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Imaging based magnetic resonance spectroscopy (MRS) localization for quantitative neurochemical analysis and cerebral metabolism studies

Phil Lee^{1,2}, Peter Adany¹, and In-Young Choi^{1,2,3}

¹Hoglund Brain Imaging Center, University of Kansas Medical Center, Kansas City, KS 66160, USA

²Department of Molecular & Integrative Physiology, University of Kansas Medical Center, Kansas City, KS 66160, USA

³Department of Neurology, University of Kansas Medical Center, Kansas City, KS 66160, USA

Abstract

Accurate quantitative metabolic imaging of the brain presents significant challenges due to the complexity and heterogeneity of its structures and compositions with distinct compartmentations of brain tissue types (e.g., gray and white matter). The brain is compartmentalized into various regions based on their unique functions and locations. *In vivo* magnetic resonance spectroscopy (MRS) techniques allow non-invasive measurements of neurochemicals in either single voxel or multiple voxels, yet the spatial resolution and detection sensitivity of MRS are significantly lower compared with MRI. A fundamentally different approach, namely spectral localization by imaging (SLIM) provides a new framework that overcomes major limitations of conventional MRS techniques. Conventional MRS allows only rectangular voxel shapes that do not conform the shapes of brain structures or lesions, while SLIM allows compartments with arbitrary shapes. However, the restrictive assumption proposed in the original concept of SLIM, i.e., compartmental homogeneity, led to spectral localization errors, which have limited its broad applications. This review focuses on the recent technical frontiers of image-based MRS localization techniques that overcome the limitations of SLIM through the development and implementation of various new strategies, including incorporation of magnetic field inhomogeneity corrections, the use of multiple receiver coils, and prospective optimization of data acquisition.

Keywords

in vivo; magnetic resonance spectroscopy (MRS); spectral localization by imaging (SLIM); localization; human brain; gray matter; white matter

Correspondence: Phil Lee, Ph.D., Hoglund Brain Imaging Center, Mail Stop 1052, 3901 Rainbow Boulevard, University of Kansas Medical Center, Kansas City, KS 66160, Phone: 913-588-0454, Fax: 913-588-9071, plee2@kumc.edu.

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Introduction

The brain is a highly complex and heterogeneous organ with distinct compartmentations of tissue types (e.g., gray matter (GM) and white matter (WM) in cortical and subcortical structures), cell types (e.g., neurons and astrocytes), subcellular structures (e.g., cell bodies and axons), and brain regions (e.g., frontal, parietal). Each compartment with its unique functions and geometries is an integral part of the brain, contributing to its integrative functions and structures. Biochemical and physiological processes are the underlying basis of structural and functional brain connectivity, and their interactions and couplings form a dynamic brain network. *In vivo* magnetic resonance (MR) technology, one of the most versatile noninvasive imaging techniques, enables us to measure nearly all aspects of the brain from the structural, physiological and functional to biochemical and metabolic parameters using MR imaging (MRI) and/or MR spectroscopy (MRS), as covered in this issue (cross-ref: “Introduction to Nuclear Magnetic Resonance” – V Mlynarik; “A practical guide to in vivo proton magnetic resonance spectroscopy at high magnetic field” – Lijing Xin).

