Published in final edited form as:

Magn Reson Med. 2015 August ; 74(2): 320–329. doi:10.1002/mrm.25438.

Minimizing lipid signal bleed in brain ^1H chemical shift imaging by post-acquisition grid shifting

Yi Zhang^{1,2}, Jinyuan Zhou^{1,3}, and Paul A. Bottomley^{1,2}

¹Division of MR Research, Department of Radiology, Johns Hopkins University, Baltimore, Maryland, USA

²Department of Electrical and Computer Engineering, Johns Hopkins University, Baltimore, Maryland, USA

³F. M. Kirby Research Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, Maryland, USA

Abstract

Purpose—Low spatial resolution in conventional ^1H brain chemical shifting imaging (CSI) studies causes partial volume error (PVE) or signal ‘bleed’ that is especially deleterious to voxels near the scalp. The standard spatial apodization approach adversely affects spatial resolution. Here, a novel automated post-processing strategy of partial volume correction employing grid shifting (‘PANGS’) is presented, which minimizes residual PVE without compromising spatial resolution.

Methods—PANGS shifts the locations of the reconstruction coordinates in a designated region of image space—the scalp, to match the tissue ‘centers-of-mass’ instead of the geometric centers of each voxel, by iteratively minimizing the PVE from the scalp into outside voxels. PANGS’ performance was evaluated by numerical simulation, and in 3T ^1H CSI human studies employing outer volume suppression and long echo times.

Results—PANGS reduced lipid contamination of cortical spectra by up to 86% (54% on average). Metabolite maps exhibited significantly less lipid artifact than conventional and spatially-filtered CSI. All methods generated quantitatively identical spectral peak areas from central brain locations, but spatial filtering increased spectral linewidths and reduced spatial resolution.

Conclusion—PANGS significantly reduces lipid artifacts in ^1H brain CSI spectra and metabolite maps, and improves metabolite detection in cortical regions without compromising resolution.

Keywords

Brain; MRS; CSI; partial volume error; lipid bleed; post-processing; metabolite quantification

INTRODUCTION

Magnetic resonance spectroscopy (MRS) is a valuable tool in the study of normal physiology and numerous diseases (1-6). Chemical shift imaging (CSI) (7) is a main-stay of multi-voxel MRS localization techniques, but its *in vivo* resolution is typically limited to 0.2–1 ml, primarily due to the low concentrations of the metabolites or moieties of interest (MOIs), and sensitivity. The low resolution renders CSI susceptible to partial volume errors (PVE) in MOI signal intensity due to tissue heterogeneity within CSI voxels, especially those adjacent to voxels generating other strong MRS signals.

In proton (^1H) brain CSI studies in particular, PVE from peripheral voxels often manifests as intense lipid signals from the scalp bleeding into adjacent brain voxels, which can obscure important metabolic information. Several schemes for suppressing lipid bleed artifacts are routinely implemented. One common approach is to avoid lipid-rich regions altogether by using a PRESS (8) or STEAM (9) pre-localization sequence prior to CSI. Another is to saturate the unwanted signal areas using outer volume suppression (OVS) (10-12) or B_1 shimming (13). These methods can be limited when the head's anatomy does not conform to the ideal rectilinear localization gradient profile, or to the RF coil's excitation profile, leaving some voxels of interest either with significant residual PVE, or artificially attenuated by the suppression. Lipid suppression based on its longitudinal relaxation time (T_1) (14), for example using the T_1 -null method (15,16), or those based on frequency-selective excitation (17-19) or signal refocusing (20,21), are other options. These will also attenuate the MOIs by saturation and/or may be susceptible to the effects of local field (B_0) inhomogeneity.

Regardless, such methods can be combined with post-processing techniques, which are the focus of the present work. Typically, a spatial apodization (cosine) filter is applied to the k -space data prior to Fourier transformation to limit bleeding of intense peripheral lipid signals. Unfortunately this reduces the nominal spatial resolution by ~40% (22). Another option is to extrapolate the k -space data based on the assumption that the lipid signal is strictly band-limited to the scalp, as identified in a separate MRI or from a lipid map extracted from the CSI data itself (23). Dual-density weighted-average k -space acquisitions can also be used on data in which the lipid regions are defined: basically, high-resolution lipid data are acquired with low-averaging and low-resolution metabolite data are acquired at high-averaging (24,25). However, this “uneven averaging” (24) strategy requires multiple averages per spatial encoding step, and is unsuitable for single acquisitions per phase-encode. One might also consider applying a linear-phase correction to the k -space data to shift the whole image field-of-view (FOV) to minimize lipid bleed, but this generally cannot solve the lipid bleed originating from the scalp on all sides of the head at the same time, and is consequently not done.

Here, a new method—partial volume correction by grid shifting (‘PANGS’) is proposed to minimize PVE and signal bleed. Instead of applying a linear-phase shift to the entire k -space, PANGS iteratively shifts the spatial reconstruction coordinates in a specific localized region of image space to minimize PVE, without otherwise affecting the k -space data or spatial resolution. PANGS is applied to ^1H brain CSI data from healthy volunteers and patients with brain tumors to reduce lipid contamination and resolve MOIs in spectra, and

metabolite maps constructed therefrom. Measures of *N*-acetylaspartate (NAA), total creatine (CR), and choline (Cho) quantified in PANGS spectra are compared to those in CSI with and without cosine spatial filtering, to demonstrate lipid artifact suppression.

