Weak-Harmonic Regularization for Quantitative Susceptibility Mapping (WH-QSM)

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Abstract

Purpose: Background-field removal is a crucial preprocessing step for quantitative susceptibility mapping (QSM). Remnants from this step often contaminate the estimated local field, which in turn lead to erroneous tissue-susceptibility reconstructions. The present work aimed to mitigate this undesirable behavior with the development of a new approach that simultaneously decouples background contributions and local susceptibility sources on QSM inversion.

Methods: Input phase data for QSM can be seen as a composite scalar field of local effects and residual background components. We developed a new Weak-Harmonic (WH) regularizer to constrain the latter and to separate the two components. The resulting optimization problem was solved with the Alternating Directions of Multipliers Method (ADMM) framework to achieve fast convergence. In addition, for convenience a new ADMM-based preconditioned nonlinear Projection onto Dipole Fields (nPDF) solver was developed to enable initializations with wrapped-phase distributions. WH-QSM, with and without nPDF preconditioning, was compared to the original (ADMM-based) Total Variation QSM algorithm in phantom and in vivo experiments.

Results: WH-QSM returned improved reconstructions irrespective of the method used for background-field removal, though the proposed nPDF method often obtained better results. Streaking and shadowing artifacts were substantially suppressed, and residual background components were effectively removed.

Conclusion: WH-QSM with field preconditioning is a robust dipole inversion technique and has the potential to be extended as a single-step formulation for initialization with uncombined multi-echo data.

Keywords

Nonlinear Inversion, Total Variation, Augmented Lagrangian, Alternating Direction Method of Multipliers (ADMM), Background Field Removal

Introduction

Phase shifts in gradient-recalled echo (GRE) MRI acquisitions capture local perturbations of the main magnetic field resulting from the self-magnetization of the imaged object as well as large-scale field inhomogeneities (e.g. from imperfect shimming (1,2)). In conventional Quantitative Susceptibility Mapping (QSM), large-scale field offsets, often called background (or external) field, are estimated and removed by specialized algorithms designed to isolate the local field (3). The latter is then used to reconstruct the underlying susceptibility distribution. According to Maxwell's Laws, external contributions must comply with Laplace's equation (i.e. the divergence of the gradient must be zero) for a region of interest (ROI) that excludes susceptibility sources (4-6). Functions that satisfy Laplace's equation are called "harmonic" functions. In fact, most background-field removal algorithms exploit the properties of such functions to separate internal from external contributions. Since the latter is typically several orders of magnitude larger than local magnetization effects originated from brain tissue (7,8), most QSM algorithms require accurate background-field suppression prior to initialization.

Broadly speaking, background-elimination methods can be classified into three families. The first family includes algorithms that exploit the spherical mean value (SMV) property of harmonic functions, i.e., given a radially symmetric convolution kernel, any harmonic function is invariant to convolutions with such a kernel (9,10). This forms the basis of the Spherical Harmonic Projection (SHARP) (11) operation and its derivatives (12-15). The second family is concerned with solving Laplace's equation (or the complementary Poisson equation) to estimate the local field directly from the total field map. In addition to Fourier-based approaches (16,17), one popular algorithm is the Laplacian Boundary-Value method (LBV) (18), which solves the Poisson equation for a given ROI imposing Dirichlet boundary conditions on the local magnetization using a multigrid method (19). The third family is based on the orthogonal property of harmonic basis functions, whereby algorithms estimate a source distribution outside the ROI that minimizes the energy of the composite field-induction measured within the ROI. The most representative algorithm within this family is the Projection onto Dipole Fields (PDF) method (20).

Although by definition all background-removal algorithms are somewhat analogous and only differ to a significant degree near the ROI boundary, the resulting local fields are often contaminated by different low amplitude—but large spatial extent—errors. These errors can severely impair the conditioning of the (already ill-posed) dipole inversion (3) and produce reconstructions with extended streaking artifacts and spurious susceptibility gradients or sources. A new generation of the so-called single-step algorithms has been proposed (21-24) to address this shortcoming. These algorithms perform simultaneous background-removal and susceptibility-inversion operations to enable dynamic modeling of internal and external sources at each iteration, which effectively reduce reconstruction artifacts. It remains unclear, however, whether appropriate phase-noise modeling, or more generally, implementation of error-propagation control strategies would further improve their performance (24-26). Phase-noise errors in low signal-to-noise (SNR) areas are a major source of streaking artifacts in QSM (25). In this context, Differential QSM (23), a robust noise-modeling approach, has been recently proposed as a nonlinear implementation of a Poisson solver. A limitation of this algorithm, however, is that data fidelity is not computed relative to the measured phase data but to a prefiltered phase

distribution (calculated through spatial convolution with Laplacian and $1/r$ functions). This precludes direct initialization with raw wrapped-phase data (to avoid the propagation of unwrapping errors). In addition, a potential caveat of Differential QSM approaches is that they might exclude local sources that generate harmonic-like magnetization profiles within the ROI.

