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Improved Reconstruction for MR Spectroscopic Imaging

Yufang Bao and

MR Center (R308), 1115 NW 14th Street, Department of Radiology, Miller School of Medicine, University of Miami, Miami, FL 33136 USA (e-mail: ybao2@med.miami.edu).

Andrew A. Maudsley

MR Center, Department of Radiology, Miller School of Medicine, University of Miami, Miami, FL 33136 USA.

Abstract

Sensitivity limitations of *in vivo* magnetic resonance spectroscopic imaging (MRSI) require that the extent of spatial-frequency (k -space) sampling be limited, thereby reducing spatial resolution and increasing the effects of Gibbs ringing that is associated with the use of Fourier transform reconstruction. Additional problems occur in the spectral dimension, where quantitation of individual spectral components is made more difficult by the typically low signal-to-noise ratios, variable lineshapes, and baseline distortions, particularly in areas of significant magnetic field inhomogeneity. Given the potential of *in vivo* MRSI measurements for a number of clinical and biomedical research applications, there is considerable interest in improving the quality of the metabolite image reconstructions. In this report, a reconstruction method is described that makes use of parametric modeling and MRI-derived tissue distribution functions to enhance the MRSI spatial reconstruction. Additional preprocessing steps are also proposed to avoid difficulties associated with image regions containing spectra of inadequate quality, which are commonly present in the *in vivo* MRSI data.

Keywords

Brain metabolite images; image reconstruction; magnetic resonance spectroscopic imaging (MRSI)

I. Introduction

By combining spatial encoding with a spectroscopic acquisition, magnetic resonance spectroscopic imaging (MRSI) provides a method for spatial mapping of MR-detected metabolites. The image quality for *in vivo* MRSI [1] is limited by both spatial sampling requirements and nonideal spectral characteristics. In the spatial domain, the number of spatial sampling points is constrained by acquisition time limitations and the low sensitivity for observation of *in vivo* metabolites. As a result, sampling is typically uniformly distributed over a relatively small extent in the spatial-frequency, or k -space, domain, of maybe 16–32 points across, which we refer to as the central, or low spatial-frequency, k -space region to distinguish it from the wider sampling region commonly used for MRI acquisitions. The most commonly implemented spatial reconstruction method typically involves zero-filling and Fourier transformation (FT); however, FT of the limited spatial-

sampling data results in the well-known Gibbs ringing and associated spatial blurring. This is particularly evident when strong subcutaneous lipid or residual water signals are left within the imaged region, although ringing artifacts are also generated from sharp edges in the metabolite images.

Reconstruction of individual metabolite images is commonly implemented by applying a spectral analysis procedure at each spatially resolved voxel of the MRSI dataset and combining the individual analysis results in an image format, which can be achieved using fully automated methods [2]. However, spectral quality over an *in vivo* MRSI dataset can vary considerably and any subsequent analysis of the reconstructed metabolite images must include tests to exclude regions with inadequate spectral quality, as for example regions subject to significant magnetic susceptibility-induced lineshape distortion. The problems associated with spectral fitting can also be exacerbated by the spatial contamination effects previously described, notably with regions of lipid or unsuppressed water affecting spectral baselines in neighboring regions.

Several methods for improving the reconstruction of metabolite maps have been proposed [3], [4]. One approach has been to focus on postprocessing of the metabolite images [5], which are assumed to have already been generated from the MRSI data, using prior spatial information from high resolution MRIs. With this approach, information in the raw MRSI data is not used and any errors in the metabolite images that may have been generated during the reconstruction are inherited. Alternatively, it is possible to reconstruct metabolite images directly from the acquired MRSI data using non-Fourier approaches, including Bayesian reconstruction methods [6], [7], which is more desirable as full use is made of the available information in the raw data. One well-known method, spectral localization by imaging (SLIM) [8], is based on the assumption of homogeneous metabolite concentrations corresponding to identified anatomical regions, to reconstruct MR spectra from each region. Furthermore, generalized (GSLIM) [9], was proposed to capture some variation within each compartment. Another generalization method, spectral localization with optimal point spread function (SLOOP) [10], was proposed to choose an optimal set of phase-encoding gradients to match the point spread function that characterized the region of interest. A recent development of this reconstruction method combines the spatial field inhomogeneity information with the SLIM algorithm [11].

Despite the improvements demonstrated by these previously proposed MRSI reconstruction methods, these remain difficult to apply to routine MRSI studies and are not widely used since the aforementioned characteristics of *in vivo* MRSI are not fully addressed. Additionally, individual metabolite information is ignored, which confines the existing reconstruction methods to the context of standard image processing techniques. Therefore, there still remains a considerable need for improved MRSI reconstruction methods to address the difficulties associated with limited spatial sampling, low signal-to-noise ratios (SNRs), and strong signal distortions.

Statistical image reconstruction methods have been shown to be useful for reconstruction and enhancement of noisy data, and Bayesian methods have been applied to medical imaging data using the expectation-maximization (EM) algorithm [12]–[14]. By incorporating an image model and a maximum *a posteriori* (MAP) optimization method, improved reconstruction has been demonstrated. Extending such a statistical estimate based on modeling of the MRSI signal should be more desirable in that individual metabolite variations could be incorporated, although may be more difficult to implement due to the complexity of the model that involves coexisting metabolites in each voxel. The typically large number of parameters to be estimated for MRSI means that the computational

requirement must be considered, which becomes of particular concern for MRSI data due to the additional parameters needed to describe the spectral model.