THEORY

In CSI, spatial voxels are resolved by discrete Fourier transform (DFT) of the k -space signals (26,27),

$$\mathbf{s}_{M \times N} = \mathbf{PE}_{M \times M} \times \boldsymbol{\rho}_{M \times N}, \quad [1]$$

where $\mathbf{s}$ is the data vector in k -space, $\mathbf{PE}$ is the Fourier phase-encoding operator in one or more spatial dimensions, $\boldsymbol{\rho}$ is the spectral matrix vector in the spatial domain, M is the number of phase-encoding steps and N is the number of temporal spectral data points. $\mathbf{PE}$ is constructed as,

$$\mathbf{PE}_{M \times M} = \begin{bmatrix} e^{i2\pi k_1 x_1/M} & e^{i2\pi k_1 x_2/M} & \dots & e^{i2\pi k_1 x_M/M} \\ e^{i2\pi k_2 x_1/M} & e^{i2\pi k_2 x_2/M} & \dots & e^{i2\pi k_2 x_M/M} \\ \vdots & \vdots & \ddots & \vdots \\ e^{i2\pi k_M x_1/M} & e^{i2\pi k_M x_2/M} & \dots & e^{i2\pi k_M x_M/M} \end{bmatrix}, \quad [2]$$

where $k_1, k_2, \dots, k_M$ refer to different phase-encoding gradient steps and $x_1, x_2, \dots, x_M$ refer to different reconstruction coordinates. k and x range from 0 to $M-1$, or from $-M/2$ to $M/2-1$, depending on where the origin is chosen.

$\mathbf{PE}$ involves two conjugate variables that relate to the sampling grid in k -space (k), and to the reconstruction grid in image space (x). For CSI, both the k -space and image space grids are uniformly distributed, resulting in a uniform DFT for reconstruction. When the DFT is uniform, the reconstruction coordinate is placed in the geometric center of each voxel, with the implicit assumption that a point source in its geometric center accurately represents the whole voxel (Fig. 1a). For voxels completely filled with homogeneous tissue this assumption is true, and therefore the PVE is small ($\sim 13\%$) (28,29) and confined to adjacent voxels as shown in Fig. 1(b). In this case, the non-zero bleed is due to intra-voxel dephasing from the CSI gradients (28). When voxels are only partially filled, such as in thin lipid layers in the scalp, the locations of their centers-of-mass (COMs) differ significantly from their geometric centers (Fig. 1d), causing much larger PVE that affects many voxels, as depicted in Fig. 1(e).

PANGS shifts the reconstruction coordinates (x) away from the geometric centers of designated voxels to match their COMs, resulting in a non-uniform (or non-integer x) DFT reconstruction. When the reconstruction coordinate is shifted to coincide with the voxel's COM, the PVE is dramatically reduced as shown in Fig. 1(f), whereas significant PVE is generated by shifting the reconstruction coordinate away from the COM (Fig. 1c). Basically PANGS modifies the encoding matrix ($\mathbf{PE}$) to minimize PVE, instead of modifying the k -space data $\mathbf{s}$ in Eq. [1] as is done by apodization filtering, for example.

Estimating the centers-of-mass (COMs)

The crucial step for PANGS is to determine the COM for each voxel, which are typically unknown. In practice, we estimate the COM based on prior knowledge. Specifically, to suppress lipid signal in ^1H brain CSI, a scalp region is defined from a co-registered anatomical image. Then, the reconstruction coordinates of the scalp voxels are iteratively shifted to minimize the lipid signals in the non-scalp region, without altering the raw k -space data. A flow diagram of the PANGS reconstruction process is shown in Fig. 2.

Two strategies are utilized to expedite the iterative optimization. First, the COMs are quickly estimated by tracing the scalp from the co-registered MRI. These estimates are used as initial values for the iterations. Second, for each iteration, the reconstruction coordinates of only one or a small number of voxels are changed. Ordinarily, whenever any reconstruction coordinate is changed, the inverse of $\mathbf{PE}$ must be recomputed. However, the inefficiency of inverting a non-uniform DFT poses a major computational bottleneck for optimization. But if only a few reconstruction coordinates (corresponding to a few columns in $\mathbf{PE}$) are changed in each iteration, the matrix inversion can be converted to a matrix multiplication (30) as

$$(\mathbf{PE} + \Delta\mathbf{PE})^{-1} = \mathbf{PE}^{-1} - \frac{1}{1 + \text{trace}(\Delta\mathbf{PE} \times \mathbf{PE}^{-1})} \mathbf{PE}^{-1} \times \Delta\mathbf{PE} \times \mathbf{PE}^{-1}, \quad [3]$$

Here, $\mathbf{PE}$ and $\mathbf{PE}^{-1}$ are the encoding matrix and its inverse with non-uniform reconstruction coordinates (x) from the previous iteration, and $\Delta\mathbf{PE}$ is the updating matrix of rank 1 (with only one non-zero column) describing the change of only one reconstruction coordinate. The right side of Eq. [3] is repeated for each changed coordinate. The computation time is significantly reduced with Eq. [3] because matrix multiplication is more computationally efficient than inversion.

METHODS

Processing and analysis

All processing and analysis were performed offline on a personal laptop computer (quad-core, 1.87 GHz).

PANGS optimization—For PANGS, raw k -space data acquired in ^1H CSI studies of the human brain were input as $\mathbf{s}$ to the left side of Eq. [1]. Reconstructions were performed with the coordinates of each scalp voxel in $\mathbf{PE}$, (x), constrained to a range of $\pm 1/2$ of the voxel dimension from the voxel's geometric center. Solving Eq. [1] for each value of x generated many spectral data sets (ρ), to which a 2Hz exponential time-domain filter and 4-fold zero-filling were applied. Then, a metric of the lipid signal bleed was computed for each spectral data set by integrating the magnitude spectra from all non-scalp voxels (including voxels inside and outside the brain) over the spectral range of the lipid signal. The best reconstruction grid and spectral data set was selected as that exhibiting the minimum lipid bleed metric. The constrained optimization routine, '*fmincon*', of *Matlab* 8.2 (Mathworks, Natick, MA) was deployed to iteratively adjust the reconstruction coordinates for scalp

voxels and automatically select the best combination of voxel locations to achieve a ‘global’ optimum. To expedite optimization, the starting values for *fmincon* were the COMs estimated from the tissue intensities in the co-registered high-resolution anatomical images. Eq. [3] was incorporated into the objective function used in *fmincon*, and the ‘Active-Set’ minimization algorithm (31,32) applied (termination tolerance on independent variables = 0.01; maximum of 100 iterations; all other *fmincon* parameters were default values including step sizes which adapt automatically with the algorithm).