A different approach was proposed in the context of Total Field Inversion (TFI) (27). TFI, however, is a severely ill-posed problem; in addition to dipole-kernel zero coefficients, the fields emanating from extra-cerebral sources are abruptly truncated at regions with poor SNR and at field-of-view (FOV) boundaries. In order to improve TFI conditioning, i.e. with a view to ameliorate the impact of large-scale dipole truncation, the authors proposed the incorporation of prior information on areas with large susceptibility differences such as air and brain tissue interfaces. Such an approach, however, requires accurate segmentation of proton-free structures such as cranial cavities, which in practice is difficult to achieve reliably.

Nonlinear formulations can appropriately model the phase-noise characteristics whilst being insensitive to unwrapping errors (25). With a robust initialization, nonlinear algorithms enable data fidelity costs to be directly calculated from wrapped phase data. This opens a new window of opportunities for developing algorithms that work as nonlinear perturbations of previous approximations, whilst concurrently computing data-fidelity costs in relation to the native phase distribution. This helps preventing the propagation of errors introduced by intermediate processing steps such as coil/multi-echo combination, unwrapping, *etc.* Given that background-field removal algorithms usually leave some field remnants, we developed a new nonlinear QSM algorithm, named Weak-Harmonic regularized QSM (WH-QSM), that incorporates prior knowledge on the harmonic property of external fields. We hypothesized such prior would provide an additional layer of spurious-background control, which should improve QSM stability. To enable direct initialization from wrapped-phase data, we also propose a sequential method that approximates the background field by forward-simulation of air-tissue magnetization effects. This strategy was devised to subsequently initialize a nonlinear Projection onto

Dipole Fields (nPDF) routine, in turn suitably preconditioning WH-QSM for improved accuracy and precision, and a flexible implementation that might enable single-step extensions.

Theory

Weak-Harmonic regularized QSM (WH-QSM)

The measured GRE phase within a given ROI, Φ , is composed of local offsets resulting from a susceptibility distribution, χ , and a composite of background contributions, ϕ_h . This can be expressed as:

$$\Phi = F^H D F \chi + \phi_h, \quad \text{Eq. 1}$$

where D is the dipole kernel in the frequency domain $D = \gamma H_0 T E \left(\frac{1}{3} - \frac{k_z^2}{k^2} \right)$, and F is the Fourier operator with its adjoint F^H . Subsequently, we formulate the following image reconstruction problem to determine χ :

$$\underset{\chi, \phi_h}{\operatorname{argmin}} \frac{1}{2} \left\| W \left(e^{i(F^H D F \chi + \phi_h)} - e^{i\Phi} \right) \right\|_2^2, \quad \text{Eq. 2}$$

where W —proportional to the signal magnitude—compensates for phase-noise non-uniformities (28). Note that the above formulation assumes a Gaussian-noise distribution in the complex GRE signal.

According to Maxwell's Laws, ϕ_h consists of harmonic functions (4-6). Consequently, through the

application of the Laplacian operator to Eq. 1 we can derive two key properties:

$$\nabla^2(F^H DF\chi + \phi_h) - \nabla^2 \Phi = 0 \rightarrow \begin{matrix} \nabla^2 \phi_h = 0 \\ \nabla^2(F^H DF\chi) = \nabla^2 \Phi \end{matrix} \quad \text{Eq. 3}$$

The Poisson relationship has been previously used in single-step formulations (21-24). Alternatively, we hereby propose incorporating the Laplacian (weak-harmonic) constraint to the functional as follows:

$$\underset{\chi, \phi_h}{\operatorname{argmin}} \frac{1}{2} \left\| W \left(e^{i(F^H DF\chi + \phi_h)} - e^{i\Phi} \right) \right\|_2^2 + \frac{\beta}{2} \left\| m \nabla^2 \phi_h \right\|_2^2 + \alpha R(\chi) \quad \text{Eq. 4}$$

The first term enforces data fidelity as in Eq. 1. The second term is the new weak-harmonic penalty (with m a binary mask defining the ROI). $R(\chi)$ is the regularizer of choice e.g., a variational term such as Total Variation (TV) or Total Generalized Variation (TGV). Finally, α and β are regularization weights. The ROI mask, m , enforces ϕ_h to be harmonic within the ROI, thus enables ϕ_h to capture phase components from external sources. However, ϕ_h is also set free to evolve dynamically outside the ROI. The rationale is two-fold: first, there might be magnetized objects within the FOV but outside the ROI (e.g. the skull or cerebrospinal fluid); and second, the local object might generate harmonic fields outside the ROI. Of note, if we enforce ϕ_h to be harmonic across the whole field of view, it would fail to capture some of these effects and would introduce errors in the susceptibility calculation. This is a somewhat different approach to most field-filtering algorithms which often neglect magnetization effects outside the ROI.

The proposed optimization problem was efficiently solved using the Alternating Directions of Multipliers Method (ADMM) algorithmic framework (29-33) which is described in further detail in the Supplementary Material.

WH-QSM preconditioning

The performance of the WH-QSM algorithm can be maximized through appropriate phase initialization, ϕ_{h0} . To this end, we propose the use of a nonlinear Projection onto Dipole Fields (nPDF) approximation defined as follows:

$$\underset{\chi_h}{\operatorname{argmin}} \frac{1}{2} \left\| W \left(e^{i F^H DFM \chi_h} - e^{i \Phi} \right) \right\|_2^2, \quad \text{Eq. 5}$$

where ϕ_{h0} is the phase associated with the external susceptibility distribution, χ_h , i.e.

