Image-guided spatial localization of heterogeneous compartments for magnetic resonance

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Purpose: Image-guided localization Spectral Localization Achieved by Sensitivity Heterogeneity (SPLASH) allows rapid measurement of signals from irregularly shaped anatomical compartments without using phase encoding gradients. Here, the authors propose a novel method to address the issue of heterogeneous signal distribution within the localized compartments.

Methods: Each compartment was subdivided into multiple subcompartments and their spectra were solved by Tikhonov regularization to enforce smoothness within each compartment. The spectrum of a given compartment was generated by combining the spectra of the components of that compartment. The proposed method was first tested using Monte Carlo simulations and then applied to reconstructing *in vivo* spectra from irregularly shaped ischemic stroke and normal tissue compartments.

Results: Monte Carlo simulations demonstrate that the proposed regularized SPLASH method significantly reduces localization and metabolite quantification errors. *In vivo* results show that the intracompartment regularization results in ~40% reduction of error in metabolite quantification.

Conclusions: The proposed method significantly reduces localization errors and metabolite quantification errors caused by intracompartment heterogeneous signal distribution.

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Key words: SLIM, SPLASH, Tikhonov regularization, SRF

1. INTRODUCTION

A key goal of spatial localization in magnetic resonance is to acquire signals from regions with natural and irregular anatomical boundaries. In magnetic resonance spectroscopy (MRS), most spatial localization methods can, in practice, only localize rectangular regions of interest. When weak signals from metabolites such as lactate, γ -aminobutyric acid (GABA), and glutamine are measured, a large voxel ($>1\text{ cm}^3$) is needed to achieve adequate sensitivity. Very often, a large rectangular voxel cannot be placed in the desired anatomical structure without enclosing a sizable amount of outside tissues, which complicates data analysis and interpretation. The image-guided compartmental localization technique Spectral Localization by IMaging (SLIM),^{1–3} initially proposed by Hu and colleagues,¹ offers an attractive alternative to commonly used localization methods. SLIM first defines several compartments of interest based on high-resolution anatomical images, and then attempts to separate spectra originated from different compartments using a limited number of phase encoding steps.

Multichannel phased-array receiver coils not only significantly increase sensitivity for tissues close to the coil elements but also have inherent spatial localization capability because of their spatially heterogeneous sensitivity profiles. Parallel imaging techniques increase the speed or spatial resolution of many magnetic resonance imaging (MRI) methods by taking advantage of this additional localization capability. Inspired by SLIM and parallel imaging,⁴ we developed the Spectral Localization Achieved by Sensitivity Heterogeneity (SPLASH) method and demonstrated its usefulness in a recent

study of stroke patients.⁵ In that study, we used SPLASH to acquire spectra from irregularly shaped ischemic stroke and normal tissue compartments from single-shot multichannel MRS data. The SPLASH method is more powerful than SLIM because it uses both amplitude and phase heterogeneity of multichannel coils for spatial localization and a large number (e.g., 32 or 64) of free induction decay (FID) signals can be acquired from individual coils in a single shot.

One limitation of SLIM, as well as SPLASH, is the approximation that each compartment is uniform. This assumption of uniform compartments is often invalid in practice due to spatially heterogeneous biological signals such as metabolite concentrations. This limitation can be overcome partially by using a relatively large number of phase encoding gradients⁶ or numerically optimized phase encoding gradients.⁷ However, adding more phase encoding gradients offsets SLIM's advantage of rapid compartment localization; strong encoding gradients can also significantly attenuate signal strength from all compartments.⁷ Several strategies have been proposed to incorporate intracompartment heterogeneity in SLIM reconstruction using multiple phase encoding steps.^{8–10}

In this work, we introduce Tikhonov regularization¹¹ to address the issue of intracompartment heterogeneity and demonstrate its effectiveness in SPLASH. This regularized SPLASH method allows rapid spatial localization of irregularly shaped anatomical compartments with heterogeneous biological signal distribution without using any phase encoding gradients. Our strategy is to (1) segment each compartment into multiple homogeneous subcompartments to allow concentration heterogeneity within the compartments of

interest; (2) reconstruct subcompartmental spectra by solving a generalized least square (GLS) problem with Tikhonov regularization; and (3) combine all subcompartmental spectra within each compartment to generate the desired compartmental spectrum. Because phase encoding steps can be dramatically reduced or totally eliminated, SPLASH generally has short scan time and high signal-to-noise ratio (SNR) efficiency. Short scan time reduces sensitivity to subject motions and thus makes it desirable to combine SPLASH with other magnetic resonance techniques such as diffusion tensor spectroscopy^{12,13} to extract other tissue parameters from irregularly shaped anatomical regions.