Spatial response functions—Spatial response functions (SRFs) (26,33) were computed to evaluate the mechanisms giving rise to PVE, and the potential reduction in PVE by PANGS. The SRF of a single voxel spectrum at -4 cm was calculated (location shown in Fig. 1d), and the effects of spatial cosine filtering (weighting, k -space center/edges = 1/0) also investigated.

Quantitative results and metabolite maps—To investigate PANGS’ ability to suppress PVE, PANGS spectra from cortical regions were compared to those from CSI with and without cosine filters. For quantitative comparisons, eight regions-of-interest (ROIs) each comprised of 4 CSI voxels, were selected from the central FOV of the brain, where corruption of the CSI scans by PVE is expected to be minimal. Average ROI spectra from PANGS and CSI were fitted in the frequency domain using the ‘circle-fit’ method (34) and identical input parameters. Metabolite maps from CSI and PANGS were computed by integrating absolute spectra over 1.9–2.1 ppm for NAA, 2.9–3.1 ppm for CR and 3.1–3.3 ppm for Cho MOIs. For display, the integrated spectral areas from the scalp and background were set to zero, and the brain metabolite maps were linearly interpolated to four-times the originally acquired spatial resolution in each direction.

Monte Carlo simulations were done to test the robustness of PANGS to variations in the starting points for the optimization routine. The starting points for estimating COMs were randomly chosen within $\pm 1/2$ of the voxel size from the geometric centers, with all other conditions unchanged. The PANGS routine was run for one hundred Monte Carlo simulations and both the lipid metrics and the resultant spectra recorded. For each run, the spectral ranges 1.9–2.1, 2.9–3.1, 3.1–3.3 ppm, corresponding to NAA, CR and Cho respectively, were integrated in 169 brain (non-scalp) voxels and the absolute peak areas plotted against the spectrum obtained using the MRI-based COMs as a reference. The ratios of the Monte Carlo simulated to the reference metabolite areas were also computed.

Because the spectral range of the lipid resonances can be broad due to poor shimming and imperfect OVS suppression, the effect of using a broader lipid frequency range on PANGS was investigated by comparing metabolite maps reconstructed with the lipid bleed metric minimized over 0.5–3 ppm instead of 0.5–1.75 ppm.

Global PANGS vs. row-by-row PANGS—To further expedite optimization, a compromised ‘row-by-row’ PANGS approach was devised and the results compared to the ‘global’ optimization approach above (Fig. 2). The central difficulty for iterative minimization is that the number of possible COM locations grows exponentially with the number of scalp voxels. For example, if there are 70 voxels in the scalp region and each

voxel can have 10 trial locations, the total number of combinations is 10^{70} —a daunting prospect to evaluate exhaustively. Although the *fmincon* function can deal with this quite well, it is rather slow. However, due to the separability property of the Fourier transform, if a row of voxels from the x (or y) direction of a 2D CSI data set is selected, any reconstruction coordinate shift in that row along the x (or y) direction will only affect the spectra in that row. This allows PANGS to be implemented in a row-by-row manner instead of the global approach above. The number of possible trials in each row can be dramatically reduced, e.g. 4 scalp voxels each with 10 possible locations in a row, results in 10^4 combinations. The *fmincon* function (with maximum iterations reduced to 50) was still used for this row-by-row PANGS implementation, even though an exhaustive search was now practical.

For the 20×18 phase-encoded human data, row-by-row PANGS was iterated 38 times. The compromise in the row-by-row PANGS compared to the global PANGS optimization, is that once a row is optimized it won't be revisited. This reduces the likelihood of finding global optimal coordinate combinations, but dramatically reduces computation time (typically by ~20-fold).

Human studies

All human studies were approved by the Johns Hopkins Institutional Review Board and were performed on a 3T Philips Achieva system (Best, Netherlands). Informed consent was obtained from all participants. In all cases, PANGS' performance was assessed by comparison of the identical MRS data processed without PANGS (with and without cosine filtering). PANGS was applied to the full *k*-space data acquired with single or multi-channel receivers prior to channel combination, and with no explicit sensitivity profile corrections.

^1H MRI and CSI data from three healthy volunteers (all females; age 22-28) were acquired with a head coil configured as a single quadrature receiver. A single-slice spin-echo CSI sequence (10,35) (repetition time, $\text{TR} = 2$ s; echo time, $\text{TE} = 144$ ms; in-plane resolution = 1×1 cm; $\text{FOV} = 20 \times 18$ cm; slice thickness, $\text{ST} = 1.5$ cm; and 12.1 min scan duration with two startup cycles) was used with OVS lipid suppression (10) and VAPOR (36) water suppression pre-pulses. Anatomic images were acquired with a 3D T_1 -weighted MP-RAGE (37) sequence (flip-angle, $\text{FA} = 8^\circ$; $\text{TR} = 6.9$ ms; $\text{TE} = 3.2$ ms; resolution = $1 \times 1 \times 1.2$ mm; $\text{FOV} = 256 \times 228 \times 156$ mm; scan duration = 4.5 min; inversion time, $\text{TI} = 813$ ms). The anatomic images and CSI data were acquired at the same location with identical angulation. A *Matlab* program was written to co-register the CSI voxel grid with its corresponding anatomical image based on the scanner-recorded fields-of-view, spatial resolution, and location of the centers in both data sets. Scalp voxels were manually identified using the program's graphical user interface.

Three patients with brain tumors (2 females, 1 male; age 39-64) were studied using the scanner's 32-receive-channel head coil. The single-slice spin-echo ^1H CSI sequence (same parameters as above except: $\text{FOV} = 22 \times 18$ cm; $\text{ST} = 13.2$ mm; scan duration = 13.3 min with two startup cycles) was employed with OVS and VAPOR pre-pulses. A multi-slice FLAIR (38,39) sequence was used to provide anatomical images ($\text{TR} = 11$ s; $\text{TE} = 120$ ms; $\text{TI} = 2.8$ s; refocusing angle = 120° ; resolution = $0.83 \times 1.04 \times 2.2$ mm; $\text{FOV} = 212 \times 189 \times 132$

mm; scan duration = 3.9 min; SENSE (40) acceleration factor = 1.5). For CSI with and without cosine filters, the multi-channel patient data was processed in the same way as the quadrature-coil studies, except that spectra from individual channels were combined using a root-of-the-sum-of-the-squares method (41,42). For PANGS, all individual channels shared the same reconstruction coordinates and the results were combined using the same root-of-the-sum-of-the-squares method.