$\phi_{h0} = F^H DFM \chi_h$ and $M = 1 - m$. Furthermore, if we had accurate prior knowledge on the source distribution outside the ROI, χ_e (as for TFI, (27)), the external field in nPDF could be initialized as the forward-simulated phase (ϕ_s) from external sources plus a 3D linear gradient (ϕ_x, ϕ_y, ϕ_z) and a constant offset ϕ_0 , i.e. $\phi_s = \kappa_e \cdot d * \chi_e + \kappa_x \phi_x + \kappa_y \phi_y + \kappa_z \phi_z + \phi_0$. Here $\kappa_e, \kappa_x, \kappa_y, \kappa_z$ and ϕ_0 are constants found by least squares fitting. We found empirically that this initialization helps to improve nPDF's accuracy and convergence, by avoiding local minima when solving the nonlinear functional. The nPDF operation, thus, can be seen as a perturbation from this initial state. The resulting background phase ϕ_{h0} may then be used as initialization of the harmonic field ϕ_h in WH-QSM, or as an independent previous step. An additional advantage of nPDF is that wrapped phases can be used as input data, which reduces the potential risk of artifact propagation from e.g. unwrapping errors. In fact, with a close initial estimate of the external simulated field ϕ_s , unwrapping algorithms are not required to initialize the internal variables. The same is true for the WH-QSM algorithm. The background field estimate, ϕ_{h0} , enabled the use of wrapped phase data as input for the data-fidelity term, avoiding further artifact propagation into the final susceptibility calculation. For more information on nPDF's ADMM implementation see the Supplementary Material. The source code for the proposed reconstruction is publicly available as a part of the FANSI (Fast Nonlinear Susceptibility Inversion) toolbox:

Methods

The proposed WH-QSM algorithm was compared with a previous nonlinear TV implementation based on the same ADMM solver (TV-FANSI) (33), which was found to perform on a par with the nonlinear Morphology Enabled Dipole Inversion algorithm (nMEDI) (25):

COSMOS-brain numerical simulation

A noise-corrupted field map was forward-simulated (additively with $\text{SNR} = 40$) using (i) the 12-head-orientations COSMOS reconstruction (34) included in the 2016 QSM Reconstruction Challenge dataset (35) from spoiled 3D-GRE scans acquired on a 3T Siemens Tim Trio system using a 32-channel head-coil with 1.06-mm isotropic voxels, 15-fold Wave-CAIPI acceleration (36), $240 \times 196 \times 120$ matrix size, echo time (TE)/repetition time (TR)=25/35 ms, flip angle=15°; and (ii) a synthetic distribution of external sources (Fig. 1). These external sources were set to have two values: 0.0 ppm for simulated tissue, and 0.94 ppm for simulated air, bone, etc. Placement of these sources was based on a threshold-based segmentation of the magnitude data. Although not strictly accurate, this provided an external magnetization field qualitatively similar to native GRE phase data.

The simulated phase map was unwrapped with Laplacian methods (37). Subsequently, background removal was performed with LBV (18), PDF (20) and the proposed preconditioned nPDF approach. The nPDF method was initialized with the iterative solution proposed by Schoefield and Zhu (37), whereas LBV and PDF were initialized with the analytical Laplacian method (37). The iterative method uses the analytical Laplacian closed-form solution to approximate the true unwrapped phase distribution; from this, a phase differential is calculated and rounded into 2π multipliers. This approach ensures only multiples of 2π are applied to wrapped-phase values for full coherence with the native field inductions. However, this method can fail if the analytic Laplacian method suppresses harmonic

fields larger than π in amplitude. Root-mean-square error (RMSE) scores (normalized as a percentage of ground-truth values) were calculated to assess the performance of all background-filtering methods. QSM reconstructions were evaluated with RMSE, High-Frequency Error Norm (HFEN) and the Structural Similarity Metric (SSIM, with default $K = [0.01, 0.03]$ and $L = 255$ parameters) (35, 38) with respect to the simulated ground truth.

For comparison, we also evaluated QSM (from background-filtered phase maps resulting from LBV, PDF and nPDF) using the STI-Suite toolbox (39, 40), which was optimized with the number of iterations that minimized RMSE.

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In vivo single-echo (Reconstruction Challenge) data

Solutions from single axial head-orientation GRE data (same imaging parameters as those described above) were also evaluated in the context of the 2016 QSM Reconstruction Challenge (35) with respect to χ_{33} and COSMOS ground-truth references using RMSE, HFEN and SSIM scores. Two algorithm initializations were explored: (i) the Challenge's local field map (i.e. two-step background prefiltering – LBV followed by 4th-order polynomial fitting) and (ii) field preconditioning with the proposed nPDF method.