In this report, a simplified MRSI signal model is proposed that uses partial volume tissue intensities over MRI-defined anatomic regions and assumes that the metabolite composition of each tissue type is relatively constant over a local region. The MRSI signal at each voxel can then be viewed as a weighted combination of the metabolite spectra from the individual tissue types, the relative volume contributions of which are obtained from a coregistered high-resolution MRI dataset. When implemented with a complete spatial and spectral model of the MRSI data, this *a priori* boundary information on tissue distributions was incorporated into the reconstruction of the MRSI data to estimate additional high-frequency k -space information. This method accounts for partial volume contributions from multiple tissue types in addition to boundary information at the edges of the brain and with CSF (which contributes no observable metabolite signal). By combining the extrapolated and the acquired k -space information, this method improves edge information of the metabolite images while preserving all information in the acquired data. This method is further enhanced to deal with imperfect spectra that are commonly present with *in vivo* MRSI data.

II. Theory

A. MRSI Data Model

MRSI data is obtained as a set of time-domain signals over a set of spatial-frequency sample points. The data is acquired in the spatial frequency domain (k -space) Ω_k and the spectral time domain Ω_t and reconstructed into the spatial Ω and spectral frequency domain Ω_ω . The acquired MRSI data, $S(k_x, k_y, k_z, t)$, where $(k_x, k_y, k_z) \in \Omega_k$, $t \in \Omega_t$, can be described as

$$\begin{aligned} S(k_x, k_y, k_z, t) &= \int_{\Omega} s(x, y, z, t) e^{-j2\pi(xk_x + yk_y + zk_z)} dx dy dz \\ &= \int_{\Omega} \int_{\Omega_\omega} \tilde{s}(x, y, z, \omega) e^{-j2\pi(xk_x + yk_y + zk_z + t\omega)} dx dy dz d\omega \end{aligned} \quad (1)$$

where $\tilde{s}(x, y, z, \omega)$ is the desired spectral information at each spatial location. This signal contains multiple contributions and can be further described in the time domain as

$$s(x, y, z, t) = \sum_{m=0}^{M-1} A_m(x, y, z) f_m(x, y, z, t) \quad (2)$$

where A_m is the detected signal intensity for metabolite m , which is proportional to the concentration, and f_m describes the relative phase, lineshape, and frequency of all resonances generated by metabolite m . To account for noise in the observed signal, the following statistical model of the observation $d(k_x, k_y, k_z, t)$ is used:

$$d(k_x, k_y, k_z, t) = S(k_x, k_y, k_z, t) + n(k_x, k_y, k_z, t) \quad (3)$$

where n is assumed independent and identically distributed (i.i.d.) Gaussian noise with zero mean and variance σ^2 .

The k -space samples are obtained for $k_x = -K_x/2$ to $K_x/2$, $k_y = -K_y/2$ to $K_y/2$, and $k_z = -K_z/2$ to $K_z/2$. In practice, the size of the sampled MRSI data is small and it is desirable to reconstruct the data with a larger number of points, N_x , N_y , and N_z in the spatial domain. We term the smaller sampled k -space region as the “central” k -space region. To reconstruct data to the higher spatial resolution it is, therefore, necessary to estimate the missing high spatial-frequency information.

III. Methods

A. Theoretical Formulation of the Improved MRSI Reconstruction Algorithm

In addition to incorporating prior information on the tissue distributions, spatially variant spectral information is also included in our signal model, including B_0 shifts, zeroth-order phase, and lineshape parameters. The discretized signal model can be written as

$$\begin{aligned} S(k_x, k_y, k_z, t) &= \sum_{x=0}^{N_x-1} \sum_{y=0}^{N_y-1} \sum_{z=0}^{N_z-1} \sum_{m=0}^{M-1} A_m(x, y, z) \\ &\quad \times f_m(x, y, z, t) e^{-j2\pi\left(\frac{xk_x}{N_x} + \frac{yk_y}{N_y} + \frac{zk_z}{N_z}\right)} \end{aligned} \quad (4)$$

with $K_x < N_x$ and $K_y < N_y$. In this report, single slice MRSI data is assumed, namely, $K_z = N_z = 1$, and the spectral parameters are assumed constant through the MRSI slice. Therefore, each metabolite signal contribution can be written as

$$\begin{aligned} f_m(x, y, z, t) &= e^{-\frac{t}{T_a(x,y)}} - \left(\frac{t}{T_b(x,y)}\right)^2 \\ &\quad \times e^{(-j2\pi((\omega_m(x,y) + \gamma\Delta B_0(x,y))t + \phi_0(x,y)))} \end{aligned} \quad (5)$$

where T_a and T_b characterize the Lorentzian and Gaussian components of the FID signal; ω_m is the frequency of a single resonance that identifies each metabolite; γ is the gyromagnetic ratio; ΔB_0 is the deviation of the magnetic field from the ideal field strength B_0 ; and ϕ_0 is zeroth-order phase term. In this report, we consider singlet resonances only for N-acetylaspartate (NAA), total choline (Cho), and total creatine (Cr), and a flat baseline model, as is appropriate for long echo time (TE) MRSI of the brain. Additional signals from lipid and unsuppressed water and the effect of baseline variations will be further discussed in Section III-B.

Prior information on the spatial distributions of each metabolite A_m is included using tissue segmentation of coregistered MRI data to obtain the distributions of gray matter (GM), white matter (WM), CSF, scalp (LIP, which includes a signal from subcutaneous lipid), and nonsignal regions. From these high-resolution tissue distributions the relative contributions of all tissue types to each MRSI voxel can be calculated. It is assumed that the metabolite concentrations are constant, or slowly varying, across each of the individual tissue types. The slowly varying metabolite concentrations allow us to further divide the image space into multiple subsections, not necessarily based on anatomic structures, over which the individual metabolite concentrations for each tissue type will be estimated. In this manner, high spatial resolution *a priori* information is incorporated into the MRSI model and the MAP method is simplified to maximum likelihood estimation. The Bayesian statistical method for estimate the metabolite intensities from the acquired data $d(k_x, k_y, k_z, t)$ is obtained by maximizing the following probability:

$$\begin{aligned} A_m(x, y, z) = \arg \max & P\left(\left\{d(k_x, k_y, k_z, t)\right\} | g_{\text{GM},r}(x, y, z), \right. \\ & \left. g_{\text{WM},r}(x, y, z), g_{\text{CSF},r}(x, y, z), g_{\text{LIP},r}(x, y, z)\right) \end{aligned} \quad (6)$$

where r is the subregion index for each tissue and g is a partial volume function for a given tissue at each voxel within a subregion r . The signal model, therefore, favors smooth changes of concentrations within each tissue while allowing for differences of metabolite signal intensities between adjacent voxels based on their relative tissue contributions.