RESULTS

Simulated SRF

Fig. 3 compares the SRF of CSI with that after PANGS is applied. The SRF of the spectrum of a MOI at -4 cm (Fig. 3a), has a zero-crossing at -6 cm where we posit that an intense scalp lipid resonance resides. If the voxel at -6 cm voxel contains uniformly distributed lipid tissue, it can reasonably be approximated by a point source at -6 cm. Since the SRF of the -4 cm spectrum has a zero-crossing at -6 cm, the MOI spectrum at -4 cm spectrum will be minimally affected by signals from the -6 cm voxel, whose contributions at -4 cm are as depicted in Fig. 1(b). However, if the -6 cm lipid voxel is not well represented by a point source at -6 cm but rather by a point source at -5.75 cm as in Fig. 1(d), then the effect of PANGS is to shift the reconstruction coordinate of the zero-crossing of the SRF from -6 cm to the COM at -5.75 cm shown in Fig. 3b. As a consequence, the -6 cm lipid signals now have negligible bleed at the other zero-crossings where the reconstruction grid is sampled (Fig. 1f), including at the location of the MOI at -4 cm (Fig. 3b). On the other hand, cosine spatial apodization disrupts the zero-crossings of the CSI SRF (Fig. 3c), which constrains the spatial extent of the SRF at the cost of a broadened spatial linewidth.

Studies of healthy subjects

For conventional CSI, the reconstruction coordinates are at the geometric centers as exemplified in Fig. 4(a). Inspection reveals that the tissue COMs of most of the voxels in the scalp do not coincide with their geometric centers. Estimated COMs based on anatomical images are shown in Fig. 4(b). After minimizing the lipid metric value over 0.5 – 1.75 ppm, the reconstruction coordinates of the scalp voxels no longer reside at the geometric centers as shown in Fig. 4(c), but the non-scalp voxels are unmoved. In this case, the lipid contamination metric was reduced 54% from 8.32 (arbitrary units) in standard CSI to 3.81 in PANGS. The average coordinate shift in Fig. 4(c) is about $1/5^{\text{th}}$ of the voxel size. Zoomed-in portions of scalp voxels before and after PANGS are depicted in Fig. 4(d). The individual PANGS coordinate shifts are displayed in Fig. 4(e).

Fig. 5 shows that PANGS spectra (Fig. 5b, e) acquired from the two cortical brain voxels highlighted in Fig. 4(a), have significantly reduced baseline contamination and artifacts (red arrows) compared to CSI from the same voxels, both without (in Fig. 5a, d) and with (in Fig. 5c, f) cosine filtering. The PANGS lipid peak height in Fig. 5(b) is reduced by 86% (to 14%) of that from CSI (Fig. 5a). The CSI spectra without cosine filtering are contaminated by PVE due to scalp lipid signals adjoining these cortical voxels. The cosine-filtered CSI spectra are also corrupted by the filter's spatial broadening effect.

Table 1 presents a comparison of NAA, CR, and Cho peak areas quantified in the eight centrally-located voxels outlined in blue in Fig. 4(b) in unfiltered CSI, PANGS, and cosine-filtered CSI. MOI peak areas from PANGS and filtered CSI did not differ significantly from non-filtered CSI ($P > 0.2$, in all cases). The mean MOI peak area measured in PANGS spectra differed by $<1\%$ from filtered and non-filtered CSI for all metabolites. However, the fitted spectral linewidths of spatially-filtered CSI spectra were significantly broader than in CSI without spatial filtering ($P < 0.03$, all MOIs), which in turn did not differ from PANGS ($<1\%$; $P > 0.3$, all MOIs). The small ($\sim 5\%$) increase in linewidth of filtered vs. non-filtered CSI likely reflects the filter's broadening effect compared to non-filtered CSI and PANGS.

Moreover, metabolite maps created from the PANGS data (Fig. 6b) were essentially free from hyper-intense lipid bleed artifacts seen in CSI (red arrows, Figs. 6a, c). In addition, bright rim artifacts (Fig. 6c) from the reduced spatial resolution of cosine-filtered maps, are absent from the PANGS images. Note that the *fmincon* routine is not guaranteed to yield a globally optimal result even though the lipid signal metric value monotonically decreases during the optimization process.

Monte Carlo simulations

Fig. 7 shows the effect of using random starting points for the PANGS optimization routine. Compared to starting with the MRI-based COMs as a reference, the mean ratio of the Monte Carlo lipid metrics (Fig. 7a) to the reference lipid contamination metric was 1.0025 ± 0.0051 (SD). The absolute peak areas of NAA (red), CR (green) and Cho (blue) measured in 169 brain voxels from each of the 100 Monte Carlo simulations, as compared to the reference areas are overlaid and plotted in Fig. 7b. The mean ratios of peak areas from the Monte Carlo simulations to the MRI-based measurements were 1.000 ± 0.048 (NAA), 0.998 ± 0.041 (CR) and 0.998 ± 0.042 (Cho).