In vivo multi-echo data

All methods were also compared qualitatively using 3T Siemens Trio data acquired with a 32-channel head coil using a 2×2 accelerated, spoiled 3D GRE sequence with 0.8-mm isotropic voxels, 224×280×320 matrix, head-foot readout direction and 30° field-of-view angulation to avoid eye-movement artefacts (hence the general form of the dipole kernel formulation was employed to account

for this angulation, $D = \gamma H_0 TE \left(\frac{1}{3} - \frac{[k_x \cdot b_{0,x} + k_y \cdot b_{0,y} + k_z \cdot b_{0,z}]^2}{k^2} \right)$, with b_0 an unitary vector in the

direction of B_0), $TE_{\min}/\Delta TE/TR = 2.34\text{ms}/2.30\text{ms}/25\text{ms}$, with eight bipolar echoes, and 12° flip-angle for a total acquisition time of 7:08 min. Raw data was reconstructed offline using SENSE (41), followed by spatial phase unwrapping (42) and magnitude-weighted least-squares phase fitting with bipolar-readout and transmit-related offset adjustment. Four types of background prefiltering were explored. In addition to LBV, PDF and nPDF, we also preprocessed phase data with a two-step algorithm consisting of first-pass LBV followed by variable SMV extraction ($r_0=25$ mm; step-size/final kernel radius=1 mm) (43) to capture LBV's remnants.

Optimization parameter selection

Both the TV-FANSI and WH-QSM algorithms included a TV regularizing penalty to condition susceptibility inversions. In the simulation study, the associated (TV-related) parameters were optimized with TV-FANSI (33) through the minimization of RMSE with respect to the COSMOS starting point. The same TV parameters—namely the regularization weight, α_1 , and ADMM's variable, μ_1 —were also used by the proposed WH-QSM method without any further adjustment. In addition, WH-QSM's harmonic-term weighting parameter, β (see Eq. 4), was optimized through a new RSME minimization. For the Challenge experiment, TV-regularization parameters for both algorithms were separately optimized for each metric (i.e. minimizing RMSE, HFEN and SSIM) as in (35). The same β parameter that was optimized from the COSMOS-based simulation work was also used in this experiment without any further adjustment. Finally, with in vivo (multi-echo) data, both algorithms' TV-related parameters were also matched through L-curve optimization (44) with TV-FANSI, whereas β was empirically optimized on visual assessment of the resulting harmonic field maps. We used the smallest β value that generated harmonic field maps without any structural features within the ROI. Unless specified otherwise, TV-FANSI was terminated with either an update rate of 1% or 50 iterations, whereas WH-QSM stopping criteria were either an update rate of 0.01% or 150/1000 iterations (for simulation and Challenge data / in vivo multi-echo data, respectively).

Computing platform

All routines were operationalized in the MATLAB 2016a environment (The Mathworks Inc., Natick, MA, USA), on an Acer Predator laptop computer running an Intel i7 6700HQ processor at 2.6GHz (3.5GHz Turbo) with 64GB RAM.

Results

COSMOS-brain numerical simulation

Resulting local fields maps are shown in Fig. 2. Overall, nPDF returned lower error (RMSE=40%) and a less-structured residual map (Fig. 4f) than linear PDF and LBV (RMSE=60% and 49%, respectively), which showed discrepancies that were clearly co-localized with large blood vessels (Fig. 4d and 4e). Such discrepancies, however, were not observed for LBV or PDF when using the iterative unwrapping method (37) but due to other—more severe—errors (see Fig. S1, RMSE=424% for LBV and 196% for PDF) these were not investigated further.

Regarding WH-QSM, on visual inspection, all reconstructions were qualitatively similar (Fig. 3b). Quantitatively, this was reflected by lower global variance (Fig. 3d) than that for TV-FANSI (Fig. 3a, variance map in Fig. 3c) across input-data types. Interestingly, the resulting WH-QSM harmonic fields captured by ϕ_h (Fig. C4a-c) were remarkably similar to phase-error distributions in Fig. 4d-g (except near large vessels for LBV and PDF). Regarding quality-metric scores, the proposed WH-QSM method resulted in a systematic improvement across input-data types, with nPDF-preconditioned results slightly improving LBV- and PDF-related performances (Fig. 35). Finally, a stability test on β returned an RMSE variation of less than 0.5% for a parameter range spanning an order of magnitude, $\beta = (10-100)$, with ADMM's $\mu_h = \beta/100$ (see Eq. S8 in Supplementary Material).

Results achieved with STI-Suite are shown in Fig. S2. Errors captured by RMSE, HFEN and SSIM were consistently larger for STI-Suite QSM reconstructions than those for WH-QSM and TV-FANSI,

and resulted in greater input-related variance (several times larger than the overall variance observed for WH-QSM). We also noted that STI-Suite QSM errors were lower with nPDF preprocessing.

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In vivo single-echo (Challenge) data

Following the methodology proposed for the 2016 QSM Challenge, reconstructions were separately optimized against each quality metric, and ground-truth. Initialized with the provided prefiltered field map, WH-QSM returned small systematic improvements with respect to TV-FANSI when using the COSMOS ground truth (Fig. 6). The latter scored 61.3% (RMSE), 58.2% (HFEN) and 0.878 (SSIM), whereas WH-QSM resulted in 60.9% (RMSE), 57.5% (HFEN) and 0.900 (SSIM), respectively. Larger improvements were observed when using the χ_{33} reference, returning 76.7% (RMSE), 75.1% (HFEN) and 0.820 (SSIM) for TV-FANSI, and 72.9% (RMSE), 70.4% (HFEN) and 0.850 (SSIM) for WH-QSM. Overall, however, “optimal” solutions using χ_{33} as the ground truth were excessively smooth (not shown). Using the COSMOS reference, in contrast, optimal reconstructions—obtained for a relatively narrow range of regularization weights—were more visually appealing. Interestingly, when initialized with nPDF, TV-FANSI returned severely corrupted results due to large-scale streaking artifacts (RMSE>150%, Fig. S3). WH-QSM’s performance, however, remained relatively unchanged (RMSE=61.7%). The largest discrepancies between methods (due to the introduction of the weak-harmonic term in Eq. 4) were observed within (or emanating from) large blood vessels (e.g. the difference map in relation to WH-QSM’s harmonic fields in Fig. 6f). Other qualitative differences between TV-FANSI and WH-QSM solutions might be related to the differential impact of TV regularization, though notably, we found TV weights for WH-QSM at most doubled those for the TV-only implementation.

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More visually appealing reconstructions were obtained for both methods (i.e. TV-FANSI and WH-QSM) using an L-curve based optimization (43) (Fig S4b-c), with both algorithms sharing the same TV parameters and maximum number of iterations ($N_{\text{iter}}=300$). Interestingly, the streaking pattern observed in the difference map (Fig. S4d) was also somewhat consistent with WH-QSM's harmonic field map in Fig. S4f. Quality metrics for this parameter optimization approach slightly favored the WH-QSM method.

In both Challenge and simulation experiments, WH-QSM was 1.5 to 1.7 times slower than TV-FANSI (i.e. 0.8-0.9s versus 1.2-1.5s) per iteration.

In vivo multi-echo data

From a qualitative standpoint, the background-filtered fields estimated by the different algorithms hereby investigated (i.e. LBV PDF and nPDF) slightly differed (see red arrows in Fig. 7). In such a scenario (of variable input data), WH-QSM demonstrated greater robustness than TV-FANSI (Fig. 8). Generally, we found WH-QSM solutions were less contaminated by streaking artifacts than those for TV-FANSI, which was particularly noticeable near the ROI boundary (see red arrows in Fig. 9e). Indeed, relative to the WH-QSM result with two-step prefiltering (Fig. 8e), errors for the different reconstructions were: TV-FANSI (two-step): 55.2%, TV-FANSI (LBV): 118.4%, TV-FANSI (PDF): 67.4%, TV-FANSI (nPDF): 73.3%, WH-QSM (LBV): 49.6%, WH-QSM (PDF): 52.5% and, WH-QSM (nPDF): 55.9%, which confirmed WH-QSM robustness irrespective of preconditioning method. Putative background-field residuals (determined by the differentials between input phases for the different single extraction methods and that for the two-step approach, Fig. 9f-h) were highly concordant with the harmonic fields estimated by WH-QSM (Fig. 9b-d). Reconstruction times for these experiments (using 1000 iterations for both methods) were in the order of 2900s for TV-FANSI and

3700s for WH-QSM.

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Discussion

Optimal preprocessing of gradient-echo phase information is crucial for accurate QSM reconstruction (3,45). The main challenge resides in the nonlocal nature of magnetization fields emanating from magnetic susceptibility sources, often causing the measured phase to be dominated by contributions from distal dipole sources (of extra-cerebral origin) that need to be either: (i) effectively eliminated through phase prefiltering, (ii) localized or estimated (by the inversion algorithm) outside the brain, or (iii) captured by additional terms in the QSM formulation. Another challenge is that in signal-starved regions (e.g. at the vicinity of air-tissue interfaces and in most of the extra-cranial space), the phase-noise distribution is nearly uniform across the $(-\pi, \pi)$ range, which severely confounds the phase measurement leading to abrupt spatial truncations in the observed magnetization field. Truncations are also generated by the arbitrary selection of an ROI. Although ROI selection is necessary to apply properties of harmonic functions, it introduces further uncertainties (i.e. variance) to the inversion problem often leading to large-scale spurious remnants in the QSM solution that obscure local behaviors. This is commonly referred as “shadowing” artifact. Past studies have shown that background-removal (and single-step) algorithms can effectively eliminate large-scale (externally sourced) fields that are severely truncated by information loss due to low SNR or FOV definition (3), hence simplifying the problem into inverting local dipole fields that are only partially truncated by ROI masking. However, due to these and other confounding factors (such as nonzero transmit-driven initial phases, unwrapping errors, etc.), the efficiency of background-removal algorithms is often impaired leading to excessive local-field contamination (see e.g. Fig. 7). In some situations, a second

background-elimination step (based on a different principle) can effectively suppress spurious remnants.