By limiting the signal model to average metabolite concentration for each tissue within each subregion, the optimization problem is simplified. The size and shape selected for the subregions represents a compromise between the degree of spatial variation allowed for each tissue and metabolite combination and the complexity of the optimization problem, with a larger number of regions resulting in a smaller rate of change of the metabolite signal as a function of distance and faster convergence of the estimation procedure. For this study, the image space was divided up into 8×8 square regions that resulted in relatively smooth changes of the metabolite distributions. This relatively slowly varying density function was chosen based on the fact that regional changes of metabolite concentration have been observed for a given tissue type, but significant rapid regional changes have not been demonstrated. Furthermore, this parameter selection provides a reasonable degree of flexibility given the relatively low SNR of the data.

For each tissue u , the m th metabolite signal intensity can be decomposed into average signal amplitudes b_{mur} for subregion r of slice z as C_{rz} . Taking into account the percentage of each tissue in a location, the intensity function can then be written as

$$A_m(x, y, z) = \sum_u \left(\sum_r \left(b_{mur} g_{C_{rz},u}(x, y, z) 1_{C_{rz}}(x, y, z) \right) \right) + h_m(x, y, z) \quad (7)$$

where $h_m(x, y, z)$ is the residual intensity of m th metabolite and $g_{C_{rz},u}(x, y, z)$ is the volume contribution of tissue u at (x, y, z) within subregion C_{rz} and $1_{C_{rz}}(x, y, z)$ indicates the subregion to which the metabolite concentration is assigned.

The time data can be written as

$$S(k_x, k_y, k_z, t) = S_b(k_x, k_y, k_z, t) + S_h(k_x, k_y, k_z, t) \quad (8)$$

where S_b is the resonance signal corresponding to the first part in (7), and S_h to the second part. The local signal variation S_h is relatively small compared to S_b , and can, therefore, be included in the noise term in a modified recursive EM algorithm to estimate the average intensities b_{mur} for tissue u in subregion r . Namely, the measured data of (3) can be written as

$$d(k_x, k_y, k_z, t) \approx S_b(k_x, k_y, k_z, t) + n(k_x, k_y, k_z, t) = \sum_m \sum_u \sum_r R(m, u, r, k_x, k_y, k_z, t) \quad (9)$$

where

$$R = b_{mur} \sum_{x=0}^{N_x-1} \sum_{y=0}^{N_y-1} \sum_{z=0}^{N_z-1} g_{C_{rz},u}(x, y, z) f_m(x, y, z, t) \times 1_{C_{rz}}(x, y, z) e^{-j2\pi \left(\frac{yk_x}{N_x} + \frac{yk_y}{N_y} + \frac{zk_z}{N_z} \right)} + n_{mur}^R(k_x, k_y, k_z, t) \equiv b_{mur} \phi(m, u, r, k_x, k_y, k_z, t) + n_{mur}^R(k_x, k_y, k_z, t). \quad (10)$$

The spectral parameters $(T_a, T_b, \omega_m, B_0, \phi_0)$ that define f_m are first determined through automatic spectral fitting [2] of the MRSI data following FT reconstruction, and remain

unchanged in the subsequent processing step. Errors for these initial parameter estimates will result in some mismatch between the modeled and the acquired signals; however, since the subsequent processing involves recombination with the acquired data and a re-estimation of these parameters, the effect of these efforts will be greatly diminished in the final result. The estimation of b_{mur} can then be obtained by

$$R^{\text{new}}(m, u, r, k_x, k_y, k_z, t) = E(\{R(m, u, r, k_x, k_y, k_z, t)\} | d, b^{\text{old}}) \quad (11)$$

$$b_{mur}^{\text{new}} = \arg \max P(\{S_b(k_x, k_y, k_z, t)\} | \{R^{\text{new}}\}). \quad (12)$$

Equation (11) is the E-step which estimates the variable R defined by (10). This step integrates data in a subregion and thus is modified in this paper to fit the estimate of R and to further estimate the subregional tissue intensities. Namely, the variance $\sigma_{m,u,r,R}^2$ of noise $n_{m,u,r,R}$ has to be weighted by the size of the subregion, for each tissue and the number of metabolites, and is $\Sigma_{m,u,r} \sigma_{m,u,r,R}^2 = \sigma^2$.

The estimated R is further used in the M-step (12) to obtain the subregional tissue metabolite intensity b_{mur}

$$b_{mur}^{\text{new}} = \arg \max (|R^{\text{new}} - b_{mur} \phi(m, u, r, k_x, k_y, k_z, t)|^2). \quad (13)$$

Upon estimating b_{mur} , the function S_b can then be obtained using the signal model of (4) and (5). This can be done for a wider k -space extent than the acquired data so as to include high-frequency k -space information corresponding to the detailed edge definition of each region. This “high-frequency” data can then be combined with the acquired “central” k -space data as shown in (14), at the bottom of the page.

This processing ensures that the acquired data is always used. In this way, any local deviations of the metabolite signal intensities that may not be modeled by any feature in the MRI-based priors are maintained. The combined k -space data is then reconstructed using the conventional FT processing and high-resolution metabolite images obtained by repeating the spectral fitting procedure. By incorporating information of the edges of the object from partial volume concentration and spectral information of each metabolite, the Gibbs ringing artifact is greatly reduced and the edge information of the metabolite images is improved. A flow diagram summarizing the algorithm is shown in Fig. 1.