Global PANGS vs. row-by-row PANGS

Fig. 8 shows the results of applying the global PANGS optimization to generate metabolite maps minimizing lipid signals over 0.5–3 ppm compared with 0.5–1.75 ppm. There are no significant differences between Fig. 8(a) and Fig. 8(b), although the lipid metric is larger in Fig. 8(b) because it integrates a larger spectral range (5.85 vs. 3.8). This means that NAA signal contributions do not appreciably affect PANGS lipid signal minimization, even when the NAA and lipid spectral frequency ranges overlap. In addition, little difference is evident between the row-by-row PANGS algorithm (Fig. 8c) and the more-exhaustive global PANGS algorithm (Fig. 8a). However, the final lipid signal metric from row-by-row PANGS is about 15% higher than the global PANGS result, representing some trade-off for a ~ 16 -fold reduction in computation time (1.2 min vs. 18.7 min) in this implementation. Replacing the '*fmincon*' algorithm used in row-by-row PANGS, by an exhaustive search over a ± 0.5 voxel interval with a 0.1-voxel step size, produced similar results to '*fmincon*' but at greatly reduced efficiency.

Brain tumor patients

Fig. 9(a) shows a FLAIR MRI from a patient following surgery for a high-grade tumor (arrow, top), with the PANGS optimized scalp reconstruction coordinates overlaid (bottom).

Fig. 9(c) shows NAA, CR and Cho images reconstructed via row-by-row PANGS for comparison with CSI without (Fig. 9b) and with (Fig. 9d) spatial apodization. Here, the lipid frequency range for minimization was extended to 0.5–3 ppm to deal with a more challenging deficiency in OVS lipid suppression. The computation time for row-by-row PANGS was 58.3 minutes due to the large amount of data from 32 channels. However, global PANGS would have taken hours, which might be considered impractical for large numbers of studies, even if it did provide better results than row-by-row PANGS. The hyper-intense lipid artifacts in the regular CSI scan (Fig. 9b, top) are eliminated in the PANGS NAA map (Fig. 9c, top), and artifacts in the cortical region of the cosine-filtered image (Fig. 9d, top; red arrow) are attenuated. The spatial resolution of cosine filtered CSI is worse than both non-filtered CSI and PANGS, which can be seen from the blurrier definition and increased size of the lateral ventricle and surgical lesion in the CR and Cho images (green arrows, Fig. 9d).

Similar results were obtained for all study subjects.

DISCUSSION

In brain ^1H CSI the scalp, being peripheral, is most susceptible to the effects of B_0 as well as RF-field inhomogeneity. The upshot is that multiple techniques are typically required to suppress the scalp's intense lipid resonances, with only mixed success or outright failure common for many nearby voxels that may include brain tissue or pathologies whose MRS data could otherwise add value. Here, we introduced a new post-processing method, PANGS, which when combined with conventional OVS, provided excellent lipid suppression compared to standard non-filtered and filtered CSI, reducing lipid artifacts in MOI maps acquired with both single and multi-channel detectors (Figs. 4-9). PANGS generated quantitatively the same fitted metabolite areas as conventional CSI in central voxels that were unaffected by lipid artifacts (Table 1), while improving the detection and resolution of metabolites in cortical regions (Fig. 5). It is the use of the nonuniform DFT that affords PANGS this unique ability to simultaneously correct PVEs while maintaining the same spatial resolution of the original acquisition.

Spatial apodization is ubiquitous in CSI. While it can effectively constrain the bleed from PVE and has a side-benefit of increasing the signal-to-noise ratio (SNR) (43), its downside of reducing spatial resolution is largely ignored. Its main value for ^1H brain CSI is the suppression of scalp lipids, which primarily affect NAA. However, lipid suppression by spatial filtering may be unnecessary for MOIs spectrally distant from the lipid, such as Cho and CR (Fig. 9b), which the broadening from apodization may needlessly compromise. The SNR benefit of spatial apodization derives from voxel averaging: the cosine filtering applied here is equivalent to shifting the FOV by a 1/2-voxel and averaging the result with non-shifted voxels (44). Even where the broadening of the spatial resolution in cosine-filtered CSI is of no concern, PANGS can still offer improved spectral resolution in cortical voxels (Fig. 5, Table 1). The spectral broadening of cosine-filtered CSI is attributable to the combined effects of spatial broadening and B_0 -inhomogeneity including variations in phase.

That the Monte Carlo simulations of both the lipid metric and absolute metabolite peak areas agree with the MRI-based initial conditions within 5% (Fig. 7), indicates that the PANGS optimization routine is relatively robust to changes in initial conditions. This also means that the algorithm is insensitive to chemical shift displacement errors of up to $\pm 1/2$ voxel in the read-out or slice-selection directions of the anatomical image. This is because the voxel COMs identified in the anatomical images are only used as initial values for PANGS optimization. The lipid metric being minimized derives only from the CSI data, which is unaffected by displacements between the two datasets. Note that PANGS does not operate in the slice-selection direction and chemical shift artifacts are negligible in all phase-encoded dimensions.

Even so, a number of defined scalp voxels may comprise a mix of lipids and brain tissue. The PANGS reconstruction coordinates that minimize lipid contamination in such voxels may be further away from the COM of brain tissue present in each voxel, than the standard CSI reconstruction coordinates. However, the potential increase in PVE from the brain metabolites, being much less intense than the lipid signals, is expected to be relatively insignificant. In general, the benefit from suppressing the much stronger lipid signals is overriding because without removing the lipid, the metabolite signal in the adjacent voxels cannot be properly quantified anyway. As illustrated by the tumor results (Fig. 9), there is indiscernible difference between non-filtered CSI and PANGS in the Cho and CR maps, suggesting that any increased metabolite bleed from this effect is negligible.

Compared to k -space extrapolation (23), image-space PANGS does not assume that the lipid signals are limited to a spatial band in the scalp, or are specifically reduced elsewhere. For example, PANGS doesn't assume that brain MOI signal strengths are $1/6^{\text{th}}$ that of the scalp lipid (23), which with OVS, may not be satisfied at all locations and could undermine the k -space extrapolation. An accurate definition of the scalp is in fact not critical to PANGS. The only consequence of excluding a few lipid-rich voxels from the scalp compartment, is that the PVE bleed artifact from those voxels won't be corrected. If the scalp lipids are completely suppressed by other means, the result of PANGS is identical to non-filtered CSI. A more detailed comparison between the PANGS method and the k -space extrapolation method is included as supplementary material. Note also that application of the PANGS algorithm is not limited to rectilinear phase-encoded acquisitions, but can be applied to MRS data acquired from any grid, including spiral acquisitions (25).

