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Magnetic resonance Spectroscopy with Linear Algebraic Modeling (SLAM) for higher speed and sensitivity

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Abstract

Speed and signal-to-noise ratio (SNR) are critical for localized magnetic resonance spectroscopy (MRS) of low-concentration metabolites. Matching voxels to anatomical compartments *a priori* yields better SNR than the spectra created by summing signals from constituent chemical-shift-imaging (CSI) voxels post-acquisition. Here, a new method of localized Spectroscopy using Linear Algebraic Modeling (SLAM) is presented, that can realize this additional SNR gain. Unlike prior methods, SLAM generates spectra from *C* signal-generating anatomic compartments utilizing a CSI sequence wherein essentially only the *C* central *k*-space phase-encoding gradient steps with highest SNR are retained. After MRI-based compartment segmentation, the spectra are reconstructed by solving a sub-set of linear simultaneous equations from the standard CSI algorithm. SLAM is demonstrated with one-dimensional CSI surface coil phosphorus MRS in phantoms, the human leg and the heart on a 3T clinical scanner. Its SNR performance, accuracy, sensitivity to registration errors and inhomogeneity, are evaluated. Compared to one-dimensional CSI, SLAM yielded quantitatively the same results 4-times faster in 24 cardiac patients and healthy subjects. SLAM is further extended with fractional phase-encoding gradients that optimize SNR and/or minimize both inter- and intra-compartmental contamination. In proactive cardiac phosphorus MRS of 6 healthy subjects, both SLAM and fractional-SLAM (fSLAM) produced results indistinguishable from CSI while preserving SNR gains of 36–45% in the same scan-time. Both SLAM and fSLAM are simple to implement and reduce the minimum scan-time for CSI, which otherwise limits the translation of higher SNR achievable at higher field strengths to faster scanning.

Keywords

spectral localization; chemical shift imaging (CSI); cardiac; constrained reconstruction; phosphorus; metabolism; heart

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1. Introduction

Scan-time and signal-to-noise ratio (SNR) are major problems for *in vivo* spatially localized magnetic resonance spectroscopy (MRS) of low-concentration metabolites. Because SNR is proportional to voxel size, matching the voxel to the desired anatomical compartment *a priori* yields the best SNR for a fixed scan time [1]. Consider for example a first chemical shift imaging (CSI) experiment [2] encoding a voxel V with an SNR of 20 per acquisition. Averaging $n=4$ acquisitions yields an SNR of 40 since SNR adds as $\sqrt{n}$. Now consider a second experiment performed at four times the resolution with $V/4$ -sized voxels. The SNR/voxel is now 5 per acquisition because noise is independent of voxel size [1]. Phase-encoding is equivalent to averaging, so after 4 gradient steps to encode the same volume, the SNR per voxel is 10. Adding the 4 signals to make a V -sized voxel now yields an SNR of 20, again because of the $\sqrt{n}$ rule. This compares to 40 from the first experiment. Thus, the SNR for the same scan-time and voxel size is doubled in the first experiment, just by pre-selecting the correct voxel size to start with [1].

The same principle applies in general wherever the CSI voxel size is smaller than the object of interest. The SNR gain factor for a fixed scan-time obtained by correctly encoding a compartment at the outset, as compared to adding signals from individual CSI voxels to form the equivalent-sized compartment post-acquisition, is:

$$g = \sqrt{\frac{\text{compartment size}}{\text{CSI voxel size}}}, \quad (1)$$

not with standing the effects of nonuniform sensitivity and concentration distributions, or differences in the integrated spatial response function (SRF). This differential g -fold SNR gain vs. CSI can be seen as arising from the time spent by CSI in acquiring the low SNR, high gradient-strength, high k -space signals that are unnecessary for resolving the larger compartment.