In vivo MRS is an important tool in investigating brain metabolism and energetics in health and disease, as it allows measurements of steady-state concentrations of neurochemicals and their metabolic activities including metabolic pool turnover rates, biochemical reaction rates and transport rates between compartments. *In vivo* MR studies have shown that numerous metabolic disorders are linked to abnormalities of the brain [1]. When assessing neurochemical, metabolic and physiological changes of the brain in normal development, aging and diseases using MRS, the heterogeneity of the brain needs to be considered. For example, various brain regions and different tissue types present heterogeneous distributions of neurochemical concentrations (Table 1). Differences between the neurochemical profiles of GM and WM can be attributed in part to the significantly higher percentage of neuronal cells in GM (68%) compared with WM (7%) in the human brain [2]. Neurochemical concentrations have been reported in different regions and tissue types, e.g., the concentrations and ratios of major metabolites reported in different brain anatomies summarized in Table 1, which are traditionally reported as anatomical regions containing ‘mostly GM’ or ‘mostly WM’ due to the limitations of traditional MRS techniques. While MRI clearly delineates the major brain structures, MRS signals may vary depending on brain regions even within major structures that appear homogeneous. The brain exhibits focal changes of neural activities, dynamic energetics and functional responses depending on stimuli, tasks, and the involvement of brain injuries or neurological conditions. Accurate and reliable spatial localization of MRS signals with appropriate signal-to-noise ratio (SNR) and detection sensitivity are critical for obtaining quality data and for effective application of MRS techniques. One of the major challenges of detecting MRS signals comes from the naturally low concentrations of neurochemicals, as much as four orders of magnitudes lower than that of water. Thus, spatial resolution and detection sensitivity of MRS signals are significantly lower than those of MRI, especially at lower magnetic field strength of up to 3 T for clinical scanners.

Ideally, spatial localization applied to well-defined volumes in the brain allows quantification of neurochemicals with regional specificity, with elimination of non-cerebral

lipid and other signals from surrounding tissues and areas. In single-voxel MRS (SVS) methods, MR spectra are obtained from a single volume of interest (VOI), while multi-voxel MRS methods yield spectra of multiple adjacent volumes usually covering a larger region than that in SVS. Commonly used SVS techniques include the stimulated echo acquisition mode (STEAM) [3], point resolved spectroscopy (PRESS) [4–6], image selected *in vivo* spectroscopy (ISIS) [7] and outer volume suppression (OVS) [8, 9]. The multi-voxel MRS methods are imaging-based localization methods and are known as magnetic resonance spectroscopic imaging (MRSI), chemical-shift imaging (CSI) or simply spectroscopic imaging (SI), each referring to the same variety of techniques [10–13]. There is a tradeoff between SVS and MRSI regarding scan time, spatial resolution, voxel definition, and signal-to-noise ratio.

The distinction between spectroscopic imaging and localization rests in the notion that the goal of MRSI is to reconstruct the spatio-spectral distribution of signals of an object and is thus an imaging method, and the goal of MRS localization is to estimate the spectra of distinct tissue structures assisted by a high resolution model of the object, and is thus an imaging-based localization method. In this paper, we aim to provide an overview of imaging-based localization techniques of MRS. Particularly, we focus on the theoretical concepts and applications of non-Fourier localization techniques of MRS including recent advances (Table 2).

Imaging-based MRS Localization

Imaging-based localization utilizes spatial encoding of MRS signals through either frequency and/or phase encoding and includes Fourier based (i.e., MRSI) and non-Fourier based MRS localization methods. Spatially encoded MRS signals without considering signal relaxation effects can be expressed as

$$s_n(\mathbf{k}_n, t) = \int_{FOV} \hat{\rho}(\mathbf{r}, t) \exp(-j 2\pi(\mathbf{k}_n \cdot \mathbf{r} + f(\mathbf{r})t)) d\mathbf{r} \quad [\text{Eq. 1}]$$

where $\hat{\rho}(\mathbf{r}, t)$ is apparent MR spin density, $\mathbf{k}_n$ is the serialized k-space vector ($n = 1 \dots N$) and $\mathbf{r}$ is a spatial coordinate vector. $f(\mathbf{r})$ is the spin precession frequency that includes constant static magnetic field (B_0) and spatially varying B_0 inhomogeneity (δB_0), i.e., $f(\mathbf{r}) = \gamma B_0 + \gamma \delta B_0(\mathbf{r})$. The apparent MR spin density $\hat{\rho}(\mathbf{r}, t)$ represents the physical spin density in time domain $\rho(\mathbf{r}, t)$, combined with radiofrequency magnetic field (B_1) inhomogeneity information during RF transmit and receive. The fundamental task of MRS signal reconstruction is to invert Eq. 1 to obtain $\rho(\mathbf{r}, t)$. The traditional MRSI approach is a special case of general imaging-based MRS localization where k-space vectors are sampled to satisfy prerequisites of the discrete Fourier transformation (DFT). Traditional MRSI uses the DFT to obtain the B_0 and B_1 modulated apparent spin density function $\hat{\rho}(\mathbf{r}, t) e^{-j 2\pi f(\mathbf{r})t}$ in each voxel. In comparison, non-Fourier based MRS localization uses generalized matrix inversion approaches to calculate the spin density function in Eq. 1 in each compartment (Fig. 1). The non-Fourier based approach has several benefits over the Fourier based approach because it allows incorporation of various constraints and/or *a priori* knowledge