Lastly, we note that the speed of the iterative optimization process could benefit many-fold from parallel computing techniques, and that PANGS could have other applications, such as reducing ringing artifacts in MRI, where a possible objective function could involve minimizing the background signal energy. For now, we posit that PANGS is a flexible post-processing technique that can significantly reduce PVE bleed artifacts in metabolite maps and spectra, and improve metabolite detection in cortical regions without altering k -space data or compromising spatial resolution.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

We thank Peter B. Barker at Johns Hopkins University for assistance with human studies, Robert G. Weiss, Kilian Weiss and Meiyappan Solaiyappan from Johns Hopkins University for helpful discussions, and Andrew A. Maudsley from University of Miami for sharing source codes of the *k*-space extrapolation method. Grant support: American Heart Association 13GRNT17050100; National Institutes of Health EB007829, HL61912, EB009731, CA166171.

REFERENCES

1. Weiss RG, Bottomley PA, Hardy CJ, Gerstenblith G. Regional myocardial metabolism of high-energy phosphates during isometric exercise in patients with coronary artery disease. *New England Journal of Medicine*. 1990; 323(23):1593–1600. [PubMed: 2233948]
2. Roebuck JR, Cecil KM, Schnall MD, Lenkinski RE. Human breast lesions: characterization with proton MR spectroscopy. *Radiology*. 1998; 209(1):269–275. [PubMed: 9769842]
3. Scheidler J, Hricak H, Vigneron DB, Kyle KY, Sokolov DL, Huang LR, Zaloudek CJ, Nelson SJ, Carroll PR, Kurhanewicz J. Prostate Cancer: Localization with Three-dimensional Proton MR Spectroscopic Imaging—Clinicopathologic Study. *Radiology*. 1999; 213(2):473–480. [PubMed: 10551229]
4. Nelson SJ. Analysis of volume MRI and MR spectroscopic imaging data for the evaluation of patients with brain tumors. *Magnetic Resonance in Medicine*. 2001; 46(2):228–239. [PubMed: 11477625]
5. Howe F, Barton S, Cudlip S, Stubbs M, Saunders D, Murphy M, Wilkins P, Opstad K, Doyle V, McLean M. Metabolic profiles of human brain tumors using quantitative in vivo ^1H magnetic resonance spectroscopy. *Magnetic Resonance in Medicine*. 2003; 49(2):223–232. [PubMed: 12541241]
6. Bottomley, PA. NMR spectroscopy of the human heart. In: Harris, RK.; Wasylishen, RE., editors. *Encyclopedia of Magnetic Resonance*. John Wiley; Chichester: 2009.
7. Brown T, Kincaid B, Ugurbil K. NMR chemical shift imaging in three dimensions. *Proceedings of the National Academy of Sciences*. 1982; 79(11):3523–3526.
8. Bottomley PA. Spatial localization in NMR spectroscopy in vivo. *Annals of the New York Academy of Sciences*. 1987; 508(1):333–348. [PubMed: 3326459]
9. Frahm J, Merboldt K-D, Hänicke W. Localized proton spectroscopy using stimulated echoes. *Journal of Magnetic Resonance* (1969). 1987; 72(3):502–508.
10. Duyn JH, Gillen J, Sobering G, Van Zijl P, Moonen C. Multisection proton MR spectroscopic imaging of the brain. *Radiology*. 1993; 188(1):277–282. [PubMed: 8511313]
11. Tran TKC, Vigneron DB, Sailasuta N, Tropp J, Le Roux P, Kurhanewicz J, Nelson S, Hurd R. Very selective suppression pulses for clinical MRSI studies of brain and prostate cancer. *Magnetic Resonance in Medicine*. 2000; 43(1):23–33. [PubMed: 10642728]
12. Luo Y, De Graaf R, DelaBarre L, Tannus A, Garwood M. BISTRO: An outer-volume suppression method that tolerates RF field inhomogeneity. *Magnetic Resonance in Medicine*. 2001; 45(6): 1095–1102. [PubMed: 11378888]
13. Hetherington HP, Avdievich NI, Kuznetsov AM, Pan JW. RF shimming for spectroscopic localization in the human brain at 7 T. *Magnetic Resonance in Medicine*. 2010; 63(1):9–19. [PubMed: 19918903]
14. Bottomley PA, Foster TH, Argersinger RE, Pfeifer LM. A review of normal tissue hydrogen NMR relaxation times and relaxation mechanisms from 1-100 MHz: dependence on tissue type, NMR frequency, temperature, species, excision, and age. *Medical Physics*. 1984; 11:425. [PubMed: 6482839]
15. Bydder G, Young I. MR imaging: clinical use of the inversion recovery sequence. *Journal of Computer Assisted Tomography*. 1985; 9(4):659–675. [PubMed: 2991345]
16. Ebel A, Govindaraju V, Maudsley AA. Comparison of inversion recovery preparation schemes for lipid suppression in ^1H MRSI of human brain. *Magnetic Resonance in Medicine*. 2003; 49(5): 903–908. [PubMed: 12704773]