B. Supplementary Methods

As described in the previous section, the proposed algorithm assumes that the form of the acquired data fits the signal model; however, in practice there are several additional signal contributions present in the *in vivo* spectral data, such as water and lipid, which cannot be realistically modeled. Preprocessing steps were implemented to remove these signal contributions, including application of a convolution-subtraction filter [15] to the time-domain MRSI data to remove residual water; application of lipid k -space extrapolation [6], [16], [17]; and removal of all data from voxels located in the subcutaneous regions outside of the brain.

There are additional signal components that cannot be effectively modeled: First, there are alterations in the spectral baseline due to degraded water suppression, primarily caused by global magnetic field inhomogeneities over the object, and signals from lipid contamination.

Second, significant distortions of the spectral lineshape can occur due to intravoxel magnetic field inhomogeneities. These signal distortions are of greater concern for the metabolite imaging method used in this report that samples the whole slice, including scalp regions, in comparison to techniques that use spatial selection methods on acquisition to limit the region over which data is acquired. The baseline signals

$$\tilde{S}(k_x, k_y, k_z, t) = \begin{cases} S(k_x, k_y, k_z, t), & \text{for } |k_x| \leq \frac{K_x}{2}, |k_y| \leq \frac{K_y}{2}, |k_z| \leq \frac{K_z}{2} \\ S_b(k_x, k_y, k_z, t), & \text{elsewhere} \end{cases} \quad (14)$$

affect the overall metabolite distributions and need to be removed, regions with the strongest spectral distortions are primarily located in lower and frontal brain regions, and it is beneficial to remove these signal contributions before proceeding with the proposed algorithm. The following two methods were, therefore, applied as part of the preprocessing step.

1) Baseline Removal—In the spectral fitting procedure, the contributions to the baseline signal that cannot be well parameterized were modeled as a smooth, slowly varying signal. In the proposed procedure, it was assumed that these baseline signals had been accurately estimated in the initial spectral analysis step, and these fitted baseline signals were then subtracted from the MRSI data. However, complete elimination of the baseline contributions is not possible; therefore, to further diminish the effect of residual baseline on the estimation procedure, a few data points close to $t = 0$ in the time domain were excluded from the estimation, as has been widely used in time-domain spectral analysis methods [18]. In the examples presented here, this corresponded to the first 25 points, or 12.5-ms sampling.

2) Subregion Removal—Voxels with significant spectral distortion were removed by the following procedure: First, a spatial mask identifying the poor-quality voxels was automatically created by testing for fitted spectral linewidths of less than 3 Hz or greater than 12.5 Hz. This mask was then manually modified, for example to remove from the mask voxels with essentially good quality spectra but small metabolite intensities that may have been incorrectly fit. The spectral data corresponding to the voxels identified in the mask were then set to zero. The inverse FT was then applied and the result then used as the raw k -space data for the proposed procedure. It is noted that this procedure does not remove the signal contributions from the removed voxels into the neighboring voxels; however, this operation was still found to improve the optimization procedure.

C. Experimental Methods

MRSI data was simulated based on the tissue distribution functions provided by the BrainWeb simulated MRI [19] and known spectral parameters for the observed metabolites of NAA, Cr, and Cho. Data was generated for a single slice of 15-mm thickness, with 32×32 points in-plane and 1024 points in the time domain. The simulation was based on data for five MRIs with 3-mm slice thickness and 2×2 mm in-plane resolution (128×128 points). Field inhomogeneity with a maximum shift of 60 Hz and Gaussian noise with standard deviation $\sigma = 4$, which resulted in SNR around 8 : 1 for NAA in the spatial-spectral domain, was added to the MRSI data. Spatial and tissue-dependent changes of the simulated metabolite concentrations were included as follows: 1) The NAA had the highest concentration and a signal intensity that linearly decreased from left to right, with no difference between GM and WM. 2) The Cr signal was 20% higher in GM than WM. 3) The Cho had the lowest concentration, and a signal that was 33% higher in WM than in GM. Additional regions were added to simulate lesions with a change of metabolite signal that were not visible in the MRIs, and therefore, no prior information on these regions was provided that had a 25%–34% increase in NAA and a 25% decrease in Cho.

To examine the relative performance of conventional FT reconstruction, the SLIM method, and the proposed reconstruction algorithms, an additional noise-free single slice MRSI dataset was generated as previously described for 5-mm slice thickness with 16×16 points in-plane, and 512 points in the time domain, in this case, no B_0 was added and the metabolite intensities were assumed to be homogeneous in each tissue. Additional noise-contaminated MRSI data were also generated by combining the simulated MRSI data in the spatial and time domain with Gaussian noise of standard deviation ranging from 0 to 20 relative to a maximum NAA intensity of 10, which resulted in SNR from 0 to around 3 : 1 for NAA in the spatial spectral domain. The 16×16 points in the central k -space are used as acquired data. The higher resolution 32×32 in-plane MRSI data were reconstructed by zero-filled FT, SLIM, and the proposed reconstruction algorithms. In each case, the metabolite images (NAA, Cho, and Cr) were generated and compared to the gold standard, namely, the simulated metabolite images of 32×32 -point in-plane resolution. For each metabolite, the error rate was formulated as

$$\frac{\sum_{y=0}^{N_y-1} \sum_{x=0}^{N_x-1} |I_{\text{rec}}(x, y) - I_{\text{ref}}(x, y)|}{\sum_{y=0}^{N_y-1} \sum_{x=0}^{N_x-1} I_{\text{ref}}(x, y)} \quad (15)$$

with I_{rec} representing the 32×32 images reconstructed using the 16×16 k -space simulated MRSI data, and I_{ref} is the 32×32 noise-free reference images simulated.