into the spectral reconstruction, resulting in improved localization performance and the ability to obtain the physical spin density $\rho(\mathbf{r}, t)$, unmodulated by B0 and B1 inhomogeneities for accurate spectral quantification.

Fourier based localization: DFT

MRSI is founded on the concept of the k-space and the discrete Fourier transform (DFT), which transforms k-space sampled data into the spatial domain yielding rectangular voxels on a Cartesian spatial grid [10, 14, 15]. In mathematical terms, k-space data and the reconstructed voxel signals comprise a Fourier transform pair, which are linked through the Fourier transformation. The discrete and truncated k-space sampling in data acquisition imparts a *sinc*-like spatial response function, whose side lobes extend far beyond the nominal voxel size. The relative contribution of signals from within a voxel is approximately 59%, 35%, and 20% for 1D, 2D and 3D DFTs, respectively, and the rest of signals originate from outside of the voxel. The consequence of this effect is inter-voxel signal contamination and enlargement of spatial extent of any given voxel, which is especially problematic for voxels adjacent to high intensity signals, e.g., subcutaneous lipid. An approach to reduce the inter-voxel signal contamination in the DFT is to apply spatial filters, e.g., hamming filter, at the expense of reducing effective spatial resolution. Another approach is to acquire high spatial resolution MRSI, which effectively reduces the signal contamination from surrounding areas at the expense of a lower SNR and longer scan time. To improve MRSI characteristics, several approaches have been proposed including constrained reconstruction, sensitivity encoded MRSI, and their variants as described in brief below.

Constrained reconstruction—Constrained reconstruction of MRI and MRSI aims to improve signal reconstruction with the use of *a priori* information. It has been shown that a flexible arrangement of spatial boxcar functions may serve as a reduced representation of the object in order to improve resolution beyond the sampling *diffraction limit* in MRI [16, 17] and in MRS [18]. Another example is the *a priori* constraint of *total variation*, effectively imposing a piecewise constancy of the object, which has been applied in MRI and MRS [19, 20]. Another important error reduction approach concerns the direct control of the voxel side-lobes. Sensitivity encoding can help to reduce side-lobes without sacrificing resolution in the Fourier-voxel representation, resulting in improved quality of MRSI [21–23]. Other examples for constrained MRSI reconstruction are minimum-norm reconstruction [21], super-resolution [24], and overdiscrete MRSI [22, 23, 25]. More recent developments in constrained MRSI reconstruction include sparsity and low-rank constrained reconstruction methods for high-resolution MRSI sparsity [26–33].

Sensitivity encoded (SENSE) MRSI—Sensitivity encoded (SENSE) MRSI [21, 34–38] incorporates the principles of SENSE MRI [39, 40], which utilizes an array of receiver coils and their spatially varying coil sensitivity information in assisting reconstruction of localized MR signals. Incorporation of the multiple receiver coil sensitivity information into the spatial reconstruction reduces the demand for the k-space coverage, resulting in reduced scan time. As an alternative to SENSE MRSI in the image domain, generalized auto-calibrating partial parallel acquisition (GRAPPA) MRSI in the k-space domain was also

developed [41]. More recently, another alternative parallel image concept, simultaneous multi-slice imaging, has been incorporated to accelerate MRSI [42].