17. Smith MA, Gillen J, McMahon MT, Barker PB, Golay X. Simultaneous water and lipid suppression for in vivo brain spectroscopy in humans. *Magnetic Resonance in Medicine*. 2005; 54(3):691–696. [PubMed: 16086301]
18. Gu M, Spielman DM. B1 and T1 insensitive water and lipid suppression using optimized multiple frequency-selective preparation pulses for whole-brain ¹H spectroscopic imaging at 3T. *Magnetic Resonance in Medicine*. 2009; 61(2):462–466. [PubMed: 19161165]
19. Zhu H, Ouwerkerk R, Barker PB. Dual-band water and lipid suppression for MR spectroscopic imaging at 3 Tesla. *Magnetic Resonance in Medicine*. 2010; 63(6):1486–1492. [PubMed: 20512851]
20. Mescher M, Tannus A, Johnson M, Garwood M. Solvent suppression using selective echo dephasing. *Journal of Magnetic Resonance, Series A*. 1996; 123(2):226–229.
21. Star-Lack J, Nelson SJ, Kurhanewicz J, Huang L, Vigneron DB. Improved water and lipid suppression for 3D PRESS CSI using RF band selective inversion with gradient dephasing (BASING). *Magnetic Resonance in Medicine*. 1997; 38(2):311–321. [PubMed: 9256113]
22. De Graaf, RA. *In vivo NMR spectroscopy: principles and techniques*. Wiley-Interscience; 2008.
23. Haupt CI, Schuff N, Weiner MW, Maudsley AA. Removal of lipid artifacts in ¹H spectroscopic imaging by data extrapolation. *Magnetic Resonance in Medicine*. 1996; 35(5):678–687. [PubMed: 8722819]
24. Hu X, Patel M, Ugurbil K. A new strategy for spectroscopic imaging. *Journal of Magnetic Resonance, Series B*. 1994; 103(1):30–38. [PubMed: 8137069]
25. Bilgic B, Gagoski B, Kok T, Adalsteinsson E. Lipid suppression in CSI with spatial priors and highly undersampled peripheral k-space. *Magnetic Resonance in Medicine*. 2013; 69(6):1501–1511. [PubMed: 22807147]
26. Zhang Y, Gabr RE, Schär M, Weiss RG, Bottomley PA. Magnetic resonance Spectroscopy with Linear Algebraic Modeling (SLAM) for higher speed and sensitivity. *Journal of Magnetic Resonance*. 2012; 218:66–76. [PubMed: 22578557]
27. Zhang Y, Gabr RE, Zhou J, Weiss RG, Bottomley PA. Highly-accelerated quantitative 2D and 3D localized spectroscopy with linear algebraic modeling (SLAM) and sensitivity encoding. *Journal of Magnetic Resonance*. 2013; 237:125–138. [PubMed: 24188921]
28. Maudsley A. Sensitivity in Fourier imaging. *Journal of Magnetic Resonance* (1969). 1986; 68(2):363–366.
29. Wang Z, Bolinger L, Subramanian VH, Leigh JS. Errors of Fourier chemical-shift imaging and their corrections. *Journal of Magnetic Resonance* (1969). 1991; 92(1):64–72.
30. Miller KS. On the inverse of the sum of matrices. *Mathematics Magazine*. 1981; 54(2):67–72.
31. Powell, MJ. *Numerical Analysis*. Springer; Berlin Heidelberg: 1978. A fast algorithm for nonlinearly constrained optimization calculations; p. 144–157.
32. Powell MJ. The convergence of variable metric methods for non-linearly constrained optimization calculations. *Nonlinear Programming*. 1978:3.
33. Brooker HR, Mareci TH, Mao J. Selective Fourier transform localization. *Magnetic Resonance in Medicine*. 1987; 5(5):417–433. [PubMed: 3431402]
34. Gabr RE, Ouwerkerk R, Bottomley PA. Quantifying in vivo MR spectra with circles. *Journal of Magnetic Resonance*. 2006; 179(1):152–163. [PubMed: 16325436]
35. Barker PB, Lin DD. In vivo proton MR spectroscopy of the human brain. *Progress in Nuclear Magnetic Resonance Spectroscopy*. 2006; 49(2):99–128.
36. Tkac I, Starcuk Z, Choi I, Gruetter R. In Vivo ¹H NMR Spectroscopy of Rat Brain at 1 ms Echo Time. *Magnetic Resonance in Medicine*. 1999; 41:649–656. [PubMed: 10332839]
37. Mugler JP, Brookeman JR. Three-dimensional magnetization-prepared rapid gradient-echo imaging (3D MP RAGE). *Magnetic Resonance in Medicine*. 1990; 15(1):152–157. [PubMed: 2374495]
38. Hajnal JV, De Coene B, Lewis PD, Baudouin CJ, Cowan FM, Pennock JM, Young IR, Bydder GM. High signal regions in normal white matter shown by heavily T2-weighted CSF nulled IR sequences. *Journal of Computer Assisted Tomography*. 1992; 16(4):506–513. [PubMed: 1629405]

39. Hajnal JV, Bryant DJ, Kasuboski L, Pattany PM, De Coene B, Lewis PD, Pennock JM, Oatridge A, Young IR, Bydder GM. Use of fluid attenuated inversion recovery (FLAIR) pulse sequences in MRI of the brain. *Journal of Computer Assisted Tomography*. 1992; 16(6):841–844. [PubMed: 1430427]
40. Pruessmann KP, Weiger M, Scheidegger MB, Boesiger P. SENSE: sensitivity encoding for fast MRI. *Magnetic Resonance in Medicine*. 1999; 42(5):952–962. [PubMed: 10542355]
41. Roemer P, Edelstein W, Hayes C, Souza S, Mueller O. The NMR phased array. *Magnetic Resonance in Medicine*. 1990; 16(2):192–225. [PubMed: 2266841]
42. Bernstein, MA.; King, KF.; Zhou, XJ. *Handbook of MRI pulse sequences*. Elsevier; 2004.
43. Parker DL, Gullberg GT, Frederick PR. Gibbs artifact removal in magnetic resonance imaging. *Medical Physics*. 1987; 14:640. [PubMed: 3627004]
44. Haacke, EM.; Brown, RW.; Thompson, MR.; Venkatesan, R. *Magnetic resonance imaging: physical principles and sequence design*. Wiley-Liss; New York: 1999.

Figure 1.

Simulated effect of shifting the reconstruction coordinates on a 16-step 1D simulation with 1 cm resolution. (a) 1 cm and (d) 0.5 cm thick uniform subjects in a 16 cm field-of-view. (b) and (e) show the single-point spectra reconstructed with standard CSI for (a) and (d), respectively. (c) and (f) show reconstructed spectra from PANGS with the third reconstruction coordinate shifted from -6 cm to -5.75 cm for (a) and (d), respectively. Minimum PVE results when the reconstruction coordinate is matched with the COM in (b) and (f). Blue and red circles denote the real and imaginary parts of the reconstructed spectra, respectively.