It would be highly desirable to have algorithms that are robust to a large range of background-field removal efficiencies, i.e. to different preprocessing methods. To this end, we explored a new formulation that exploits the harmonic property of external fields to add an additional layer of background control to a previously proposed fast-inversion method (33). We called this new approach Weak-Harmonic QSM or WH-QSM, which we hypothesized it would operate robustly when initialized with differently pre-processed data. Indeed, the COSMOS-based simulation and in vivo results were consistent with this hypothesis. The proposed method resulted in improved performance (Fig. 5), improved robustness to different types of phase prefiltering (Fig. 8) and improved efficiency (relative to TV-FANSI) at mitigating streaking and shadowing artifacts, particularly those originated near the ROI boundary (Fig. 9e). We also found the harmonic field components captured by ϕ_h (e.g. Fig. 4a-c) were highly concordant with field remnants for each input-data type (Fig. 4d-g), confirming the validity of the new term in Eq. 4, and warranting a future investigation on its additional relevance to e.g. informing adaptive data-fidelity weights.

In this work, we also developed an initialization method using wrapped-phase data through a nonlinear reformulation of the widely used Projection onto Dipole Field algorithm (Eq. 5) (20). We called this method nPDF, which in the synthetic experiment outperformed linear PDF and LBV methods (Fig. 5) probably due to improved noise management. Nonlinear PDF has the advantage of being compatible with Schofield and Zhu's iterative phase-unwrapping method (37). This is an important feature for future developments since the analytical operator that solves the relevant Poisson equation for Laplacian phase unwrapping also eliminates harmonic fields originated outside the FOV. Although this might be a desirable side benefit of QSM preprocessing, when integrating multi-echo or coil-combination procedures into single-step formulations approximating true (i.e. unfiltered) phases might be crucial.

Finally, it is worth noting that when extending TV-FANSI to WH-QSM we introduced two additional parameters, β and μ_h . The former is the regularization weight to Eq. 4's weak-harmonic term, and the latter is specific to the ADMM algorithm (see second variable split in Eq. S8). We found empirically that: (i) small values were preferred, and that (ii) μ_h could be reliably set to $\beta/100$. Generally, numerical performance remained relatively stable for a wide range of parameter values, which is desirable. Similarly, the nPDF algorithm was stable to variations of the free parameter, μ_{out} (Eq. S14) within the (0.0015-0.003) range. We also found that the proposed ADMM-based algorithm was fast converging. Optimal results near the ROI boundary required 3 to 20 times more iterations than TV-FANSI (33). Increasing the number of iterations also seemed to provide sharper results, which in turn may lead to further fine-tuning of regularization weights. In clinical applications, the regularizing-weight, α , could be optimized with the much faster TV-FANSI implementation, whereas β and μ_h could be preset to previously optimized values, allowing overall a considerable computational gain.

Conclusions

The proposed Weak-Harmonic regularization method for dipole inversion (WH-QSM) consistently yielded reconstructions with less artifacts and improved quality-metrics than a *state-of-the-art* algorithm based on the same solver. Importantly, WH-QSM was robust to input-data variations with no significant penalty. The estimated harmonic field was highly consistent with background-removal residuals from previous steps, which warrants further work to explore its value for data-fidelity error control. In addition, the wrap-insensitive, preconditioned background-elimination method (nPDF) demonstrated improved noise management, reduced artifact propagation due to errors inherited from previous steps, and overall, improved robustness to inaccuracies near the ROI boundary – a highly desirable behavior that results in minimal or no erosion to the trustable region, in turn, enabling its use for the study of the cerebral cortex. Since the proposed QSM pipeline can be initialized with wrapped

phase data, the present framework can be extended to enable simultaneous coil and multi-echo data combination – a subject for future research.

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Figure captions

Figure 1. COSMOS-based simulation. (a) Simulated susceptibility distribution. (b) Magnitude from a single head-orientation spoiled 3D GRE acquisition. (c) Simulated field map. (d) Simulated wrapped-phase distribution. Phase unwrapping results with (e) Laplacian and (f) Laplacian iterative methods, as described by Schofield and Zhu (35).

Figure 2. COSMOS-based simulation. Background-filtered field maps using (a) Laplacian unwrapping followed by LBV, (b) Laplacian unwrapping followed by linear PDF, and (c) iterative unwrapping followed by nPDF with linear preconditioning.

Figure 3. COSMOS-based simulation. (a) TV-FANSI and (b) WH-QSM reconstructions for LBV, linear PDF and nPDF, respectively. Variance maps across input-data types for (c) TV-FANSI and (d) WH-QSM.

Figure 4. COSMOS-based simulation. Harmonic fields estimated by the WH-QSM algorithm with (a) LBV-, (b) PDF- and (c) nPDF-based preprocessing. Local phase error maps with respect to the COSMOS-only forward-simulation for (d) LBV-, (e) PDF- and (f) nPDF-based preprocessing.

Figure 5. COSMOS-based simulation. Performance scores (RMSE, HFEN and SSIM) for each reconstruction.

Figure 6. In vivo single-echo (Challenge) data. (a) Two-step prefiltered local field map. (b) 12 head-orientation based COSMOS reconstruction. (c) TV-FANSI and (d) WH-QSM reconstructions minimizing RMSE with respect to the COSMOS reference. (e) Difference between QSM reconstructions. (f) WH-QSM's harmonic field estimate.

Figure 7. In vivo multi-echo data. (a) Unwrapped phase, and local field estimates from: (b) two-step prefiltering, (c) LBV, (d) PDF and (e) nPDF methods. Red arrows highlight putative background field remnants.

Figure 8. In vivo multi-echo data reconstructions with (left) TV-FANSI and (right) WH-QSM algorithms from (a, e) two-step, (b, f) LBV, (c, g) PDF and (d, h) nPDF prefiltered data. The same TV parameters were used for all reconstructions. Additionally, for WH-QSM, $\beta=500$ and $\mu_h=30$.

Figure 9. In vivo multi-echo data. WH-QSM's harmonic-field estimate from (a) two-step, (b) LVB, (c) PDF and (d) nPDF preprocessed data. (e) Difference between QSM reconstructions using the two-step prefiltered input with red arrows highlighting streaking sources putatively due to artifact suppression in WH-QSM (see Fig. 8a versus Fig. 8e). Phase differentials between the two-step filtered phase and: (f) LVB, (g) PDF and (h) nPDF preprocessed phase distributions.

Supplementary figure captions

Figure S1. Local field estimates obtained with (a) LBV and (b) PDF methods both initialized with the same simulated phase distribution unwrapped with Schofield and Zhu's iterative method; (c) and (d) their corresponding error maps with respect to the simulated ground truth.

Figure S2. Susceptibility reconstructions using STI-Suite. (a) LBV result as input (7 iterations). RMSE = 78.2, HFEN = 70.2, SSIM = 0.695. (b) PDF as input (10 iterations). RMSE = 77.4, HFEN = 68.2, SSIM = 0.790. (c) nPDF as input (8 iterations). RMSE = 69.5, HFEN = 58.3, SSIM = 0.852. (d) Variance map of these solutions.

Figure S3. (a) In vivo local field estimates inferred from single head-orientation, 15-fold accelerated, wrapped Challenge data preconditioned with nPDF. (b) TV-FANSI (50 iterations) and (c) WH-QSM reconstructions minimized RMSE with respect to the COSMOS reference, i.e. $\alpha_1=0.016$ and $\mu_1=1.6$, the same for both methods; $\beta=500$, $\mu_h=10$ and 150 iterations for WH-QSM only. (d) Harmonic field associated with WH-QSM reconstruction. Computational times were: 17s for TV-FANSI and 43s for WH-QSM.

Figure S4. Optimal reconstructions using L-curve analysis with (a) COSMOS, (b) TV-FANSI and (c) WH-QSM; (d) QSM difference between methods; (e) local phase input; and (f) harmonic phase estimated by the WH-QSM method. Optimization parameters were: 300 iterations and $\alpha_1 = 2e-4$ for both methods, and $\beta=500$ and $\mu_h=10$ specifically for WH-QSM. Computational times were 149s for TV-FANSI and 227s for WH-QSM. Metric scores with respect to COSMOS were (TV-FANSI / WH-QSM): RMSE = 82.6 / 78.8; HFEN = 80.2 / 79.0; and SSIM = 0.855 / 0.860.

Weak-harmonic regularization for quantitative susceptibility mapping (WH-QSM)

Carlos Milovic, Berkin Bilgic, Bo Zhao, Christian Langkammer, Cristian Tejos and Julio Acosta-Cabronero

Supplementary material

Weak-Harmonic QSM (WH-QSM) ADMM implementation

It was previously shown that the ADMM framework can solve a nonlinear QSM functional faster than gradient-descent strategies (1s). We hereby extend that work by incorporating a weak-harmonic term to the formulation.

In order to solve the problem with ADMM, we first need to introduce an auxiliary variable, $z = F^H DF\chi + \phi_h$, to decouple the equation system. The augmented functional can thus be expressed as:

$$\operatorname{argmin}_{\chi, \phi_h, z} \frac{1}{2} \left\| W(e^{iz} - e^{i\phi}) \right\|_2^2 + \frac{\mu}{2} \left\| F^H DF\chi + \phi_h - z + s \right\|_2^2 + \frac{\beta}{2} \left\| m \nabla^2 \phi_h \right\|_2^2 + R(\chi) \quad , \quad \text{Eq S1}$$

where s is the associated Lagrangian multiplier (a relaxation term) and μ is a Lagrangian weight. This effectively splits the regularization and data-fidelity terms which can then be solved as two different subproblems. The subproblem for χ becomes a linear problem:

$$\operatorname{argmin}_{\chi} \frac{\mu}{2} \left\| F^H DF\chi + \phi_h - z + s \right\|_2^2 + R(\chi) \quad , \quad \text{Eq. S2}$$

which can be solved using the closed-form solutions proposed by Bilgic (2s) and Milovic (1s) both for TV and TGV regularization.

In addition, the sub-problem for z becomes:

$$\operatorname{argmin}_z \frac{1}{2} \left\| W(e^{iz} - e^{i\phi}) \right\|_2^2 + \frac{\mu}{2} \left\| F^H DF\chi + \phi_h - z + s \right\|_2^2 \quad , \quad \text{Eq. S3}$$

which is equivalent to:

$$\operatorname{argmin}_z -W^2 \cos(z - \Phi) + \frac{\mu}{2} \|F^H DF\chi + \phi_h - z + s\|_2^2 \quad . \quad \text{Eq. S4}$$

The gradient of this functional is obtained in a voxelwise decoupled structure such that:

$$\partial_z f = W^2 \sin(z - \Phi) + \mu z - \mu (F^H DF\chi + \phi_h + s) \quad . \quad \text{Eq. S5}$$

Then, to find the roots of the nonlinear function we use a Newton-Raphson voxelwise solver, i.e.:

$$z_n = z_{n-1} - \frac{W^2 \sin(z - \Phi) + \mu z_{n-1} - \mu (F^H DF\chi + \phi_h + s)}{W^2 \cos(z - \Phi) + \mu} \quad \text{Eq. S6}$$

The subproblem for ϕ_h is given by:

$$\operatorname{argmin}_{\phi_h} \frac{\mu}{2} \|F^H DF\chi + \phi_h - z + s\|_2^2 + \frac{\beta}{2} \|m \nabla^2 \phi_h\|_2^2 \quad , \quad \text{Eq. S7.}$$

which requires an additional splitting variable, $z_h = \nabla^2 \phi_h$:

$$\operatorname{argmin}_{z_h, \phi_h} \frac{\mu}{2} \|F^H DF\chi + \phi_h - z + s\|_2^2 + \frac{\mu_h}{2} \|\nabla^2 \phi_h - z_h + s_h\|_2^2 + \frac{\beta}{2} \|m z_h\|_2^2 \quad \text{Eq. S8}$$

Eq. S8 has the following closed-form solutions (with $\nabla^2 = F^H L F$):

$$F \phi_h = \frac{\mu F(z - s) - \mu DF\chi + \mu_h L^H F(z_h - s_h)}{\mu + \mu_h L^H L} \quad , \quad \text{Eq. S9}$$

and

$$z_h = \frac{\mu_h (F^h L F \phi_h + s_h)}{\mu_h + \beta m^2} \quad . \quad \text{Eq. S10}$$

Finally, s and s_h are updated as follows:

$$s = s - z + F^H DF\chi + \phi_h \quad \text{Eq. S11}$$

$$s_h = s_h - z_h + F^H LF\phi_h \quad \text{Eq. S12}$$

We iterate the solutions for each subproblem (χ , z , ϕ_h and z_h) until convergence.

Nonlinear PDF (nPDF) ADMM implementation

We first perform variable splitting by introducing an auxiliary variable, $z_{pdf} = F^H DF \chi$, to decouple the equation system into different subproblems and iterate between solutions until convergence. The subproblem for χ then becomes:

$$\operatorname{argmin}_{\chi} \frac{\mu}{2} \|F^H DF \tilde{m} \chi - z_{pdf} + s_{pdf}\|_2^2 \quad \text{Eq. S13}$$

where s_{pdf} is the associated Lagrangian multiplier, μ_{pdf} is a Lagrangian weight and $\tilde{m} = 1 - m$. We introduce the variable $z_{out} = \tilde{m} \chi$ to further decouple the problem leading to:

$$\operatorname{argmin}_{\chi, z_{out}} \frac{\mu_{pdf}}{2} \|F^H DF z_{out} - z_{pdf} + s\|_2^2 + \frac{\mu_{out}}{2} \|\tilde{m} \chi - z_{out} + s_{out}\|_2^2 \quad \text{Eq. S14}$$

which has closed-form solutions:

$$\chi = \tilde{m} (z_{out} - s_{out}) \quad , \quad \text{Eq. S15}$$

and

$$F z_{out} = \frac{\mu D^h F (z_{pdf} - s_{pdf}) + \mu_{out} F (\tilde{m} \chi + s_{out})}{\mu_{pdf} D^h D + \mu_{out}} \quad \text{Eq. S16}$$

Finally, the z_{pdf} nonlinear subproblem can also be solved iteratively with the Newton-Raphson solver. The initialization of z_{pdf} should be set to an unwrapped phase value or could use prior information to precondition the solution.

The proposed nPDF background filtering step was empirically set to converge for 1500 iterations with $\mu_{pdf} = 0.0017$.

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Supplementary results

Cosmos-brain simulation

Figure S1. Local field estimates obtained with (a) LBV and (b) PDF methods both initialized with the same simulated phase distribution unwrapped with Schofield and Zhu's iterative method; (c) and (d) are their corresponding error maps with respect to the simulated ground truth.

In vivo single-echo (Challenge) data

Figure S2. (a) In vivo local field estimates inferred from single head-orientation, 15-fold accelerated, wrapped Challenge data preconditioned with nPDF. (b) TV-FANSI (50 iterations) and (c) WH-QSM (150 iterations) reconstructions minimized RMSE with respect to the COSMOS reference, i.e. $\alpha_1=0.016$ and $\mu_1=1.6$, the same for both methods; $\beta=500$ and $\mu_h=10$ for the WH-QSM method. (d) Harmonic field associated with WH-QSM reconstruction.

In vivo multi-echo data

Figure S3. In vivo data. (a) Unwrapped phase, and local field estimates from: (b) two-step prefiltering, (c) LBV, (d) PDF and (e) nPDF methods. Red arrows highlight putative background field remnants.

Figure S4. In vivo multi-echo data results using different background-elimination prefiltering. (a) TV-FANSI and (b) WH-QSM reconstructions for LBV, linear PDF and nPDF, respectively. (c) Corresponding harmonic fields estimated by the WH-QSM algorithm.