2. THEORY

2.A. Regularization of SPLASH reconstruction

Based on anatomical images, the MRS volume of interest (VOI) is segmented into J compartments. Our goal is to obtain the spectrum of each compartment, $C_j(\nu)$, for $j = 1, 2, \dots, J$. To allow intracompartment heterogeneity, the user-defined compartments are further partitioned into a total of N subcompartments and the spectrum of each subcompartment, $C_{s_n}(\nu)$, will be solved first.

In the frequency domain, spectrum $D_{m,h}(\nu)$ which is the Fourier transform of the FID received by the m th coil element at phase encoding step h can be expressed by⁵

$$D_{m,h}(\nu) = \sum_{n=1}^N \tilde{S}_{(m,h),n} C_{s_n}(\nu) + \tilde{\epsilon}_{m,h}(\nu) \quad (1)$$

$m = 1, 2, \dots, M, \text{ and } h = 1, 2, \dots, H,$

where M is the total number of coil elements and H the total number of phase encoding steps; $\tilde{\epsilon}_{m,h}(\nu)$ is the random noise in the m th channel at phase encoding step h ; and $\tilde{S}_{(m,h),n}$ is the integrated sensitivity defined by

$$\tilde{S}_{(m,h),n} = \int_{\text{subcompartment } n} S_m(\mathbf{r}) \exp(-i2\pi \mathbf{k}_h \cdot \mathbf{r}) d^3r, \quad (2)$$

with $s_m(\mathbf{r})$ being the sensitivity of the m th coil element at location $\mathbf{r}$ and $\mathbf{k}_h$ being the k -vector due to the h th phase encoding

gradient. For each frequency ν , Eq. (1) can be expressed in matrix form as

$$\mathbf{D} = \tilde{\mathbf{S}}\mathbf{C}_s + \tilde{\mathbf{\epsilon}}, \quad (3)$$

where $\mathbf{D}$ and $\tilde{\mathbf{\epsilon}}$ are MH -element column vectors; $\mathbf{C}_s$ is an N -element column vector; and $\tilde{\mathbf{S}}$ is an $MH \times N$ matrix. From the noise vector $\tilde{\mathbf{\epsilon}}$, one can directly compute the expanded noise covariance matrix $\tilde{\Psi}$ using $\tilde{\Psi} = E[\tilde{\mathbf{\epsilon}}\tilde{\mathbf{\epsilon}}^\dagger]$, where $E[\cdot]$ denotes the expectation value of a random variable and “ $\dagger$ ” denotes conjugate transpose. The GLS solution¹⁴ to Eq. (3) with Tikhonov regularization is given by

$$\mathbf{C}_s = (\tilde{\mathbf{S}}^\dagger \tilde{\Psi}^{-1} \tilde{\mathbf{S}} + \lambda \mathbf{G}^\dagger \mathbf{G})^{-1} \tilde{\mathbf{S}}^\dagger \tilde{\Psi}^{-1} \mathbf{D}. \quad (4)$$

The derivation of Eq. (4) is given in the Appendix. In Eq. (4), λ is the regularization parameter and $\mathbf{G}$ is an $N \times N$ matrix such that an element of vector $\mathbf{G}\mathbf{C}_s$ is the difference between the corresponding subcompartment and its neighboring subcompartments in the same compartment. The construction of matrix $\mathbf{G}$ is illustrated in Fig. 1. The regularization term enforces the spatial smoothness among neighboring subcompartmental spectra within the same compartment. Abrupt changes across compartments are not penalized. The value of the regularization parameter λ depends on the relative scaling of $\tilde{\mathbf{S}}^\dagger \tilde{\Psi}^{-1} \tilde{\mathbf{S}}$ and $\mathbf{G}^\dagger \mathbf{G}$. We computed a reference regularization parameter λ_0 to remove this dependence and expressed the regularization parameter λ as a ratio to λ_0 which is defined as

$$\lambda_0 = \text{eig}_{\max}(\tilde{\mathbf{S}}^\dagger \tilde{\Psi}^{-1} \tilde{\mathbf{S}}) / \text{eig}_{\max}(\mathbf{G}^\dagger \mathbf{G}), \quad (5)$$

where $\text{eig}_{\max}(\cdot)$ represents the maximum eigenvalue of a Hermitian matrix.

After the subcompartmental spectra are obtained, the spectrum of each compartment is computed as the weighted sum of all subcompartmental spectra in the compartment. A J -element vector $\mathbf{C}$, containing the spectra for all compartments, can be computed as

$$\mathbf{C} = \mathbf{W}\mathbf{C}_s. \quad (6)$$

FIG. 1. Construction of the regularization matrix for an illustrative two-compartment model consisting of six subcompartments.