Figure 2.
Block diagram of the steps required to implement the PANGS algorithm.

Figure 3.

Spatial response functions (SRFs) of (a) CSI, and (b) PANGS with a 0.25 cm shift, for a voxel at -4 cm. Arrows denote the SRF amplitude at the sampled location of the subject in Fig. 1(d). (c) The cosine-filtered SRF corresponding to (a). Blue and red lines denote the real and imaginary parts, respectively. In practice the voxels are discretely sampled at the vertical dashed lines, except for the -5.75 cm point in (b) (arrow).

Figure 4.

CSI grids of voxels co-registered with anatomical MRI and labelled with scalp voxels (red x = reconstruction coordinates). (a) In conventional CSI, the reconstruction coordinates are coincident with the geometric centers of each voxel. Spectra from voxels shaded red and blue are displayed in Fig. 5. (b) Same image showing estimated COMs (red x) based on the anatomical MRI, as starting coordinates for PANGS. The blue outlines denote 8 ROIs quantified for Table 1. (c) Final PANGS coordinates (red x) that minimize the lipid signals in non-scalp regions. (d) Zoomed-in view of voxels inside the green box in part (a), (top) and part (c), (bottom). (e) Spatial coordinate shifts, color-coded in units of fractional pixel dimension, along the horizontal (X, top) and vertical (Y, bottom) directions for the final PANGS coordinates in part (c), as compared to part (a).

Figure 5.

(a-c) Magnitude spectra from CSI and PANGS from the solid blue voxel in Fig. 4(a). The spectra in (d-f) are from the red voxel in Fig. 4(a). Parts (a) and (d) are from CSI without a cosine filter; (b) and (e) are the PANGS spectra; and (c) and (f) are from CSI with the cosine filter applied. Red arrows in (a) and (c) indicate artifacts. No baseline corrections were applied.

Figure 6.

Metabolite maps of NAA, CR and Cho (top to bottom) from a healthy volunteer obtained with: (a) regular CSI; (b) PANGS with lipid signals minimized over 0.5–1.75 ppm; and (c) CSI with a cosine filter. Image contrast thresholds are set identically. Red arrows indicate hyper-intense lipid artifacts.

Figure 7.

Comparison of 100 Monte Carlo simulations using random starting points with PANGS implemented with the MRI-based initial conditions. The data are from 169 brain voxels. (a) The lipid metric (arbitrary units) from each run. (b) The absolute peak areas of NAA (red), CR (green, partly obscured), and Cho (blue) measured in each voxel in each of the 100 runs, as compared to the MRI-based reference. The larger scatter in NAA may be attributable to its higher sensitivity to lipid contamination.

Figure 8.

NAA, CR and Cho metabolite maps (top to bottom) obtained from a healthy subject and reconstructed with: (a) global PANGS with lipid signals minimized over 0.5–1.75 ppm; (b) global PANGS and lipid minimized over 0.5–3 ppm; and (c) row-by-row PANGS and lipid minimized over 0.5–1.75 ppm. Reconstruction times were 18.7, 31.9, and 1.2 min respectively. Image contrast thresholds are set identically.

Figure 9.

(a) FLAIR image from a patient with a resected glioblastoma (green arrow), overlaid with optimized PANGS scalp coordinates (red x, bottom). Parts (b-d) are corresponding NAA, CR and Cho metabolite maps (top to bottom) reconstructed from: (b) CSI without a cosine filter, (c) PANGS and (d) CSI with a cosine filter. Image contrast thresholds are set identically. Regions outside the brain (including scalp) are masked from these maps. Hyper-intense lipid artifacts are indicated in red in (b) and (d).

Table 1

Metabolite peak areas (arbitrary units) and linewidths (Hz) quantified in non-filtered CSI, PANGS and filtered CSI from the 8 selected ROIs outlined in blue in Fig. 4(b).

CSI w/o cosine	PANGS	CSI w/ cosine	CSI w/o cosine	PANGS	CSI w/ cosine
NAA peak areas (a.u.)			NAA peak linewidth (Hz)		
4931	4870	4803	7.38	7.31	7.58
5007	5133	5013	5.98	6.11	6.26
4930	4964	5055	6.17	6.20	6.87
5071	4983	4993	7.62	7.51	7.90
4700	4884	4826	10.48	10.78	10.46
5628	5595	5373	7.64	7.61	8.22
4395	4496	4411	5.52	5.61	5.84
4443	4543	4648	6.77	6.88	7.30
Error ^a	1.02%	0.21%		0.76%	5.39%
p-value ^b	0.23	0.97		0.27	0.003
CR peak areas (a.u.)			CR peak linewidth (Hz)		
1930	1992	1968	6.95	7.12	7.19
2060	2097	2191	6.68	6.80	7.15
2730	2688	2638	9.25	9.14	9.43
2423	2430	2357	8.19	8.19	8.48
2809	2798	2585	11.19	11.21	10.88
1816	1842	1916	7.28	7.35	8.06
2568	2537	2545	6.77	6.70	7.12
2599	2580	2556	8.40	8.37	8.81
Error ^a	0.36%	-0.34%		0.38%	4.25%
p-value ^b	0.78	0.60		0.52	0.028
Cho peak areas (a.u.)			Cho peak linewidth (Hz)		
1627	1666	1667	6.19	6.29	6.58
1737	1751	1736	5.01	5.05	5.25
2023	2008	1928	5.68	5.65	5.89
2263	2260	2359	6.35	6.34	7.01
2001	2001	2062	8.07	8.08	8.47
2140	2160	2091	6.99	7.03	7.39
2098	2067	1939	6.81	6.75	6.72
1762	1748	1796	6.04	6.03	6.31
Error ^a	0.14%	-0.35%		0.15%	4.86%
p-value ^b	0.86	0.78		0.66	0.005

^a ROI-wise difference from non-filtered CSI in percentage and averaged for 8 ROIs.

^b paired t-test vs. non-filtered CSI.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript