to this simplified model incorporating heterogeneous tissue microstructure have also been proposed\(^13-15\).

However, the inverse problem of estimating \( \chi(\mathbf{r}) \) from the measured \( \Omega(\mathbf{r}) \) has proven to be very difficult. In particular, the inversion is singular as the dipole kernel contains a zero-valued cone. Besides the ill-posed nature of the inversion, and irrespective of the assumed model for tissue complexity, an additional challenge arises from the limited volume in which the Larmor frequency is measured\(^16\), which we refer to as the sample. Moreover, due to the non-local effects of susceptibility, the sample in fact does not include all sources of the induced magnetic field within it: for example, magnetization induced in the body affects the Larmor frequency measured in the brain. The effect of such sources is reduced by so-called background field removal techniques\(^17\), but present QSM algorithms\(^7,8,18-22\) utilizing the Fourier domain for susceptibility deconvolution, result in magnetic susceptibility distributed within the whole field of view (FOV), not limited to the actual sample volume.

Here, we investigate the effect of informing susceptibility fitting algorithms that the Larmor frequency is only measured inside the sample, and constraining susceptibility sources to the volume in which the Larmor frequency has been measured and corrected by the background field removal. Using a digital susceptibility phantom, we measure the fitting accuracy of openly-available QSM algorithms for varying peak signal SNR with and without the proposed constraint. We also demonstrate the effect on real MRI images of ex-vivo mouse brain.
Theory

Forward problem - finding $\Omega$

We consider the relationship between the induced Larmor frequency $\Omega(r)$ in a sample and measured at discrete sampling positions. For simplicity, we assume each discrete location is characterized by a scalar susceptibility $\chi(r)$ with no microstructure. Hence, the sample resembles an isotropic media with voxel-wise constant $\chi(r)$, as in conventional QSM. The relationship between $\chi(r)$ and $\Omega(r)$ can then be written as a linear matrix-vector equation

$$\vec{\Omega} = A \vec{\chi}, \quad \text{(Forward Model)}. \quad (1)$$

Here $\vec{\Omega}$ and $\vec{\chi}$ are $N \times 1$ vectors denoting the measured Larmor frequencies and susceptibility sources in vector form, respectively, where $N$ is the number of voxels in the field of view (FOV). The matrix $A$ is an $N \times N$ symmetric matrix describing the induced frequency from neighboring positions due to the magnetizing external field. The diagonal of $A$ is zero for isotropic liquids, but if the sample exhibits anisotropic magnetic tissue properties, it acquires a non-zero diagonal\(^{14}\). $A \vec{\chi}$ amounts to a linear convolution\(^ {2-4,23}\) of $A$ with $\vec{\chi}$, which can conveniently be implemented in Fourier space using the convolution theorem. Notice that Eq. (1) predicts a non-zero frequency in the whole FOV.

Inverse problem - finding $\chi$

The aim of QSM is to estimate $\vec{\chi}$ from the measured $\vec{\Omega}$ using the known $A$ in Eq. (1). This amounts to inverting (deconvolving with) $A$, which is a well-known ill-posed problem due to the functional form of the dipole field. The list of algorithms with various weights and regularizations to invert Eq. (1) is long, see e.g. refs. \(^ {8,19-22,24-26}\) for a few examples. Prior to fitting (assuming an ideal signal acquisition), $\vec{\Omega}$ must be extracted from the signal phase. First, the phase must be unwrapped\(^{17,27}\). Second, contributions from external magnetized sources must be accurately removed for Eq. (1) to represent sources residing inside the brain, a task for which numerous different algorithms exist\(^ {17}\).
However, after successfully eliminating contributions from external sources, we are left with the following two points (P1 and P2) of consideration:

**P1)** Eq. (1) predicts a non-zero frequency $\Omega$ in the whole FOV, while we only measure it inside the sample due to lack of water outside.

Instead of setting it to zero as is normally done, we account for the lack of data by introducing a sample mask $\tilde{M}$, an $N \times N$ diagonal matrix with $\tilde{M}_{i,i} = 1$ if and only if voxel $i$ is inside the sample. Then the information about actual positions of measurement is captured by replacing $A \rightarrow \tilde{M}A$.

**P2)** Susceptibility $\chi$ should only be non-zero inside the sample upon successful background-field-removal.

We enforce P2 using the same mask $\tilde{M}$, so $\chi \rightarrow \tilde{M}\chi$.

Analogous constraints have previously been used to remove background fields\(^\text{28}\), but here we emphasize that such measures must also be taken for internal sources to represent the measured data correctly. Including P1 and P2 into Eq. (1) forms the new inverse problem we wish to solve given the measured data, which is the focus of the present study:

$$
\min_\chi \| \tilde{\Omega} - \tilde{M}M\chi \|_2^2, \text{ (inverse problem).}
$$

Here $\| \cdot \|_g$ denotes the $L_g$-norm ($g = 2$ in Eq. (2)). Similar to conventional weighted least squares in QSM\(^\text{8}\), $\tilde{M}$ limits the utility of solving the inverse problem exclusively in Fourier space as it becomes a convolution also in Fourier space. This suggests the use of iterative least squares to estimate $\chi$.

Here, we use a digital brain phantom to investigate the effect of including the masking constraint $\tilde{M}$ in various iterative QSM algorithms. Next, we demonstrate the difference in susceptibility fitting on ex-vivo mouse brain images acquired at ultra-high field.
Methods

Digital phantom simulation

All simulations were performed in Matlab (The MathWorks, Natick, MA, USA). We tested the minimization problem, Eq. (2), on a digital brain phantom with a spatially varying scalar susceptibility $\chi_{GT}$ provided with the MEDI toolbox and their MRI signal generator. This produced a complex multi-echo gradient signal $S(t) = \frac{\chi_{GT}}{|\chi_{GT}|} \exp(-i\Omega t) + (\epsilon(t) + i\eta(t))$ with independent Gaussian noise $(\epsilon(t) + i\eta(t)) \sim N\left(0, \frac{1}{\text{SNR}^2}\right)$ in the real and imaginary signal channels for each voxel. We investigated a peak signal SNR ranging from 10 to 200 and with no noise (SNR=∞). Using the toolbox, the Larmor frequency $\Omega$ used for fitting $\chi$ was estimated based on fitting a complex exponential to the signal. No unwrapping and background-field removal was necessary as such effects were not introduced.

Ex-vivo brain imaging

All animal experiments were preapproved by the competent institutional and national authorities and carried out according to European Directive 2010/63.

Animal preparation

Animal experiments were performed on a perfusion-fixed C57BI6 mouse brain. Briefly, the mouse was euthanized prior to the experiment with pentobarbital, transcardially perfused with phosphate-buffered saline (PBS) followed by a 4% paraformaldehyde (PFA) solution. The brain was then extracted and stored in 4% PFA. Before imaging, the brain was washed with PBS to minimize relaxation-effects induced by the fixative. The brain was subsequently placed axially in a 10 mm NMR tube and filled with Fluorinert (Sigma Aldrich, Lisbon, Portugal).

MRI experiments

Experiments were performed on a 16.4 T Bruker Ascend Aeon (Bruker, Karlsruhe, Germany) interfaced with an Avance IIIHD console and a 10 mm Micro5 probe equipped with gradients capable of delivering...
up to 3 T/m in all directions. Remmi sequences (Remmi) were used to acquire 3D gradient-recalled multi-echo images (MGE). Repetition time was 75 ms and bandwidth 150 kHz. The Field-Of-View (FOV) for these 3D acquisitions was $10.2 \times 17.0 \times 10.2$ mm$^3$, matrix size $170 \times 282 \times 170$ which resulted in an isotropic resolution of $(60 \ \mu m)^3$. For MGE, the echo times were 2, 4.5, ..., 49.5 ms. 16 averages were acquired with a total acquisition time of 8.5 hours.

**Processing pipeline**

Complex MRI images were denoised using MP-PCA$^{32}$, with a window size of $[10 \ 10 \ 10]$, and subsequently Gibbs-unrung$^{33}$. The Larmor frequency was then extracted using the MEDI toolbox. The Larmor frequency was then unwrapped using SEGUE$^{27}$ and the projection-onto-dipole-fields (PDF) method$^{34}$ was used for background field removal.

**Fitting algorithms**

To be on par with current standards, we took openly available iterative QSM algorithms and measured their performance in estimating the ground truth scalar susceptibility $\chi_{GT}$ of the digital phantom, and fitting ex-vivo data. Next, we implemented the masks into the algorithms and compared it to the results without masking. We investigated MEDI$^{18,24,25,29,30}$ and two additional $l_1$ and $l_2$ regularized iterative algorithms$^{20}$, which we denote $Fl1$ and $Fl2$, respectively. Including the masks described by P1 and P2, we obtain the following minimization algorithms (* added to label the modified standard algorithms and fitted susceptibility $\bar{\chi}^*$): 

\[
\text{MEDI}^*: \min_{\bar{\chi}^*} \left\| W_1 \nabla \bar{\chi}^* \right\| + \lambda \left\| W_2 \left( \Omega - \tilde{M} \tilde{A} \tilde{M} \bar{\chi}^* \right) \right\|_2 \quad (\text{Liu et al, 2012}),
\]

\[
\text{Fl1}^*: \min_{\bar{\chi}^*} \bar{\chi} \left\| \nabla \bar{\chi}^* \right\| + \frac{1}{2} \left\| \Omega - \tilde{M} \tilde{A} \tilde{M} \bar{\chi}^* \right\|_2 \quad (\text{Bilgic et al, 2012}),
\]

\[
\text{Fl2}^*: \min_{\bar{\chi}^*} \beta \left\| \nabla \bar{\chi}^* \right\|_2 + \frac{1}{2} \left\| \Omega - \tilde{M} \tilde{A} \tilde{M} \bar{\chi}^* \right\|_2 \quad (\text{Bilgic et al, 2012}).
\]
is a structural weighting matrix derived from the gradient of the signal magnitude, while \( W_2 \) is proportional to signal magnitude to compensate for noise variations (see the original articles).

**Analysis and optimal parameter values**

Fitting tolerances, maximum iterations etc. was kept as the default settings for all algorithms (we refer to source code).

**Digital brain phantom**

For the phantom, we compared the ground truth and fitted susceptibilities from the simulations using relative errors \( \varepsilon_x \)

\[
\varepsilon_x = \frac{\bar{\chi}_{GT} - \bar{\chi}_{FIT}}{\bar{\chi}_{GT}},
\]

where the division is understood to be point-wise, and the normalized root-mean-square error (RMSE)

\[
\text{RMSE} = \sqrt{\frac{\left(\bar{\chi}_{GT} - \bar{\chi}_{FIT}\right)^2}{\max(\bar{\chi}_{GT}) - \min(\bar{\chi}_{GT})}}
\]

for the calculations with and without masking, where the mean \( \langle \cdot \rangle \) is over voxels inside the sample (cf. \( \bar{M} \)).

As the fitting parameters \( \lambda, \alpha, \beta \) (cf. Eqs.(3)-(5)) vary for different SNRs, we optimized them by measuring the RMSE (cf. Eq. (7)) at every SNR we considered. We varied the parameters \( \lambda_j = 500 \cdot j \), \( \alpha_j^{-1} = 2000 \cdot j \) and \( \beta_j^{-1} = 500 \cdot j \) for \( j = 1, \ldots, 40 \). The RMSE was calculated for each parameter. The optimal steps \( j_j, j_\alpha, j_\beta \) minimizing the RMSE determined the preliminary optimal regularizations. Then, we varied the parameters in smaller steps \( \lambda_j = 500 \cdot (j_j - 1) + 50 \cdot j \), \( \alpha_j^{-1} = 2000 \cdot (j_\alpha - 1) + 200 \cdot j \) and
\( \beta_j^{-1} = 500 \cdot (j_\beta - 1) + 50 \cdot j \), for \( j = 1, \ldots, 20 \). The fits with the lowest RMSE were then used for further analysis.

**Ex-vivo imaging**

For ex-vivo images, we computed the relative error \( \varepsilon_x \) and RMSE (cf. Eqs.(6)-(7)) based on the estimated susceptibilities \( \chi^* \) and \( \chi \) with and without masks, respectively, and normalized by \( \chi^\prime \).

While the performance of all three algorithms were analyzed, we present here the result using MEDI. Due to the lack of a known ground truth, we fitted \( \chi^* \) and \( \chi \) for \( \lambda_j = 500 \cdot j \), for \( j = 1, \ldots, 40 \). We then considered A) the lowest RMSE between \( \chi^* (\lambda^* = 1e5) \) and \( \chi (\lambda_j) \). We also considered B) \( \chi^* (\lambda^* = 1e5) \) and \( \chi (\lambda) \) that produced the same least squares difference. Lastly, we considered C) \( \chi^* (\lambda^*) \) with equal norm \( \| \chi^* (\lambda^* ) \| \) to the solution \( \chi (\lambda) \) found in A.

**Results**

**Digital brain phantom**

**Optimal parameter values**

Optimal fitting parameters for Eqs. (3)-(5) are shown in Figure 1. The regularization parameters \( \alpha, \beta, \lambda^{-1} \) decrease for higher SNR, amounting for all three algorithms to less regularization when SNR increases. The fitting with and without masking are found to give different behaviors of regularization parameters as SNR increases. The RMSE landscape for \( \beta \) when fitting without masks quickly became
very shallow for increasing SNR. This made its optimal value versus SNR less smooth compared to the other parameters.

Optimal susceptibility fits

The fitted $\vec{\chi}$ for all considered methods is exemplified in Figure 2 for different SNRs. Adding the masking to the fitting algorithm, as specified by P1 and P2, produced a noticeable change in contrast in the susceptibility maps closer to ground truth $\vec{\chi}_{\text{GT}}$ in appearance. The relative error maps $\varepsilon_\chi$ clearly appear more random for high SNR across all fitting algorithms and show less anatomical features and an overall smaller magnitude. The reduced error magnitude is also visible in the error distributions shown in Figure 3, where the errors have been color coded to distinguish fitting with or without masks. For all three algorithms (MEDI, $F_{l1}$, $F_{l2}$), adding masks to the fitting algorithms reduced the error variance for both positive and negative susceptibilities. The mean error was closer to zero, and similar for both positive and negative susceptibilities. In contrast, when fitting without masks the mean error for negative ground truth susceptibility was negative, and vice versa for positive ground truth susceptibility. This sign-dependent bias became clearer when SNR increased, as the variance of each peak decreased. For low SNR, the error distributions became increasingly similar as the benefit of masking was eroded by noise. The difference in RMSE is shown in Figure 4. MEDI with masking showed a decrease in RMSE by a factor of 0.97 to 0.06, $F_{l1}$ 0.75 to 0.1 and $F_{l2}$ 0.76 to 0.23 for increasing SNR.

Ex-vivo brain imaging

The estimated magnetic susceptibility from ex-vivo data is shown in Figure 5 using MEDI. We found large quantitative differences when comparing solutions with minimum RMSE, equal LS$_\Omega$ or equal norm $\|\vec{\chi}\|_2$, which is easiest appreciated by looking at the relative differences in Figure 5. Here we see that regions with sharp boundaries between positive and negative susceptibility exhibited a positive and negative relative difference, which is similar to the bias observed with the phantom. The relative difference can be seen to be order of $\pm100\%$. 
Discussion

To mask or not to mask?

The absence of signal outside the sample is an unavoidable feature in MRI, and not including this limitation can lead to erroneous susceptibility estimations. The error imposed can be understood by considering the inverse problem, Eq. (2), using the iterative conjugate gradient method. Here the solution \( \chi_{k+1} \) at iteration \( k+1 \), depends on all the previous residual vectors \( r_k = \Omega - A\chi_k \). Since \( A\chi \) generates a frequency in the whole FOV, no matter the constraint imposed on \( \chi \), and \( \Omega \) is zero outside the sample, every residual \( r_k \) obtains an error, as the fitting algorithm will try to find a solution that reproduces the zeroes in \( \Omega \), which in turn leads to erroneous solutions \( \chi_{k+1} \). This error can be avoided by introducing a sample mask \( \tilde{M} \), so the residual vectors spanning the solutions become \( r_k = \Omega - \tilde{M}A\tilde{\chi}_k \). The second constraint on allowed positions of susceptibility sources arose, not directly because of unavoidable limitations in how we measure, but rather due to how \( \Omega \) is processed before fitting. Namely, as external sources to the sample produce slowly varying frequency contributions inside the sample, such contributions must be removed prior to susceptibility fitting. While many different algorithms exist for this purpose, common to them all is that an ROI (e.g. \( \tilde{M} \)) must be defined, where frequency contributions from sources outside the ROI is removed. This leaves us with the natural assumption that the only remaining frequency contributions originate from sources within that ROI. If the ROI is \( \tilde{M} \), the residual vectors in our conjugate gradient example should be \( r_k = \Omega - \tilde{M}A\tilde{\chi}_k \), to avoid sources outside \( \tilde{M} \) when estimating \( \chi_{k+1} \). If the background field removal is unsuccessful, the susceptibility fits \( \chi_{k+1} \) will incur an error, and errors may arise due to the constraint itself. It is therefore important that this processing step is done correctly if, ultimately, internal sources are to be accurately estimated.

Simulations
Using optimized regularization parameters in the simulations, we found great improvements in fitting quality by incorporating masks to the fitting algorithms. The error decreased for increasing SNR, and these observations were especially evident in the error distributions, Figure 3, and the RMSE, Figure 4. We found reduced residual anatomical information in the error maps when including the masks. This stemmed from a sign-dependent bias in the fitted susceptibility in the absence of masks, which is evident from Figure 4 for high SNR: here susceptibility values are seen to be effectively repelled from 0.

At a realistic peak signal SNR\(^{36}\) (cf. Figure 4) the performance gain became substantial. For MEDI, the ratio in RMSE with mask vs. without was 0.5, and in the limit of no noise, the ratio dropped to 0.06.

**Ex-vivo imaging**

Fitting the susceptibility of ex-vivo images with and without masks, showed that the differences observed with the phantom was also present in real data. Here we found changes in susceptibility up to 100%, especially in regions with sharp boundaries between positive and negative susceptibility. Such large differences demonstrates that we must be careful the spatial distribution of measured frequency and allowed susceptibility sources.

**Limitations**

Simulating the effect of masking on a digital phantom, enabled us to compare with a known ground truth and control the amount of noise in the MRI signal. In the ex-vivo images, other mechanisms could potentially erode the effect of masking. This includes improper phase unwrapping and background field removal etc.

A few iterative algorithms were investigated here, as it was infeasible to include masks in closed form solutions. Similar to weighted least squares in QSM, fitting can no longer be done exclusively in either real or Fourier space, which favors the use of iterative least squares solutions in which masks can easily be implemented.
Upon inspection of source codes, we found other examples of available QSM algorithms without masking, such as TKD\textsuperscript{7} (closed-form), COSMOS\textsuperscript{8} (closed-form or iterative) and STI\textsuperscript{22} (iterative, based on source code from QSM challenge\textsuperscript{36} 2016), and FANSI\textsuperscript{19} (closed-form + iterative). Hence, a similar error is expected in these algorithms due to the absence of masks.

Here we illustrate the level of improvement achievable in representative existing algorithms, and how easy it is to incorporate these important corrections. A more accurate estimation of $\chi$ could be achieved with a dedicated focus on finding optimal fitting algorithms to incorporate masks, as specified by P1 and P2. $A$ may also contain additional complexity, for example in terms of mesoscopic effects, which introduces diagonal terms to $A$ capturing local structural and/or magnetic anisotropy\textsuperscript{13,14}.

**Conclusion**

We demonstrated a substantial improvement in susceptibility fitting by incorporating the constraints that the Larmor frequency is only measured inside the sample, and susceptibility sources should not reside outside the sample after proper background-field-removal. By simulating the effect in a digital susceptibility brain phantom, a reduced root-mean square error was found for realistic signal SNR. Applying the constraints to images ex-vivo mouse brain also resulted in substantial changes in susceptibility estimation up to 100%. Hence, such effects should not be ignored in QSM and can easily be adopted into iterative QSM algorithms.

**Abbreviations**

QSM: Quantitative Susceptibility Mapping, SNR: Signal-to-noise ratio, FOV: Field-Of-View, MEDI: Morphology-enabled Dipole Inversion, PDF: Projection- Onto-Dipoles, $\ell_1$: Fitting algorithm with $\ell_1$ regularization, $\ell_2$: Fitting algorithm with $\ell_2$ regularization, RMSE: Root-Mean-Squared-Error, TKD: Truncated K-space Division, COSMOS: Calculation of Susceptibility through Multiple Orientation Sampling, STI: Susceptibility Tensor Imaging, FANSI: FAst Nonlinear Susceptibility Inversion.
Figures

Figure 1 - Optimal regularization parameters: A: The optimal weighting parameters for each fitting algorithm, with and without masks (rows) are shown for each of the three algorithms (columns), and for every SNR with finite noise (color-coded). Optimal parameters were found by sweeping through a range of potential values (solid lines), and the parameters that minimized the RMSE was chosen for analysis. $\lambda$ increases since it controls the relative weight of the least squares term, while the others decreases since they control the l1 or l2 penalization term. B: The optimal regularization values for each algorithm.
Figure 2 - Representative susceptibility maps and their relative errors from a mid-axial slice: Top panel shows the resulting susceptibility maps from fitting with or without masks, using MEDI, F11 or F12, respectively. Rows corresponds to different SNRs from 10 to ∞. The bottom panel shows the relative error to the ground truth. The colorbar is truncated at ±20%. 
Figure 3- Histogram of relative error in susceptibility fits: Rows corresponds to different peak signal SNRs going from 10 to $\infty$. The first two columns are the error using MEDI, color-coded to distinguish fitting with and without masks. The first column shows the error for negative susceptibility values, while the second column shows positive. The next two columns show the error using Fl1, while the last two is for Fl2. Notice a negative bias for $\chi_{\text{GT}} < 0$ susceptibility and a positive bias for $\chi_{\text{GT}} \geq 0$, when fitting is done without mask.
Figure 4 - Normalized root-mean-squared error: The normalized RMSE decreases for increasing SNR. The decrease is stronger for fitting with masking. For an SNR around 100, the RMSE for MEDI, Fl1 and Fl2 decreased by factors of 0.5, 0.2, 0.3, respectively. This emphasizes the importance of including proper masking in susceptibility fitting.
Figure 5 - QSM fitting using MEDI w. and w.o. mask: We compare the estimated susceptibility using MEDI for different regularization parameters $\lambda$, w. masks and w.o. masks, that A) minimized the RMSE between the two (vertical). For this we considered $\lambda = 1e5$ and $\lambda = 63 \cdot 1e3$, respectively. Next we considered B) the estimated susceptibility that produced the same least squares $LS_\Omega = \| \Omega - \hat{A} \hat{\chi} \|_2$. For this we chose $\lambda = 1e5$ and $\lambda = 35 \cdot 1e3$, respectively. Lastly, we considered C) the susceptibility with the same norm $\| \hat{\chi} \|_2$ by choosing $\lambda = 26 \cdot 1e3$ and $\lambda = 63 \cdot 1e3$, respectively. All three cases show substantial changes in susceptibility estimation, and contrast, which is visible from looking at the relative error.
References

1. Fukunaga M, Li TQ, Van Gelderen P, et al. Layer-specific variation of iron content in cerebral cortex as a source of MRI contrast. *Proc Natl Acad Sci U S A*. 2010;107(8):3834-3839. doi:10.1073/pnas.0911177107

2. Salomir R, de Senneville BD, Moonen CT. A fast calculation method for magnetic field inhomogeneity due to an arbitrary distribution of bulk susceptibility. *Concepts Magn Reson*. 2003;19B(1):26-34. doi:10.1002/cmr.b.10083

3. Jenkinson M, Wilson JL, Jezzard P. Perturbation method for magnetic field calculations of nonconductive objects. *Magn Reson Med*. 2004;52(3):471-477. doi:10.1002/mrm.20194

4. Marques JP, Bowtell R. Application of a Fourier-based method for rapid calculation of field inhomogeneity due to spatial variation of magnetic susceptibility. *Concepts Magn Reson Part B Magn Reson Eng*. 2005;25B(1):65-78. doi:10.1002/cmr.b.20034

5. Deistung A, Schweser F, Reichenbach JR. Overview of quantitative susceptibility mapping. *NMR Biomed*. 2017;30(4):e3569. doi:10.1002/nbm.3569

6. Li L, Leigh JS. Quantifying arbitrary magnetic susceptibility distributions with MR. *Magn Reson Med*. 2004;51(5):1077-1082. doi:10.1002/MRM.20054

7. Wharton S, Schäfer A, Bowtell R. Susceptibility mapping in the human brain using threshold-based k-space division. *Magn Reson Med*. 2010;63(5):1292-1304. doi:10.1002/MRM.22334

8. Liu T, Spincemaille P, De Rochefort L, Kressler B, Wang Y. Calculation of susceptibility through multiple orientation sampling (COSMOS): A method for conditioning the inverse problem from measured magnetic field map to susceptibility source image in MRI. *Magn Reson Med*. 2009;61(1):196-204. doi:10.1002/mrm.21828

9. Eskreis-Winkler S, Zhang Y, Zhang J, et al. The clinical utility of QSM: disease diagnosis, medical management, and surgical planning. *NMR Biomed*. 2017;30(4). doi:10.1002/nbm.3668

10. Eskreis-Winkler S, Deh K, Gupta A, et al. Multiple sclerosis lesion geometry in quantitative susceptibility mapping (QSM) and phase imaging. *J Magn Reson Imaging*. 2015;42(1):224-229.
11. Wang Y, Spincemaille P, Liu Z, et al. Clinical quantitative susceptibility mapping (QSM): Biometal imaging and its emerging roles in patient care. *J Magn Reson Imaging*. 2017;46(4):951-971. doi:10.1002/jmri.25693

12. Ruh A, Kiselev VG. Calculation of Larmor precession frequency in magnetically heterogeneous media. *Concepts Magn Reson Part A*. 2018;47A(1):e21472. doi:10.1002/cmr.a.21472

13. Kiselev VG. Larmor frequency in heterogeneous media. *J Magn Reson*. 2019;299:168-175. doi:10.1016/j.jmr.2018.12.008

14. Sandgaard AD, Kiselev VG, Shemesh N, Jespersen SN. Larmor frequency shift from magnetized cylinders with arbitrary orientation distribution. Published online March 2, 2022. doi:10.48550/arxiv.2203.01191

15. Yablonskiy DA, Sukstanskii AL. Generalized Lorentzian Tensor Approach (GLTA) as a biophysical background for quantitative susceptibility mapping. *Magn Reson Med*. 2015;73(2):757-764. doi:10.1002/mrm.25538

16. Wang Y, Liu T. Quantitative susceptibility mapping (QSM): Decoding MRI data for a tissue magnetic biomarker. *Magn Reson Med*. 2015;73(1):82-101. doi:10.1002/mrm.25358

17. Schweser F, Robinson SD, de Rochefort L, Li W, Bredies K. An illustrated comparison of processing methods for phase MRI and QSM: removal of background field contributions from sources outside the region of interest. *NMR Biomed*. 2017;30(4). doi:10.1002/NBM.3604

18. Liu J, Liu T, De Rochefort L, et al. Morphology enabled dipole inversion for quantitative susceptibility mapping using structural consistency between the magnitude image and the susceptibility map. *Neuroimage*. 2012;59(3):2560-2568. doi:10.1016/J.NEUROIMAGE.2011.08.082

19. Milovic C, Bilgic B, Zhao B, Acosta-Cabronero J, Tejos C. Fast nonlinear susceptibility inversion with variational regularization. *Magn Reson Med*. 2018;80(2):814-821. doi:10.1002/MRM.27073
20. Bilgic B, Pfefferbaum A, Rohlfing T, Sullivan E V., Adalsteinsson E. MRI estimates of brain iron concentration in normal aging using quantitative susceptibility mapping. *Neuroimage*. 2012;59(3):2625-2635. doi:10.1016/J.NEUROIMAGE.2011.08.077

21. Bilgic B, Fan AP, Polimeni JR, et al. Fast quantitative susceptibility mapping with L1-regularization and automatic parameter selection. *Magn Reson Med.* 2014;72(5):1444-1459. doi:10.1002/MRM.25029

22. Liu C. Susceptibility tensor imaging. *Magn Reson Med.* 2010;63(6):1471-1477. doi:10.1002/mrm.22482

23. Ruh A, Scherer H, Kiselev VG. The larmor frequency shift in magnetically heterogeneous media depends on their mesoscopic structure. *Magn Reson Med.* 2018;79(2):1101-1110. doi:10.1002/mrm.26753

24. Liu T, Liu J, De Rochefort L, et al. Morphology enabled dipole inversion (MEDI) from a single-angle acquisition: Comparison with COSMOS in human brain imaging. *Magn Reson Med.* 2011;66(3):777-783. doi:10.1002/MRM.22816

25. De Rochefort L, Liu T, Kressler B, et al. Quantitative susceptibility map reconstruction from MR phase data using bayesian regularization: validation and application to brain imaging. *Magn Reson Med.* 2010;63(1):194-206. doi:10.1002/MRM.22187

26. Bilgic B, Xie L, Dibb R, et al. Rapid multi-orientation quantitative susceptibility mapping. *Neuroimage*. 2016;125:1131-1141. doi:10.1016/J.NEUROIMAGE.2015.08.015

27. Karsa A, Shmueli K. SEGUE: A Speedy rEgion-Growing Algorithm for Unwrapping Estimated Phase. *IEEE Trans Med Imaging*. 2019;38(6):1347-1357. doi:10.1109/TMI.2018.2884093

28. Liu T, Khalidov I, de Rochefort L, et al. A novel background field removal method for MRI using projection onto dipole fields (PDF). *NMR Biomed.* 2011;24(9):1129. doi:10.1002/NBM.1670

29. Liu T, Wisnieff C, Lou M, Chen W, Spincemaille P, Wang Y. Nonlinear formulation of the magnetic field to source relationship for robust quantitative susceptibility mapping. *Magn Reson
30. Liu Z, Spincemaille P, Yao Y, Zhang Y, Wang Y. MEDI+0: Morphology enabled dipole inversion with automatic uniform cerebrospinal fluid zero reference for quantitative susceptibility mapping. *Magn Reson Med.* 2018;79(5):2795-2803. doi:10.1002/MRM.26946

31. Birkl C, Langkammer C, Golob-Schwarzl N, et al. Effects of formalin fixation and temperature on MR relaxation times in the human brain. *NMR Biomed.* 2016;29(4):458-465. doi:10.1002/nbm.3477

32. Veraart J, Novikov DS, Christiaens D, Ades-aron B, Sijbers J, Fieremans E. Denoising of diffusion MRI using random matrix theory. *Neuroimage.* 2016;142:394-406. doi:10.1016/j.neuroimage.2016.08.016

33. Kellner E, Dhital B, Kiselev VG, Reisert M. Gibbs-ringing artifact removal based on local subvoxel-shifts. *Magn Reson Med.* 2016;76(5):1574-1581. doi:10.1002/mrm.26054

34. Zhou D, Liu T, Spincemaille P, Wang Y. Background field removal by solving the Laplacian boundary value problem. *NMR Biomed.* 2014;27(3):312-319. doi:10.1002/nbm.3064

35. Hestenes MR, Stiefel E. Methods of Conjugate Gradients for Solving Linear Systems 1. *J Res Natl Bur Stand (1934).* 1952;49(6).

36. Milovic C, Tejos C, Acosta-Cabronero J, et al. The 2016 QSM Challenge: Lessons learned and considerations for a future challenge design. *Magn Reson Med.* 2020;84(3):1624-1637. doi:10.1002/MRM.28185