Matrix $\mathbf{W}$ is a $J \times N$ matrix, defined as

$$W_{j,n} = \begin{cases} V_{s_n}/V_j & \text{if subcompartment } n \text{ is inside compartment } j \\ 0 & \text{otherwise} \end{cases}, \quad (7)$$

where V_{s_n} is the volume of subcompartment n and V_j is the volume of compartment j . Substituting Eq. (4) into Eq. (6) and introducing an unfolding matrix F , we have

$$\mathbf{C} = \mathbf{F}\mathbf{D}, \quad (8)$$

and $\mathbf{F}$ is given by

$$\mathbf{F} = \mathbf{W}(\tilde{\mathbf{S}}^\dagger \tilde{\mathbf{\Psi}}^{-1} \tilde{\mathbf{S}} + \lambda \mathbf{G}^\dagger \mathbf{G})^{-1} \tilde{\mathbf{S}}^\dagger \tilde{\mathbf{\Psi}}^{-1}. \quad (9)$$

The unfolding matrix F is independent of frequency ν and thus only needs to be computed once for all resonance frequencies.

2.B. Localization error and SNR efficiency

Spatial response functions (SRFs) have been used to evaluate the quality of spatial localization for spectroscopic imaging.^{5,7,15} The SRF of a compartment⁷ describes how each point in space contributes in magnitude and phase to the reconstructed compartmental spectrum. The SRF for the j th compartment is defined as

$$\text{SRF}_j(\mathbf{r}) = \sum_{m=1}^M \sum_{h=1}^H F_{j,(m,h)} s_m(\mathbf{r}) \exp(-i2\pi \mathbf{k}_h \cdot \mathbf{r}), \quad j = 1, 2, \dots, J. \quad (10)$$

The signal contribution of compartment j_1 to the spectrum of compartment j_2 is computed as the integral of $\text{SRF}_{j_2}(\mathbf{r})$ inside compartment j_1 . Because the regularization matrix G only operates on subcompartments within the same compartment, it can be verified that the integral of a SRF function has the following property:

$$\int_{\text{compartment } j_1} \text{SRF}_{j_2}(\mathbf{r}) d^3\mathbf{r} = \delta_{j_1, j_2}, \quad (11)$$

where δ denotes the Kronecker delta function. Since the ideal SRF of a compartment is the reciprocal of the compartment volume inside the compartment and zero outside the compartmental, the difference between the actual SRF and the ideal SRF for compartment j , $\Delta\text{SRF}_j(\mathbf{r})$, is given by

$$\Delta\text{SRF}_j(\mathbf{r}) = \begin{cases} \text{SRF}_j(\mathbf{r}) - 1.0/V_j & \text{for } \mathbf{r} \text{ inside compartment } j \\ \text{SRF}_j(\mathbf{r}) & \text{for } \mathbf{r} \text{ outside compartment } j \end{cases}. \quad (12)$$

Localization that heavily depends on ΔSRF signal cancellation in all compartments is unreliable because the uniform compartment assumption is often violated to some degree in reality. A more robust localization will be achieved if the spatially smoothed ΔSRF has a low intensity everywhere. A parameter of localization error for gauging the reliability of

localization is defined as

$$\text{loc_error}_j = \int_{\text{whole VOI}} |\text{Smooth}[\Delta\text{SRF}_j(\mathbf{r})]| d^3\mathbf{r}, \quad (13)$$

where the $\text{Smooth}[\cdot]$ function can be implemented using a 2D boxcar averaging filter. Because the spatial heterogeneity within each compartment is usually slow varying on the scale of typical chemical shift imaging (CSI) voxels, the low spatial frequency components of ΔSRF generally contribute most of the errors in compartmental spectra. This justifies our use of the smoothed ΔSRF to estimate localization error. A smaller localization error for a compartment will generally result in less reconstruction error in the compartmental spectra.

In order to evaluate SNR performance, a SNR efficiency parameter E for each compartment is defined as⁷

$$E_j = \text{SNR}_j^{\text{actual}} / \text{SNR}_j^{\text{ideal}}, \quad (14)$$

where $\text{SNR}_j^{\text{actual}}$ is the SNR of the j th compartment when the compartmental spectra are computed using the proposed method; $\text{SNR}_j^{\text{ideal}}$ is the best-possible SNR of the j th compartment, which is computed as if the j th compartment were isolated from the rest of the sample and its entire magnetization were detected by the multielement coil in H acquisitions without any phase encoding gradients. When computing SNR for a compartment, the signal can be represented by the integrated SRF within the compartment, which is 1 for both the actual and ideal cases. Therefore, SNR efficiency is inversely proportional to the noise ratio. The actual noise σ_j^{actual} is given by

$$\sigma_j^{\text{actual}} = \sqrt{(\mathbf{F}\tilde{\mathbf{\Psi}}\mathbf{F}^\dagger)_{j,j}}, \quad (15)$$

where $\mathbf{F}\tilde{\mathbf{\Psi}}\mathbf{F}^\dagger$ is the noise covariance matrix for the compartmental spectra. The ideal noise σ_j^{ideal} is given by⁵

$$\sigma_j^{\text{ideal}} = 1 / \sqrt{H(\mathbf{S}^\dagger \mathbf{\Psi}^{-1} \mathbf{S})_{j,j}}, \quad (16)$$

where $\mathbf{\Psi}$ is the noise covariance matrix of different channels and $\mathbf{S}$ is the integrated sensitivity matrix for the compartments defined as

$$S_{m,j} = \int_{\text{compartment } j} s_m(\mathbf{r}) d^3\mathbf{r}. \quad (17)$$

Substituting Eqs. (15) and (16) into Eq. (14), we have

$$E_j = 1 / \sqrt{(\mathbf{F}\tilde{\mathbf{\Psi}}\mathbf{F}^\dagger)_{j,j} H(\mathbf{S}^\dagger \mathbf{\Psi}^{-1} \mathbf{S})_{j,j}}. \quad (18)$$

Localization error and SNR efficiency are independent of metabolite concentration distributions as can be seen from Eqs. (13) and (18). Therefore, localization errors and efficiencies for all compartments can be computed for different λ values prior to reconstructing the compartmental spectra. The λ value used in Eq. (9) for reconstructing the compartmental spectra depends on the noise level in the data and is a trade-off between making the localization errors as small as possible and keeping the SNR efficiencies as high as possible. The optimal λ value can be determined by examining the localization errors versus λ and the SNR efficiencies versus λ curves.

3. MATERIALS AND METHODS

3.A. Monte Carlo simulations

Coil sensitivity maps and the noise covariance matrix obtained from *in vivo* study of a stroke patient were used in Monte Carlo simulations. A software program was developed to display anatomical images with the option of overlaying the MRS VOI box on them.⁵ The software also allowed the user to manually draw polylines to define compartment boundaries and to pick a few image pixels, one in each compartment, to be used as initial seed points for a region growing process. In the region growing process, each compartment was grown separately starting from one initial seed point and stopping at the boundaries defined by the VOI box and the user-drawn polylines. After this process, the VOI was segmented into a few compartments defined by the user-drawn boundaries. Figure 2(a) displays one slice of the diffusion weighted imaging (DWI) images, along with the MRS VOI (green box), user-drawn compartment boundaries (blue polyline), and two initial seed points for region growing (red dots).

Two compartments containing lactate (Lac), *N*-acetyl-aspartate (NAA), creatine (Cr), and choline (Cho) were simulated. The lactate level in compartment 2 was set to zero. In both compartments, all four metabolites had a T_2^* of 32 ms. To simulate the effects of intracompartment heterogeneity of metabolite distribution, several model functions describing slow intracompartment variations of metabolite concentrations were evaluated. In addition to intrinsic spatial variations of metabolite concentrations, contribution to the MRS spectrum measured by a certain coil element was modulated by the sensitivity heterogeneity of the coil element. By summing signal contributions from all four metabolites at all spatial points in the VOI, multichannel noise-free FID signals were generated. Next, correlated multichannel Gaussian noise was

generated based on the noise covariance matrix of the coil elements from the *in vivo* experiment and added to the noise-free FID signals generated from analytical models of intracompartment heterogeneity of metabolite distributions. The noise level was set to a value that made the SNRs of the Cr peaks in the reconstructed compartmental spectra comparable to those in the single-shot *in vivo* spectra using the same reconstruction method.

Compartmental spectra were reconstructed from the simulated multichannel FIDs using the previous unregularized and the current regularized SPLASH methods, respectively. For unregularized SPLASH, the simulated FIDs were Fourier transformed to frequency domain and two compartmental spectra were subsequently computed using Eqs. (8) and (9) with $\lambda = 0$ and $\mathbf{W}$ being a 2×2 identity matrix because no subcompartments were used. The compartmental spectra were normalized by the average Cr peak area in both compartments. The simulation was repeated 200 times with different noise realizations using the same noise covariance matrix. For each noise realization, the metabolites in each compartment were quantified by simultaneously fitting four Voigt-shaped curves¹⁶ to the compartmental spectrum. The relative error between the computed metabolite concentrations and the corresponding ground truth values was defined as the ratio of the sum of their absolute differences to the sum of ideal metabolite concentrations in both compartments. The mean relative error, computed from 200 noise realizations, was an indicator of the overall quality of the spectra. The relative error of the averaged compartmental spectra, averaged over 200 noise realizations, was also computed. The SRF maps, Δ SRF maps, localization errors, and SNR efficiencies for the two compartments were computed using Eqs. (10), (12), (13), and (18), respectively. When computing the localization errors using Eq. (13), the smoothing function was a 2.5×2.5 cm² boxcar filter and the same filter was used for computing all localization errors in this paper. The average values of the localization errors and SNR efficiencies over the two compartments were taken as the localization error and SNR efficiency for the reconstruction.

For regularized SPLASH, the user-defined compartments were further partitioned into smaller subcompartments using our in-house developed software. First, the user chose an $N_x \times N_y$ grid, and then the software automatically divided the whole VOI into $N_x \times N_y$ rectangular shaped voxels. The software directly assigned the voxels that were located entirely in a single compartment as subcompartments. Some voxels lied on the irregular compartment boundaries and thus were split into multiple fractions by the compartment boundaries. The software fused these subvoxels with a neighboring voxel or subvoxel in the same compartment. After the subcompartments were generated, localization error and SNR efficiency averaged over the two compartments were computed for different λ/λ_0 values. An optimal λ/λ_0 value was chosen by examining the localization error versus λ/λ_0 and SNR efficiency versus λ/λ_0 curves. The optimal λ/λ_0 value was used in Eq. (9) to compute compartmental spectra for 200 noise realizations. Thereafter, the mean relative error and the relative error for the averaged compartmental spectra were computed.

FIG. 2. Monte Carlo simulations of a two compartment model based on anatomical data collected from a stroke patient. (a) A DWI image of the patient, along with the VOI (green box), user-drawn compartment boundaries (blue polyline), and two initial seed points for region growing (red dots). Four metabolites—Lac, NAA, Cr, and Cho—were simulated. In addition to abrupt changes across the compartment boundary, the metabolite concentrations changed continuously along the x (patient's right to left) direction according to a sine-modulated model function described by $1.0 - 0.3\sin(\pi x/\text{VOI}_x)$. (b) Ground truth spectra of the two compartments. Peak areas represent mean metabolite concentrations within a compartment.

3.B. *In vivo* data analysis

In vivo study of a stroke patient was performed on a Philips 3 Tesla scanner (Achieva R2.6; Philips Healthcare, Best, The Netherlands) using a Philips eight-channel receive-only SENSE head coil.⁵ The parameters for the CSI scan were repetition time (TR) = 2 s, echo time (TE) = 144 ms, VOI = $11 \times 5 \times 1.4 \text{ cm}^3$, number of signal averages = 2, phase encoding matrix = 11×5 , number of time points = 1024, and full spectral width = 2000 Hz. The VOI had a thickness of 1.4 cm and enclosed exactly four DWI slices. The k-vectors for the 11×5 phase encoding steps were given by

$$\mathbf{k}_h = (h_x \Delta k_x, h_y \Delta k_y), \quad (19)$$

where $h_x = -5$ to 5 , $h_y = -2$ to 2 , $\Delta k_x = 1/11 \text{ cm}^{-1}$, and $\Delta k_y = 1/5 \text{ cm}^{-1}$. Similar to the previously described Monte Carlo simulations, the VOI was partitioned into two compartments and compartmental spectra were reconstructed using the unregularized and regularized SPLASH methods, respectively, from the *in vivo* data of the stroke patient with $h_x = h_y = 0$ (i.e., no phase encoded data were used for SPLASH reconstruction).

4. RESULTS

4.A. Monte Carlo simulations

To illustrate the effect of intrinsic intracompartiment heterogeneity, results from a model function generating continuous variation along the x (patient's right to left) direction according to $1.0 - 0.3\sin(\pi x/\text{VOI}_x)$ are described here. The average metabolite concentrations in each compartment were used to generate the ground truth spectra of the two compartments, which are plotted in Fig. 2(b). Spectra of the two compartments were first reconstructed from noise-free eight-channel single-shot data using the unregularized and regularized SPLASH methods to see how well the two methods can perform when there was no noise in the data. The two compartments generated by region growing are displayed and labeled in Fig. 4(a). For regularized SPLASH, an 11×5 grid was used to generate 54 subcompartments [Fig. 4(c), top]. Since there was no noise, a very small regularization parameter value of $\lambda = 10^{-4}\lambda_0$ was used in Eq. (4) to compute the subcompartmental spectra. Then, the compartmental spectra were computed according to Eq. (6). Figure 3(a) depicts the subcompartmental NAA concentrations in the middle row of the subcompartment map. For the purpose of comparison, the NAA concentrations in the two compartments computed using unregularized SPLASH are also plotted in Fig. 3(a). It can be seen that the NAA concentration values given by regularized SPLASH matched the ground truth values very well except some small errors for the third and fourth subcompartments in the plot, which were located at the boundary of the two compartments. The NAA concentration levels given by unregularized SPLASH had much larger errors. Figure 3(b) displays the compartmental spectra computed using unregularized SPLASH (left) and regularized SPLASH (right). It is clear that regularized SPLASH had much smaller errors

Fig. 3. Simulation results computed from noise-free eight-channel single-shot MRS data. (a) Subcompartmental NAA concentrations in the middle row of the subcompartment map computed using regularized SPLASH with 54 subcompartments. NAA concentrations in the two compartments computed using unregularized SPLASH are also plotted at the corresponding subcompartment indices of regularized SPLASH. (b) Compartmental spectra computed using unregularized SPLASH (left) and regularized SPLASH (right).

than unregularized SPLASH for all four metabolite peaks. Correspondingly, regularized SPLASH had a much smaller relative error (1.4%) than unregularized SPLASH (10%).

Next, unregularized SPLASH and regularized SPLASH were used to reconstruct compartmental spectra from FIDs that contain correlated multichannel noise. For regularized SPLASH, several different grid sizes for generating subcompartments were simulated and analyzed. Results for two grid sizes, 6×3 and 11×5 , are given here. A total of 18 subcompartments were generated using the 6×3 grid and 54 subcompartments were generated using the 11×5 grid. For each of the two sets of grid, localization error and SNR efficiency were computed for 21 different λ/λ_0 values, geometrically increasing from 0.01 to 1000 to determine the optimal λ/λ_0 .

Simulation results for unregularized SPLASH, regularized SPLASH with 18 subcompartments (6×3 grid), and regularized SPLASH with 54 subcompartments (11×5 grid) are given in Figs. 4(a)–4(c), respectively. For regularized SPLASH with 18 subcompartments, localization error vs λ/λ_0 curve [Fig. 4(b)] turned upward sharply when λ/λ_0

FIG. 4. Simulation results computed from eight-channel single-shot MRS data that contain correlated multichannel noise. (a) Unregularized SPLASH. From top to bottom: compartment maps (two different gray levels are used to differentiate the two compartments), SRF maps, smoothed SRF error maps, localization errors and SNR efficiencies for both compartments, overall localization error and SNR efficiency, compartmental spectra and corresponding error spectra reconstructed from a single noise realization, the mean relative error, averaged compartmental spectra and corresponding error spectra computed from 200 noise realizations, and the relative error of the averaged spectra. (b) Regularized SPLASH using 18 subcompartments. The subcompartment map is displayed on top, below which are the localization error vs regularization parameter and SNR efficiency vs regularization parameter curves. (c) Regularized SPLASH using 54 subcompartments.

was around 1.5. Therefore, $\lambda = 1.5\lambda_0$ was chosen since it minimized localization error while maintaining high SNR efficiency. Similarly, $\lambda = 20\lambda_0$ was chosen for regularized SPLASH with 54 subcompartments [Fig. 4(c)]. The SRF

maps, Δ SRF maps, localization errors, SNR efficiencies, and compartmental spectra given in Figs. 4(b) and 4(c) were all very similar, which indicates that regularized SPLASH is not sensitive to subcompartment size as long as they are small

enough with respect to coil sizes. The processing time for 54 subcompartments was less than 40 ms longer than that of 18 subcompartments on a laptop computer. The localization error was reduced from 0.87 for unregularized SPLASH to 0.53 for regularized SPLASH.

The compartmental spectra reconstructed from single noise realization for unregularized and regularized SPLASH (11×5 grid) are displayed in Figs. 4(a) and 4(c), respectively. The regularized SPLASH had a mean relative error of 6.7% which was about 40% smaller than the 11% mean relative error for unregularized SPLASH. The averaged compartmental spectra computed from 200 noise realizations are displayed at the bottom of Figs. 4(a) and 4(c), respectively. It is quite obvious that the averaged compartmental spectra for regularized SPLASH had significantly smaller errors than those of unregularized SPLASH. Correspondingly, the relative error of the averaged spectra for regularized SPLASH (4.1%) was about 60% smaller than that of the unregularized SPLASH (10%). Therefore, the accuracy of metabolite quantification for regularized SPLASH was significantly improved.

4.B. *In vivo* stroke study

The ground truth metabolite concentrations were estimated by the following procedure: (a) the compartments were segmented into 18 subcompartments using the 6×3 grid; (b) the corresponding subcompartmental spectra were reconstructed from the full CSI dataset (11×5 phase encodings with two averages) without regularization; and (c) the estimated ground truth ischemic stroke and normal tissue compartmental spectra were calculated by averaging all subcompartmental spectra in each compartment. The SRF and Δ SRF maps for the estimated ground truth spectra are displayed in Fig. 5(a). It can be seen that the SRF maps in Fig. 5(a) closely matched compartment boundaries. Localization error for the estimated ground truth spectra was 0.06. The small localization error justified the above procedure for estimating the ground truth compartmental spectra.

Compartmental spectra reconstructed using unregularized and regularized SPLASH from the dc-component of the k -space data (i.e., $h_x = h_y = 0$, no phase encoding gradients) are displayed in Figs. 5(b) and 5(c), respectively. For regularized SPLASH, the two compartments were segmented into 54 subcompartments using the 11×5 grid, similar to the Monte Carlo simulations. The compartmental spectra for regularized SPLASH [Fig. 5(c)] had significantly smaller differences from the ground truth spectra than those of unregularized SPLASH [Fig. 5(b)]. The relative error was reduced by 40% from 22% for unregularized SPLASH to 13% for regularized SPLASH.

5. DISCUSSION

Regularized SPLASH tackles the intracompartment heterogeneity problem by subdividing the compartments into smaller subcompartments and uses Tikhonov regularization to enforce intracompartment smoothness. A major benefit of this approach is that the inverse problem is still a linear problem.

FIG. 5. Compartmental spectra and other results computed using data from a stroke patient. The pulse sequence used TR = 2 s, TE = 144 ms, VOI = $11 \times 5 \times 1.4$ cm³, phase encoding matrix = 11×5 , number of signal averages = 2. (a) Estimated ground truth spectra and corresponding SRF maps, smoothed SRF error maps, localization errors, and SNR efficiencies. The reference spectra were computed without regularization using 18 subcompartments (6×3 grid) from the full CSI dataset (11×5 phase encodings with two averages). (b) Compartmental spectra computed using unregularized SPLASH from the dc-component of the k -space data (effective scan time = 4 s, no phase encoding gradients). (c) Compartmental spectra computed using regularized SPLASH with 54 subcompartments (11×5 grid) from the dc-component of the k -space data.

The compartmental spectra can be obtained by a generalized least square solution given in Eqs. (8) and (9). The unfolding matrix $\mathbf{F}$ is independent of frequency ν and thus only needs to be computed once for all resonance frequencies. Therefore, regularized SPLASH is computationally simpler than many other techniques such as compressed sensing. It only took 0.2 s on a laptop computer to reconstruct the *in vivo* compartmental spectra using regularized SPLASH.

The regularization matrix $\mathbf{G}$ only operates on neighboring subcompartments within the same compartment. Abrupt changes across different compartments are not penalized as desired. When the value of the regularization parameter λ becomes extremely large, the subcompartmental spectra within the same compartment are forced to be very similar. As a result, the compartmental spectra for the regularized SPLASH become very similar to those of unregularized SPLASH. In other words, regularized SPLASH falls back to unregularized SPLASH when λ becomes extremely large.

The localization error parameter used here is an extension of the localization criterion parameter proposed by von Kienlin and Meji,⁷ which is the integral of the absolute value of

the SRF outside a compartment. The localization criterion of von Kienlin and Meji indicates how much undesired phase-dispersed signal intensity in the outside regions contributes to the spectrum of a compartment. Therefore, the localization criterion measures intercompartment signal contamination. On the other hand, the localization error for a compartment defined in this work includes not only signal intensity outside the compartment but also signal deviation from the ideal uniform SRF inside the compartment because the latter will also cause metabolite quantification errors when the metabolite concentrations are not uniformly distributed inside the compartment.

Regularized SPLASH also makes it easier to define the compartments based on an anatomical image. When drawing the compartment boundaries, one does not need to be concerned about the relative sizes and geometrical relationships of the compartments from a technical perspective because the subcompartments generated by the software will have similar sizes and are spatially separated. As a result, the user acquires more freedom in defining the irregularly shaped anatomical compartments based on biological questions to be answered. For unregularized SPLASH (and SLIM), however, one needs to draw the compartments such that they have comparable sizes and one compartment should not be enclosed in another. Otherwise, the inverse problem of reconstruction might be ill-defined, leading to large reconstruction errors.

Instead of using L2 regularization, it is also possible to use compressed sensing algorithms (L1 regularization) to address the issue of intracompartment heterogeneity for SLIM and SPLASH reconstructions.¹⁷ L1 regularized problems are well-known to be computationally inefficient. In the case of SLIM or SPLASH reconstruction using L1 regularization, the L1 regularized least square problem needs to be solved point-by-point for all resonance frequencies. We have found that for the eight-channel compartment localization problem described here, L2 regularization provides conceptually simple and computationally efficient solutions. With the rapid commercialization of phased-array coils with a large number of coil elements accompanied by increased SNR, we expect that our demonstration of regularization for image-guided compartment localization will find more clinical applications because both reduced coil element size and increased number of coil elements are expected to increase the conditioning of Eq. (3). Furthermore, Fig. 3 demonstrates that regularized SPLASH will greatly benefit from increased SNR, which is expected from improved phased-array technology and higher magnetic field strength.

6. CONCLUSIONS

A regularized SPLASH method was proposed to allow reconstruction of compartmental spectra from irregularly shaped compartments with heterogeneous distribution of metabolite concentrations without using phase encoding gradients. Each compartment was subdivided into smaller subcompartments and their spectra were obtained by solving a gener-

alized least square problem with Tikhonov regularization. The spectrum of a given compartment was generated by combining the spectra of the components of that compartment. A localization error parameter was proposed to measure the quality of spatial localization. The optimal value for the regularization parameter was determined by examining the localization error and SNR efficiency as functions of the degree of regularization. Monte Carlo simulations demonstrated that regularized SPLASH significantly reduced localization errors and metabolite quantification errors. *In vivo* results from a stroke patient showed a 40% reduction of error in metabolite quantification. Although the proposed method was demonstrated using MRS, it serves as a general spatial localization method and can be used to rapidly measure other tissue properties from irregularly shaped compartments with heterogeneous signal distribution.

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APPENDIX: DERIVATION OF EQUATION (4)

In this appendix, we derive Eq. (4) from Eq. (3). The eigendecomposition of the expanded noise covariance matrix $\tilde{\Psi}$ can be expressed as $\tilde{\Psi} = \tilde{\mathbf{U}}\tilde{\Lambda}\tilde{\mathbf{U}}^\dagger$, where $\tilde{\mathbf{U}}$ is an $MH \times MH$ orthonormal matrix whose columns are the eigenvectors and $\tilde{\Lambda}$ is an $MH \times MH$ diagonal matrix whose entries are the eigenvalues. Matrix $\tilde{\Psi}$ and its eigendecomposition can be efficiently obtained as follows. $\tilde{\Psi}$ is given by $\tilde{\Psi} = \mathbf{I}_H \otimes \Psi$, where $\mathbf{I}_H$ is an $H \times H$ identity matrix, and “ $\otimes$ ” denotes Kronecker product; the $M \times M$ noise covariance matrix Ψ is computed by $\Psi = E[\epsilon\epsilon^\dagger]$, where the M -element column vector ϵ represents random noise in each channel. By eigendecomposition, Ψ is given by $\Psi = \mathbf{U}\Lambda\mathbf{U}^\dagger$. The eigenvectors and eigenvalues of $\tilde{\Psi}$ are simply given by $\tilde{\mathbf{U}} = \mathbf{I}_H \otimes \mathbf{U}$ and $\tilde{\Lambda} = \mathbf{I}_H \otimes \Lambda$.

After moving $\tilde{\mathbf{S}}\mathbf{C}\mathbf{s}$ to the left side of Eq. (3) and multiplying the noise whitening matrix $\tilde{\Lambda}^{-1/2}\tilde{\mathbf{U}}^\dagger$ to both sides of Eq. (3), we have

$$\tilde{\Lambda}^{-1/2}\tilde{\mathbf{U}}^\dagger(\mathbf{D} - \tilde{\mathbf{S}}\mathbf{C}\mathbf{s}) = \tilde{\Lambda}^{-1/2}\tilde{\mathbf{U}}^\dagger\tilde{\epsilon}. \quad (\text{A1})$$

The covariance matrix of the new noise vector $\tilde{\Lambda}^{-1/2}\tilde{\mathbf{U}}^\dagger\tilde{\epsilon}$ is an identity matrix. With enough data, $\mathbf{C}\mathbf{s}$ can be solved by minimizing the L2-norm of the left side of Eq. (A1),

$$\text{minimize } \|\tilde{\Lambda}^{-1/2}\tilde{\mathbf{U}}^\dagger(\mathbf{D} - \tilde{\mathbf{S}}\mathbf{C}\mathbf{s})\|_2^2, \quad (\text{A2})$$

which leads to the GLS solution¹⁴

$$\mathbf{C}\mathbf{s} = (\tilde{\mathbf{S}}^\dagger\tilde{\Psi}^{-1}\tilde{\mathbf{S}})\tilde{\mathbf{S}}^\dagger\tilde{\Psi}^{-1}\mathbf{D}. \quad (\text{A3})$$

However, the number of elements in $\mathbf{C}\mathbf{s}$ is often larger than the number of elements in $\mathbf{D}$. Therefore, we add a Tikhonov regularization term to Eq. (A2),

$$\text{minimize } \|\tilde{\mathbf{A}}^{-1/2}\tilde{\mathbf{U}}^\dagger(\mathbf{D}-\tilde{\mathbf{S}}\mathbf{C}\mathbf{s})\|_2^2 + \lambda\|\mathbf{G}\mathbf{C}\mathbf{s}\|_2^2. \quad (\text{A4})$$

Let $\partial/\partial\mathbf{C}\mathbf{s}^\dagger[\|\tilde{\mathbf{A}}^{-1/2}\tilde{\mathbf{U}}^\dagger(\mathbf{D}-\tilde{\mathbf{S}}\mathbf{C}\mathbf{s})\|_2^2 + \lambda\|\mathbf{G}\mathbf{C}\mathbf{s}\|_2^2] = 0$ and we can readily obtain the following solution:

$$\mathbf{C}\mathbf{s} = (\tilde{\mathbf{S}}^\dagger\tilde{\mathbf{\Psi}}^{-1}\tilde{\mathbf{S}} + \lambda\mathbf{G}^\dagger\mathbf{G})^{-1}\tilde{\mathbf{S}}^\dagger\tilde{\mathbf{\Psi}}^{-1}\mathbf{D}. \quad (\text{A5})$$

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