Dydak et al. [34] acquired MRSI with the size of the field of view reduced by half of the excited volume in two dimensions, producing aliasing of the outer signals into the FOV in a phantom and the human brain. Whereas signal mixing among compartments were clearly visible due to aliasing in the naïve reconstruction from half-FOV, in the SENSE-SI reconstruction, the voxel signal mixing was minimized and similar to full-FOV. The SNR characteristic in SENSE SI is an important aspect to consider due to the potential noise amplification in SENSE-SI. Ideally, the SNR of full-FOV acquisition to the SNR of SENSE-SI will be equal to the square root of the dimensional reduction factor R [34]. In a phantom with R of 2.0, the SNR ratio was found to be around 2.11 for NAA and 2.07 for lactate. Using the same reduction factor in vivo, the SNR ratio was found to be 2.16 for NAA, 2.32 for Cr and 1.92 for Cho [34]. These results indicate a good performance of SENSE-SI in minimizing additional SNR loss with SENSE reconstruction.

Recent *in vivo* applications of sensitivity encoded MRSI have included 3D sensitivity encoded MRSI of gliomas at 3 T [38], fast parallel spiral CSI with iterative SENSE reconstruction [37], and SENSE proton echo-planar spectroscopic imaging (PEPSI) in the human brain [36] among others.[41, 42]

Non-Fourier based localization

Non-Fourier reconstruction is a more general form of reconstruction approach that encompasses partial and fractional Fourier phase encoding schemes and other types of spatial encoding, and can be expressed by an analogous matrix inversion problem. Non-Fourier techniques originated early in the field of MR (see, for example, [43]) and can utilize not just *a priori* structural information but also spatial encoding through non-uniform receiver coil sensitivity profiles. Generally, the non-Fourier reconstruction methodology entails the formulation of a model matrix, or *geometry matrix*, as well as the method of its solution [44–46]. Improvements in localization by non-Fourier reconstruction have focused on the incorporation of structural information from high resolution MRI, compensation for B1 and B0 inhomogeneities, and techniques for constrained optimization.

Spectral Localization by Imaging (SLIM)—The basic concept of Spectral Localization by Imaging (SLIM) has been introduced by Hu and colleagues, proposing the theoretical foundations to acquire MR spectra of tissue compartments rather than voxels [44]. SLIM was first applied to *in vivo* data of the human leg to reconstruct the chemical shift spectra of fat, bone marrow and muscle compartments [44]. Comparison of SLIM and MRSI of identical k-space size showed significant improvement of the inter-compartmental, or inter-voxel, signal contamination using SLIM [44].

SLIM has favorable noise and convergence properties [45, 47], in that SLIM will yield the error-free average of the inhomogeneous compartment in the limit of very large k-space sizes. However, the common cases of the small size k-space, inhomogeneity of signals within compartments will lead to signal leakage. It is important to note that signal leakage only occurs from the inhomogeneous compartments and signal leakage resulting in SLIM is

less severe than the corresponding Fourier reconstruction [47]. A limited number of *in vivo* applications of SLIM have been reported, which include multiple quantum filtered chemical shift imaging of GABA in the human brain [48], lipid signal extraction in MRSI of human calf muscles [49], and diffusion imaging of the rat uterine horn [50]. However, the requirement of compartmental homogeneity compartments of SLIM poses a significant limitation in applying SLIM techniques to many practical problems with significant compartmental inhomogeneities due B0 and B1 inhomogeneities and complex compartmental shapes such as gray matter and white matter of the human brain. Various approaches have been proposed to overcome the limitation of SLIM and extend its capabilities. These approaches include GSLIM [51], SLOOP [52], BSLIM [53], SPLASH [54], SLAM [55, 56], starSLIM [57], and BASE-SLIM [58, 59].