Single-slice ^1H MRSI and multiplane high-resolution MRI data were obtained for healthy volunteer subjects, one age 58 and three age 23–25. The first of these MRSI datasets (#1) was acquired at 1.5 Tesla using 36-point circular k -space, 512 points time domain data, 15-mm slice thickness and 280×280 mm field of view, TE = 135 ms, TR = 1800 ms, and lipid inversion recovery with TI = 170 ms. MRI was obtained at the same angulation as the SI with 1×1 mm in-plane resolution and 3-mm slice thickness (256×256 points), which was resized to 128×128 points and 15-mm slice thickness following tissue segmentation, which was done using the SPM program [20]. The three additional datasets (#2, #3, #4) were obtained at 3 Tesla with 32×32 k -space points, 2048 time domain data, 15-mm slice thickness, and 256×256 mm field of view, TE = 73 ms, TR = 1900 ms, and TI = 198 ms. Tissue segmentation results were obtained using 15 MRI slices of 0.5×0.5 mm in plane resolution and 1-mm slice thickness (512×512 points), which was again resampled to the desired resolution.

All MRSI data were reconstructed using the preprocessing steps described in Section III-B and our proposed reconstruction, to obtain metabolite images for NAA, Cr, and Cho with an in-plane spatial resolution of 128×128 points. For the amplitude estimation, the image space was divided into 8×8 sub-regions and the initial values to be estimated were initialized to zero. The modified EM optimization algorithm was typically run overnight (Athlon 1.67 GHz CPU), although no significant change in image quality was observed after approximately 5 h. Results were compared with metabolite images obtained using the standard methods of Fourier transform reconstruction of the zero-filled MRSI data followed by the same automated spectral analysis procedure.

IV. Results

The performance of the developed algorithm was compared to that of the SLIM algorithm, which was interpreted as a cross correlation estimator as summarized in the Appendix, and also to that of the conventional reconstruction method. Fig. 2 shows the errors for NAA

images as a function of the standard deviation of the added noise. The proposed algorithm achieves the lowest error rate and the reconstruction remains robust for reasonable noise levels used. One reason for the difference in performance is that a single compartment definition was used for the SLIM algorithm that does not account for partial volume contribution across the MRSI slice. Although only a 5-mm slice thickness was assumed, compared to the more typical 15-mm used for *in vivo* acquisitions, partial volume effects were still present, which contributes to the error caused by SLIM algorithm even in the noise-free case. The errors with the conventional reconstruction method are mainly caused by Gibbs ringing effects. The proposed algorithm makes full use of partial volume information over the slice, thereby reducing the errors caused by the choice of compartment boundaries. In addition to the finding that the SLIM algorithm is sensitive to the choice of compartment boundaries, it was also found that the errors with the algorithm become worse when spatially variant metabolite intensities were simulated for each tissue.

Fig. 3 shows tissue segmentation and metabolite images for the simulated MRSI data. All metabolite images correctly reflect the underlying spatial and tissue-specific signal changes used for the simulation model. The high-resolution reconstructions (Row iv) all show considerable improvement of edge information and reduced Gibbs ringing. The visibility of the lesion areas [which is most easily identified in the original image shown in Fig 3(ii.a)] is increased in the NAA and Cho images, in comparison to the standard reconstruction which shows Gibbs ringing from the edges of the metabolite regions (Row iii). However, the lesion area appears with somewhat straightened edges, which corresponds to the underlying shape of the subregions used in the model. This effect could be reduced by using a smaller sub-region selection at the expense of increased computational demand. The increased noise in the Cho image corresponds to the lower signal used for this data.

Fig. 4 shows results for the four experimental data sets. In comparison to the previous data of Fig. 3, these are characterized by decreased SNR and increased spectral distortions. In comparison to the conventional FT metabolite image reconstruction, shown in the images in the second row, the high-resolution metabolite image reconstruction (third row) is characterized by improved edge definition and reduced Gibbs ringing. Some local anomalies can be seen in several of the metabolite images (e.g., evident in Fig. 4(d), center row) which occur when the spectral analysis routine fails to converge, which typically occurs due to baseline or lineshape anomalies and could be improved by reprocessing with adjusted parameters if necessary. The first set of images [Fig. 4(a)] shows the results for data obtained from the older subject, which exhibits prominent sulcal CSF space. It can be seen that Cho, and to a lesser extent NAA, are of lower intensity in GM than in WM, which is consistent with previous reports [21]–[25] (though not all [26], [27]); for example, [23] have reported 15% lower NAA and 28% lower for Cho in GM than WM in elderly subjects, using the same acquisition parameters. This difference, particularly for Cho, is more clearly distinguished in the high-resolution metabolite image reconstruction. No significant regional differences in the Cr image are evident, although [22] have indicated a 9%–40 % increase of Cr in GM than in WM. Spectra from both FT and the proposed reconstruction are shown in Fig. 5 for the dataset of Fig. 4(a), corresponding to the location shown in the image at the second row and the first column. Since the purpose of this reconstruction method is to improve the spatial definition, there is limited expectation for improving spectral SNR or quality; however, it does suggest some overall improvement of spectral quality as shown in Fig. 5.

In the remaining datasets, all obtained from the younger subjects and at 3 T, a similar improvement in the image appearance is obtained relative to the zero-filled FT reconstruction. While there is some evidence of differing metabolite signal within each tissue type, this is difficult to distinguish from the noise-induced variations in these images.

For all reconstructions shown in the previous figures, the value of b_{mur} was initialized to zero. Additional studies were implemented using different initial values, but results were consistent regardless of the initial settings, indicating that the convergence using the modified EM algorithm is robust.

V. Discussion and Conclusion

This study has demonstrated a reconstruction algorithm that uses *a priori* high-resolution spatial information and metabolite spectral information to improve edge definition in metabolite images. In comparison to the conventional zero-filled Fourier transform reconstruction, the proposed method results in decreased Gibbs ringing and improved quality of metabolic images. The method extrapolates the MRSI k -space data based on high-resolution information of object boundaries, and although it does not increase the spatial resolution for metabolite image features that are not reflected in the tissue segmentation images, it nevertheless improves visualization of metabolite signal features as a result of the improved image quality. An important aspect of this algorithm is that the original data is maintained; therefore, all metabolite image features presented in the acquired low-resolution data remained unchanged.

An alternative approach to enhanced reconstruction of low spatial resolution MRSI by making use of *a priori* spatial information is a full parametric modeling and optimization approach, similar to that proposed for MRI [13]. For this, however, the addition of at least seven parameters in the spectral dimension, for the relatively simple metabolite model used in this report, makes this type of approach computationally difficult, undoubtedly requiring parallel processing implementation [28]. In comparison, the proposed method simplifies the problem by separating the determination of the signal amplitudes for the higher spatial resolution from the determination of the spectral parameters. The optimization problem is also simplified by estimating localized average tissue metabolite concentrations while applying *a priori* partial volume structural information. This softens the strict boundary definition of compartments that is used in the SLIM algorithm, which is important in light of the relatively thick through-plane dimensions typically used for MRSI relative to the rapidly varying nature of brain structures.

In this initial examination, the experimental *in vivo* brain MRSI data sets were acquired with long TE to minimize difficulties associated with stronger baseline variations and lipid contamination that are associated with short TE acquisitions. However, the current spectral model could be extended to accommodate these characteristics. Even with long TE acquisition used in this study, *in vivo* MRSI data are characterized by poor SNR and a number of spectral distortions. One unique aspect of the proposed algorithm is the approach to dealing with these potentially interfering signals, which includes minimizing the influence of poorly characterized baseline variations and the removal of signals from regions outside of the brain or of inadequate quality. These steps were found to simplify the parameter optimization problem, and if not done, would have resulted in a larger minimum value in the optimization and potentially affect the ability to find the global minimum of the parameter space.

One concern with extrapolation methods is that amplitude and phase discontinuities are generated between the acquired and extrapolated data [17], [29]. In the proposed algorithm, these parameters are defined by the initial spectral analysis stage, which is based on the acquired central k -space data, and by the definition of the region boundaries used in the optimization. Of these, the coregistration between the segmentation and the MRSI images is perhaps most critical in determining the instantaneous phase of the extrapolated signals. Given the higher spatial resolution of the segmentation relative to the reconstructed MRSI

and the use of partial volume information in the model, it is felt that potential discontinuities are small. However, for general implementation of these reconstruction methods, it is necessary to allow for some in-plane realignment between the SI and segmentation image to account for possible subject movement between these acquisitions.

Several improvements to the proposed algorithm are possible. First, in this study, the through-slice *a priori* spatial information was averaged over the thicker MRSI slice; however, the model can be extended to a fully volumetric MRSI to improve spatial resolution in all dimensions. Second, this study kept the initially determined spectral parameters of lineshape, B_0 , and phase unchanged during the second-stage amplitude estimation procedure, although all spectral parameters were again determined for the final spectral analysis stage. In general, these spectral parameters do not vary greatly on a local voxel-to-voxel scale; therefore, it is considered unlikely that there would be a significant improvement in image quality if these parameter values were also included in the optimization, while this would undoubtedly increase the computational requirements. Finally, in this study, the coregistration of the MRSI with the MRI and final selection of the spatial regions to include in the optimization was achieved using manual intervention; however, both procedures can be fully automated.

In conclusion, an algorithm has been presented that provides an improvement in the quality of low spatial resolution MR-detected metabolite images by making use of high spatial resolution *a priori* tissue distribution functions. The algorithm has been demonstrated for simulated and experimentally acquired MRSI data of the brain.

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Appendix Review of the SLIM Algorithm as a Statistical Estimation Method

The SLIM algorithm is one of the first approaches that incorporated prior spatial information to constrain spatially resolved spectral reconstruction, and in this section we review this method for comparison with the proposed technique.

In SLIM, nonintersecting anatomic compartments, C_l , $l = 0, \dots, L - 1$, are identified from high-resolution MRI images as regions that have homogeneous distributions of the detected compounds. The intensity A_m are and the spectral signal f_m are viewed as homogeneous in a compartment, leading to a simplification of (2) as

$$\begin{aligned} s(x, y, z, t) &= \sum_{l=0}^{L-1} \left(\sum_{m=0}^{M-1} A_m f_m(k, t) \right) 1_{C_l}(x, y, z) \\ &= \sum_{l=0}^{L-1} 1_{C_l}(x, y, z) c_l(t) \end{aligned} \quad (16)$$

where $c_l(t)$ is the spectrum for the l th compartment. Inserting (1) and (16) in the statistical model (3) yields

$$d(k_x, k_y, k_z, t) = \sum_{l=0}^{L-1} g_l(k_x, k_y, k_z, t) c_l(t) + n(k_x, k_y, k_z, t) \quad (17)$$

with $t \in [0, -K_x/2, -K_y/2, -K_z/2, K_x/2, K_y/2, K_z/2]$, and $g_l(k_x, k_y, k_z) = \int_C e^{-j2\pi(xk_x + yk_y + zk_z)} dx dy dz$, the spatial FT of the compartment C_l is referred to as a regional function in this paper.

$$\begin{aligned} \langle g_i, g_j \rangle &= \int_{\Omega_k} g_i(k_x, k_y, k_z) g_j^*(k_x, k_y, k_z) dk_x dk_y dk_z \\ &= \int_{\Omega_k} \int_{\Omega_k} 1_{C_i}(x, y, z) 1_{C_j}(x', y', z') \\ &\quad \times \int_{\Omega_k} e^{-j2\pi((x-x')k_x + (y-y')k_y + (z-z')k_z)} dk_x dk_y dk_z dx dy dz dx' dy' dz' \\ &= 0 \end{aligned} \quad (18)$$

In continuous functional space, a measure of inner-product is defined as $\langle f, g \rangle = \int_{\Omega} f(x) \cdot g^*(x) \cdot dx$, where $g^*(x)$ is the conjugate of $g(x)$. A function $f(x)$ is said to be orthogonal to $g(x)$ if they satisfy $\langle f, g \rangle = 0$. Under this definition, $\{g_l(k_x, k_y, k_z)\}_{l=0, \dots, L-1}$ are orthogonal to each other, since, for $i \neq j, i, j = 0, \dots, L-1$ we have (18) at the top of the page.

By applying the inner product to (5), we obtain

$$\langle g_i, d(t) \rangle = \sum_l \langle g_l, g_i \rangle c_l(t) + n_i, \quad i=0, \dots, L-1 \quad (19)$$

and the least squares estimate of $c_l(t)$ is obtained as

$$c_i(t) = \frac{\langle g_i, d(t) \rangle}{\langle g_i, g_i \rangle}, \quad i=0, \dots, L-1. \quad (20)$$

This equation shows that, in continuous functional space, the SLIM algorithm is a cross-correlation estimator. However, due to the undersampling problem with MRSI data, the orthogonality is lost in a subspace where the functions are constrained. To estimate the spectra, (20) can be written in a vector format as

$$D(t) = GC(t) + n \quad (21)$$

with $G = (\langle g_i, g_j \rangle)_{i,j=0, \dots, L-1}$, and $D(t) = (d_i(t)) = \langle g_i, d(t) \rangle, i = 0, \dots, L-1$. The least squares estimate [30] of (21) is

$$C(t) = (G'Q^{-1}G)^{-1}G'Q^{-1}D(t) \quad (22)$$

where Q is the covariance matrix of noise $\sigma^2 I$. The source of G ensures that it is a positive definite Hermitian matrix and it is invertible [21], thus, the solution is simplified as

$$C(t) = G^{-1}D(t). \quad (23)$$

This formulation provides an understanding of the SLIM algorithm from a statistical perspective and provides a basis for comparison with the algorithm described in this report. This shows that the SLIM algorithm does not take into account partial volume effect, since the overlay of multiple tissue compartments would result in a source of nonorthogonality. Although an increase in the number of phase encodes may be able to account for the

information lost, this would require an increase in the imaging time and offset the advantage of this approach.

References

1. Maudsley, AA. MR spectroscopic imaging. In: Toga, AW.; Mazziotta, JC., editors. *Brain Mapping: The Methods*. Academic; Amsterdam, The Netherlands: 2002. p. 351-378.
2. Soher BJ, Young K, Govindaraju V, Maudsley AA. Automated spectral analysis III: Application to in vivo proton MR spectroscopy and spectroscopic imaging. *Magn. Reson. Med.* 1998; 40:822–831. [PubMed: 9840826]
3. Liang Z-P, Boada FE, Constable RT, Haacke EM, Lauterbur PC, Smith MR. Constrained reconstruction methods in MR imaging. *Rev. Magn. Reson. Med.* 1992; 4:67–186.
4. Wear, KA. Advanced methods in spectroscopic imaging. In: Yan, H., editor. *Signal Processing for Magnetic Resonance Imaging and Spectroscopy*. Marcel Dekker; New York: 2002.
5. Plevritis SK, Macovski A. MRS imaging using anatomically based k -space sampling and extrapolation. *Magn. Reson. Med.* 1995; 34:686–693. [PubMed: 8544688]
6. Hu X, Patel MS, Garwood M, Ugurbil K, Merkle H, Grad J, Stillman AE. Reduction of lipid contamination in proton chemical shift imaging by a Bayesian reconstruction. *Proc. Int. Soc. Magn. Reson. Med.* 1992:4253.
7. Spielman D, Webb P, Macovski A. A statistical framework for in vivo spectroscopic imaging. *J. Magn. Reson.* 1988; 79:66–77.
8. Hu X, Levin DN, Lauterbur PC, Spraggins T. SLIM: Spectral localization by imaging. *Magn. Reson. Med.* 1988; 8:314–322. [PubMed: 3205158]
9. Liang Z-P, Lauterbur PC. A generalized series approach to MR spectroscopic imaging. *IEEE Trans. Med. Imag.* Jun.; 1991 10(2):132–137.
10. von Kienlin M, Mejia R. Spectral localization with optimal pointspread function. *J. Magn. Reson.* 1991; 94:268–287.
11. Bashir A, Yablonskiy DA. Natural linewidth chemical shift imaging (NL-CSI). *Magn. Reson. Med.* 2006; 56:7–18. [PubMed: 16721752]
12. Green PJ. Bayesian reconstructions from emission tomography data using a modified EM algorithm. *IEEE Trans. Med. Imag.* Mar.; 1990 9(1):84–93.
13. Miller MI, Schaewe TJ, Bosch CS, Ackerman JJH. Model-based maximum-likelihood estimation for phase-and frequency-encoded magnetic-resonance-imaging data. *J. Magn. Reson. B.* 1995; 107:210–221. [PubMed: 7788095]
14. Shepp LA, Vardi Y. Maximum likelihood reconstruction in positron emission tomography. *IEEE Trans. Med. Imag.* Oct.; 1982 MI-1:113–122.
15. Coron A, Vanhamme L, Antoine JP, Van Hecke P, Van Huffel S. The filtering approach to solvent peak suppression in MRS: A critical review. *J. Magn. Reson.* 2001; 152:26–40. [PubMed: 11531361]
16. Haupt CI, Schuff N, Weiner MW, Maudsley AA. Removal of lipid artifacts in ^1H spectroscopic imaging by data extrapolation. *Magn. Reson. Med.* 1996; 35:678–687. [PubMed: 8722819]
17. Metzger G, Sarkar S, Zhang X, Heberlein K, Patel P, Hu X. A hybrid technique for spectroscopic imaging with reduced truncation artifact. *Magn. Reson. Imag.* 1999; 17:435–443.
18. Vanhamme L, Sundin T, Hecke PV, Huffel SV. MR spectroscopy quantitation: A review of time-domain methods. *NMR Biomed.* 2001; 14:233–246. [PubMed: 11410941]
19. Collins, DL.; Zijdenbos, AP.; Kollokian, V.; Sled, JG.; Kabani, NJ.; Holmes, CJ.; Evans, AC. Design and construction of a realistic digital brain phantom; *IEEE Trans. Med. Imag.* Jun.. 1998 p. 463-468.[Online]. Available: <http://www.bic.mni.mcgill.ca/brainweb/>
20. Friston, KJ. Spatial registration and normalization of images; *Hum. Brain Mapp.* 1995. p. 165-189. [Online]. Available: <http://www.fil.ion.ucl.ac.uk/spm/>
21. Angelie E, Bonmartin A, Boudraa A, Gonnard PM, Mallet JJ, Sappey-Marini D. Regional differences and metabolic changes in normal aging of the human brain: Proton MR spectroscopic imaging study. *Amer. J. Neuroradiol.* 2001; 22:119–127. [PubMed: 11158897]

22. Lundbom N, Barnett A, Bonavita S, Patronas N, Rajapakse J, Tedeschi, Di Chiro G. MR image segmentation and tissue metabolite contrast in ¹H spectroscopic imaging of normal and aging brain. *Magn. Reson. Med.* 1999; 41:841–845. [PubMed: 10332862]
23. Schuff N, Ezekiel F, Gamst A, Amend D, Capizzano AA, Maudsley AA, Weiner MW. Region and tissue differences of metabolites in normally aged brain using ¹H magnetic resonance spectroscopic imaging. *Magn. Reson. Med.* 2001; 45:899–907. [PubMed: 11323817]
24. Soher BJ, van Zijl PC, Duyn JH, Barker PB. Quantitative proton MR spectroscopic imaging of the human brain. *Magn. Reson. Med.* 1996; 35:356–363. [PubMed: 8699947]
25. Wiedermann D, Schuff N, Matson GB, Soher BJ, Du AT, Maudsley AA, Weiner MW. Short echo time multislice proton magnetic resonance spectroscopic imaging in human brain: Metabolite distributions and reliability. *Magn. Reson. Imag.* 2001; 19:1073–1080.
26. Lim KO, Spielman DM. Estimating NAA in cortical gray matter with applications for measuring changes due to aging. *Magn. Reson. Med.* 1997; 37:372–377. [PubMed: 9055227]
27. Pfefferbaum A, Adalsteinsson E, Spielman D, Sullivan EV, Lim KO. In vivo spectroscopic quantification of the N-acetyl moiety, creatine, and choline from large volumes of brain gray and white matter: Effects of normal aging. *Magn. Reson. Med.* 1999; 41:276–284. [PubMed: 10080274]
28. Chen SC, Schaewe TJ, Teichman RS, Miller MI, Nadel SN, Greene AS. Parallel algorithms for maximum-likelihood nuclear magnetic resonance spectroscopy. *J. Magn. Reson. A.* 1993; 102:16–23.
29. Papoulis A. A new algorithm in spectral analysis and bandlimited extrapolation. *IEEE Trans. Circuits Syst. Sep.*; 1975 CAS-22(9):735–742.
30. Luenberger, DG. *Optimization by Vector Space Methods*. Wiley; New York: 1968.

Fig. 1.
Flow diagram of the proposed algorithm.

Fig. 2. Average reconstruction error rate of NAA as a function of the standard deviation of the noise added into the simulated MRSI data of 5-mm slice thickness, which assumed homogenous metabolite intensities within each tissue. Results are shown for SLIM ($\diamond$), zero-filled FT (+), and the proposed reconstruction method (*). For the SLIM algorithm, specific compartments were defined, whereas for the proposed algorithm, the partial volume information was used in the reconstruction.

Fig. 3.

Results for the simulated brain MRSI data of 15-mm slice thickness. Row (i): High resolution MRI tissue segmentation images used to create the simulated MRSI data, as (a) GM, (b) WM, and (c) CSF. Row (ii): Resultant metabolite images reconstructed from the full k -space (128×128) noise-free MRSI data, for (a) NAA, (b) Cr, and (c) Cho. Row (iii): Same metabolite images reconstructed from the zero-filled central k -space MRSI data (32×32) with noise added. Row (iv): Same metabolite images reconstructed using the proposed algorithm.

Fig. 4.

Tissue segmentation and metabolite images for each of the four experimental datasets. For each set of images, the first row displays the high resolution tissue segmentations for (i) GM, (ii) WM, and (iii) CSF; the second row displays the metabolite image results from spectral fitting of the zero-filled MRSI data, as (i) NAA, (ii) Cr, and (iii) Cho; and the third row displays the corresponding metabolite images reconstructed using the proposed algorithm. Note that the frontal lobe is variably cut off for the images as a result of our subregional removal method. A small circle is overlaid in the second row and first column of (a) to indicate the location for the spectra displayed in Fig. 5.

Fig. 5. Example spectrum obtained from the location shown in Fig. 4(a), for both (a) zero-filled FT reconstruction and (b) the proposed reconstruction method. The real part of the spectrum is shown and the scales are in PPM using water as a reference.