Principles of SLIM—In SLIM, phase-encoded acquired signals $s_n(t)$ are described in terms of M spatially uniform compartmental signals, $c_m(t)$, through a geometry matrix G [44]:

$$s(t) = G c(t) \quad [\text{Eq. 2}]$$

where $s(t)$ and $c(t)$ are column vectors of $s_n(t)$ and $c_m(t)$, respectively. The geometry matrix, G_{nm} , is defined as

$$G_{nm} = \sum_{r \in D_m} \left(e^{-j 2\pi \mathbf{k}_n \cdot \mathbf{r}} \right) \quad [\text{Eq. 3}]$$

where D_m indicates the spatial domain of the m^{th} compartment as found by MRI segmentation, and $\mathbf{k}_n$ indicates the n^{th} phase encoding vector. G is assumed to be independent of time, a simplification that ignores B0 inhomogeneity effects. Hence, the SLIM equation can be solved by a matrix inversion of G . As G is generally presumed to be square or over-determined, the Eq. [1] is solved in the least-squares sense by the pseudoinverse operation, $\text{pinv}(G)$, so that compartmental signals, $\hat{c}(t)$, are reconstructed from acquired signal as

$$\hat{c}(t) = \text{pinv}(G) s(t). \quad [\text{Eq. 4}]$$

A useful means to calculate $\text{pinv}(G)$ is the singular value decomposition (SVD) [46], while the least squares solution can also be written in the form,

$$\hat{c}(t) = (G^H G)^{-1} G^H s(t) \quad [\text{Eq. 5}]$$

where H indicates the conjugate transpose. This formulation yields some insight to the mechanism of SLIM localization. The $M \times M$ matrix $(G^H G)^{-1}$ contains information about the overlapping contributions of signals from every compartment, such that its off-diagonal elements yield desired cancellations of signals external to each compartment. Consider a case when $s(t)$ contains the signal contribution of only one compartment $m = m'$, and all other compartments give zero signal contributions. Then it can be observed that $s(t)$ consists of a column of G , labeled $G_{m'}$, multiplied by the compartment constant of the chosen compartment, i.e., $s(t) = G_{m'} c_{m'}(t)$. Substituting this into Eq. [5], it follows that the product $G^H G_{m'}$ is identical to the m'_{th} column of $(G^H G)$. Therefore, with $(G^H G)^{-1}(G^H G) = I$, where I is the identity matrix, for any such $s(t)$ generated from m'_{th} compartment, it follows that $\hat{c}_m(t) = 0$ $m \neq m'$ for all and $\hat{c}_{m'}(t) = c_{m'}(t)$, i.e. the reconstructed signal is identical to the compartmental source signal. This illustrates a compartmental orthogonality in the SLIM reconstruction. By comparison, orthogonality of the DFT is a property of voxels composed of spatial harmonics, not tissue compartments, and due to the under-sampled condition of the DFT in MRS, the object spatial function is not uniquely recoverable by DFT.

Further insight of localization characteristics of SLIM can be obtained by introducing an elegant concept of the spatial response function (SRF) or point spread function (PSF) [52, 60]. The spatial response function for a compartment m is defined as:

$$SRF_m(\mathbf{r}) = \sum_n h_{mn} N A_n \left(e^{-j 2\pi \mathbf{k}_n \cdot \mathbf{r}} \right), \quad [\text{Eq. 6}]$$

where h_{mn} is the matrix elements $H = \text{pinv}(G)$ and $N A_n$ is the number of averages of individual phase encodings. When the compartmental homogeneity condition is met in SLIM reconstruction, the integration of SRF of a given compartment over outside compartments become zero through phase cancellation, indicating the outside compartments do not contribute to the SLIM reconstructed signals of the compartment. However, any spatial inhomogeneities will lead to incomplete phase cancellation and inter compartmental signal contamination [52].

Generalized SLIM (GSLIM)—The major limitation of SLIM, namely the compartmental homogeneity requirement, needs to be addressed in most applications of SLIM [45, 47]. Generalized SLIM (GSLIM) [51] provides a means to discover the inhomogeneous signal components in SLIM reconstruction. GSLIM introduces a new term, a series expansion $a(f)$, in addition to the SLIM G matrix, to model both the homogeneous and inhomogeneous signal parts. GSLIM applies a data consistency constraint as the optimization parameter to find $a(f)$, through which the homogeneous part (partial SLIM reconstruction) and the inhomogeneous part (partial Fourier series reconstruction) can be isolated [47]. GSLIM reconstruction has shown less quantitation error compared to the Fourier transform in a phantom, to reveal unexpected heterogeneity of the frog skeletal muscle [61] and ischemic regions of the brain in the a gerbil model of stroke [62].

SLOOP—Spectral localization with optimal point spread function (SLOOP) has been proposed to improve SLIM in localization performance and SNR by optimizing phase

encoding gradients, i.e., k-space sampling [52]. In the SLIM reconstruction with standard Fourier phase encodings, the SRF can have large amplitudes in the external compartments, which makes SLIM reconstruction susceptible to inter-compartmental signal leakage due to compartmental inhomogeneities. SLOOP addresses this limitation of SLIM by optimizing the k-space sampling to minimize the amplitudes of the SRF in the outside compartments [52]. Specifically, SLOOP achieves the optimization by finding a set of k-space vectors that minimizes the integral of the magnitude of the SRF over outside of each compartment of interest and simultaneously minimizes noise of those compartments through numerical simulation.

Applications of SLOOP have mostly focused on human cardiac ^3P MRS [60, 63–69]. The initial demonstration of SLOOP included ^1H MRS measurement of the rabbit kidney *in vitro* [52]. Subsequent SLOOP applications to cardiac ^3P MRS in humans expanded SLOOP to use surface coils by incorporating B1 inhomogeneities of the surface coils in the SLIM model [66].

SLAM—Spectroscopy localization by algebraic modeling (SLAM) focuses on optimizing SNR of the non-Fourier localization [55, 56]. SLAM can be considered as a special case of SLIM, in that 1) the geometry matrix G is replaced by a matrix that represents Fourier transforms composed of phase factors for each discretized spatial coordinates [46]; 2) compartments in SLIM are replaced by a set of coalesced CSI voxels with the same concentrations of CSI; 3) the number of phase encodings in SLAM is identical to the number of final compartments; and 4) SLAM chooses low-gradient k-space vectors to maximize SNR. SLAM incorporates a prospective optimization to choose k-space vectors to minimize inter-compartmental signal leakage as well as to maximize SNR, similar to the case in SLOOP. One difference between SLAM and SLOOP is that SLAM does not require the k-space encodings to be in integer steps and provides more flexibility in selecting k-space vectors.

Initial applications of SLAM have focused on ^3P MRS in the calf and heart [55], demonstrating its characteristics of SNR gain and localization efficiency. The SLAM technique has been extended to use coil sensitivity information from multiple receiver coils and demonstrated detection of altered metabolite concentrations in tumors in the human brain and significant scan time reduction in ^3P MRS of the human heart [56].

SPLASH (SLIM using sensitivity encoding by multiple receiver coils)—As demonstrated with SENSE-SI [34], *sensitivity encoding* can accelerate spectroscopic imaging based on the FOV-unfolding concept. In addition to this Fourier-based application, sensitivity encoding has also been incorporated into the framework of SLIM as spectral localization achieved by sensitivity heterogeneity (SPLASH) [54, 70].

As in SLIM, SPLASH utilizes structural information obtained from high resolution anatomical MRI to define boundaries of tissue compartments [54, 70]. SPLASH further incorporates multiple signals from an array of receiver elements with differing sensitivity profiles into the reconstruction equation. Incorporation of the multiple coil information effectively increase the number of k-space encodings, i.e., (number of k-space encodings $\times$

number of receive coil elements), therefore, reducing the requirement of the number of k-space encodings.

Successful application of SPLASH in the human brain *in vivo* has been demonstrated on stroke patients [54]. In that work, the authors showed that the lesion-affected and normal-appearing compartments with large differences of metabolite concentrations could be successfully separated with minimal inter-compartment signal contamination. In addition, the authors demonstrated feasibility of separating the two compartment using only coil sensitivity information, i.e., using only the zero-th term k-space data. More recently, SPLASH was updated to mitigate the effect of intracompartmental heterogeneities [70].

NL-CSI and BSLIM (B0 inhomogeneity corrected SLIM)—A major factor that was addressed by various techniques mentioned above is B0 field inhomogeneity, which imparts additional spatially varying phase and frequency modulations of the detected MRS signals, resulting in loss of SNR, lineshape distortion, increased uncertainty in metabolite quantification, and inter-compartmental signal leakage in the SLIM reconstruction. Several approaches have been proposed to correct for B0 field inhomogeneity, primarily involving a time-dependent SLIM-like matrix formulated as a function of a spatially-dependent phase evolution term [53, 59, 71].

Natural-lineswidth CSI (NL-CSI) [71] and SLIM with explicit B0 field inhomogeneity correction (BSLIM) [53] proposed to use a time-dependent SLIM framework and solve the SLIM-like equation for every time point, in which the SLIM geometry matrix is updated based on the B0 inhomogeneities present in each compartment [71]. By incorporating B0 inhomogeneity information in the SLIM framework, both methods demonstrated improved spectral lineshapes in phantoms and in the human brain. NL-CSI used regularization to improve the performance of the reconstruction in presence of rapidly decaying signals.

starSLIM and BASE-SLIM (B0 and B1 inhomogeneity corrected SLIM)—Despite many advancements in non-Fourier based reconstruction, separating MR signals among compartments with convoluted geometry such as GM and WM in the human brain still proves significantly challenging due to uncorrected residual inhomogeneities. The recently proposed B0-Adjusted Sensitivity Encoded SLIM (BASE-SLIM) successfully reconstructed GM and WM spectra from the human brain (Fig. 2), demonstrating the unique spectral patterns of GM and WM [58, 59]. Neurochemical concentrations in GM and WM quantified from BASE-SLIM reconstructed data were consistent with those determined from regression analysis of CSI data with GM fractions of each CSI voxel. BASE-SLIM incorporates both B0 and B1 inhomogeneity information to address compartmental inhomogeneity limitation in SLIM and to improve spectral lineshapes similar to static and radiofrequency-compensated SLIM (starSLIM) [57]. In addition, BASE-SLIM utilizes sensitivity information of multiple receive coils to improve localization performance. BASE-SLIM uses a time dependent geometry matrix that incorporates B0 inhomogeneity information and performs SLIM reconstruction at each time point similar to BSLIM and NL-CSI. The ability to quantify metabolite concentration in GM and WM using BASE-SLIM provides a new opportunity to address uncertainties and discrepancies in reported neurochemical

concentration in literature, which could reflect varying proportions of GM and WM tissue contents in the VOI of each study.

Future Directions

Recent advances in non-Fourier based reconstruction techniques overcame many limitations of the original SLIM theory that provided a new framework of compartment-based reconstruction and enabled separation of signals from compartments with convoluted geometry such as GM and WM. Together with technological advancements of RF hardware technology such as increased number of receive coils, non-Fourier based reconstruction techniques could contribute significantly in establishing MRS as an essential tool in biomedical research. The areas of further technical development include effective optimization strategies for data acquisition for optimal localization accuracy and SNR, as well as effective methods to combine multiple receive coil signals for both assisting localization and SNR improvement.

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Figure 1. Comparison of Fourier-based MRSI and non-Fourier based imaging based localization techniques

In traditional Fourier-based MRSI (left), a full or almost full k-space data are acquired, then the Fourier transform is performed to obtain mutually orthogonal voxels (yellow) inside the VOI (white), leading to mixed tissue signals caused by the broad point spread function of Fourier reconstruction. In compartment-localized methods (right), only fraction of full k-space data can be acquired, the localization equation is solved by generalized matrix inversion to obtain mutually orthogonal compartment signals (compartment outlined in yellow), and, thus, tissue signals, e.g., gray matter (GM) and white matter (WM), can be separated.

Figure 2. Comparison of in vivo spectra of the human brain reconstructed by Fourier-based MRSI and BASE-SLIM

(A) In traditional MRSI, each voxel contains signals from multiple tissue types due to the rectangular shape of the voxel and the broad point spread function. Spectra are marked as 'mostly GM' and 'mostly WM' reflecting a mixture of tissue types. (B) In compartment-localized techniques such as BASE-SLIM, signals from a single tissue type, GM or WM, can be reconstructed without contamination from other tissue types. Typical spectral patterns of GM and WM, i.e., high creatine-to-choline ratio and glutamate + glutamine signals in GM, and low creatine-to-choline ratio and glutamate + glutamine signals in WM, are clearly visible in BASE-SLIM reconstructed spectra, indicating minimal inter-compartmental spectral contamination. Abbreviations in the spectra are: creatine (Cr); choline (Cho); glutamate (Glu); glutamine (Gln); *myo*-inositol (mI).

Ratios of GM/WM metabolite concentrations and regional absolute metabolite concentrations in the human brain

Table 1

Ratios of GM/WM metabolite concentrations in the brain						
Brain Region	NAA	SD	tCr	SD	tCho	SD
global	1.19	(0.15)	1.40	(0.19)	1.00	(0.20)
global	1.51	(0.20)				
frontal	0.94	(0.20)	1.09	(0.24)	0.78	(0.22)
frontal	0.86	(0.17)	1.07	(0.25)	0.76	(0.23)
parietal	0.86	(0.19)	1.05	(0.23)	0.60	(0.15)
parietal	0.84	(0.22)	1.15	(0.37)	0.69	(0.33)
Regional absolute metabolite concentrations in the brain (mmol/L)						
region	NAA		tCr		tCho	
average GM	8.0	(1.5)	5.9	(1.0)	1.7	(0.4)
mesial frontal	8.1	(1.2)	6.0	(1.0)	2.1	(0.3)
frontal WM	10.6	(0.7)	8.0	(0.7)	2.2	(0.2)
frontal	14.2	(2.0)	11.5	(2.4)	3.6	(0.8)
parietal	14.0	(1.8)	10.7	(1.5)	2.9	(0.4)
parietal	8.1	(1.2)	5.8	(1.1)	1.5	(0.4)
occipital cortex	12.9	(0.4)	8.5	(0.4)	1.0	(0.1)
medial temporal lobe	14.1	(2.5)	12.0	(4.0)	3.6	(1.1)
posterior cingulate	12.0	(0.3)	8.8	(0.4)	1.4	(0.2)
anterior cingulate cortex	13.7	(1.3)	9.6	(1.0)	2.2	(0.2)
average corpus callosum	7.7	(1.9)	4.2	(1.6)	1.9	(0.6)
thalamus	16.3	(2.0)	12.0	(1.1)	3.4	(0.8)
putamen	11.2	(0.4)	10.3	(0.5)	2.3	(0.3)
hippocampus	11.6	(1.1)	9.7	(0.9)	2.2	(0.3)
pons	18.4	(3.0)	10.5	(3.2)	4.7	(1.1)
pons	10.8	(0.7)	6.7	(0.7)	3.0	(0.3)
cerebellum	16.4	(2.8)	15.7	(2.1)	3.9	(0.9)

Table 2

Imaging based localization techniques and their features by year of introduction.

Method	Year	Mode of reconstruction	Fourier phase encoding	Fractional-Fourier phase encoding	Sensitivity encoding or B1 correction	B0 correction	Reference
CSI	1982	voxels	x				[10]
SLIM	1988	compartments	x	x			[44]
SLOOP	1991	compartments		x			[52]
GSLIM	1999	compartments	x	x			[62]
SENSE-SI	2001	voxels	x		x		[34]
NL-CSI	2006	compartments	x			x	[71]
BSLIM	2007	compartments	x			x	[53]
SPLASH	2011	compartments	x		x		[54]
SLAM	2013	compartments	x	x	x		[56]
BASE-SLIM	2013	compartments	x	x	x	x	[58]