Prior phase-encoding gradient based MRS localization methods such as SLIM [3], GSLIM [4] and SLOOP [5], could realize the g -fold SNR gain if the desired compartments were prescribed from scout MRI prior to acquisition, and if an appropriately SNR-optimized gradient set were then applied. In SLIM, the compartment's signal is modeled as the integral of phase-encoded signal contributions in each compartment, assumed homogeneous. The approach is prone to *inter*-compartmental [6] and *intra*-compartmental errors when metabolite distributions are non-uniform within each compartment, and as the number of phase-encoding gradient steps are reduced. GSLIM [4] and SLOOP [5] were introduced to minimize the *inter*-compartmental errors. GSLIM does this by applying non-Fourier generalized series modeling to the SLIM result [4, 6]. SLOOP minimizes the *inter*-compartmental error by optimizing the SRF for the desired compartment, ideally by specifically tailoring the phase-encoding gradient set for the acquisition [5]. Several other proposed improvements add constraints to deal with inhomogeneity in the main (B_0) field [7–9], registration errors [9], and multi-element receivers [10].

Even though all of these techniques can generate spectra from multiple compartments from the same data set, they are seldom used pro-actively for human MRS. Thus, SLIM was applied retroactively to ^1H CSI data sets acquired from the human calf [3, 11] and brain [9], and both GSLIM and SLIM were used in ^1H MRS CSI acquisitions from a gerbil brain [12]. Although SLOOP ^1H MRS was initially performed with proactively optimized gradients on an excised rabbit kidney [5], all subsequent applications to human heart applied SLOOP retroactively to phosphorus (^{31}P) MRS data acquired with regular CSI gradients [13–16]. Because all of these human applications employed conventional CSI gradient sets and

uniform k -space sampling, a g -fold SNR advantage versus CSI, beyond that obtained by simply summing the signals from the constituent CSI voxels or accounting for differences in the integrated SRF, was not realized or reported. The lack of pro-active implementation and absence of a demonstrated SNR advantage have likely contributed to the failure of these methods to supplant routine CSI. In any case, the prescribing of compartments and tailoring of gradient encoding steps to match the desired compartment and achieve the full SNR gain predicted by Eq. (1) has, to the best of our knowledge, never been realized *in vivo* or in humans.

Here we apply a sharply-reduced SNR-optimized gradient set to perform localized Spectroscopy with Linear Algebraic Modeling (SLAM) to acquire and reconstruct average spectra from C signal-generating anatomical compartments that are identified by scout MRI routinely acquired for spatially-localized MRS. Spectral reconstruction for this new SLAM method differs from SLIM, GSLIM and SLOOP in that it solves, by matrix analysis, a set of linear simultaneous equations essentially equal to C (provided that all signal-generating tissues are included) by eliminating un-needed phase-encoding steps from the standard CSI algorithm. The SLAM pulse sequence differs in that the number of phase-encoding steps is also $\sim C$, and they are always selected from the center of the integer-stepped k -space of CSI where SNR is highest. Other than determining the number, C , the need for image-guided gradient optimization, prescription and implementation at the scanner-side prior to acquisition, is avoided. Using SLAM, g -fold SNR gains of 30–200% are demonstrated in 3T ^{31}P studies of the human leg and heart *in vivo*, compared to conventional [17–22] one-dimensional (1D) CSI spectra from the same net volume and scan-time. Moreover, we show that application of SLAM to raw ^{31}P 1D CSI data acquired from heart patients and scout MRI-based segmentation yields, after discarding 75% of the data, essentially the same *quantitative* measures of adenosine triphosphate (ATP) and phosphocreatine (PCr), four-times faster.

Finally, we extend the SLAM approach to allow for fractional gradient increments instead of conventional, integer-stepped, CSI gradients. In this “fSLAM” method, the phase-encoding gradients are pro-actively optimized at the scanner-side to maximize SNR and/or minimize *both* the inter-compartmental leakage as well as the intra-compartmental errors produced by nonuniform signal distributions. Intra-compartmental errors have not been addressed in prior methods [3–5]. fSLAM is demonstrated in pro-active human cardiac ^{31}P studies.

2. Theory

Consider the basic equation for 1D CSI:

$$s(k, t) = \iint \rho(x, f) e^{-i2\pi(kx + ft)} df dx \quad (2)$$

where k is the spatial frequency, $s(k, t)$ is the acquired time-domain signal and $\rho(x, f)$ is the spectrum to reconstruct. Since localization is in the spatial domain which is independent of the chemical shift domain, we denote the spectrum at spatial position x after $s(k, t)$ is Fourier transformed (FT), as $\rho(x)$ in the spectral frequency domain. Assuming there are M phase encoding steps, $k_1 \dots k_M$, Eq. (2) is discretized as:

$$\begin{bmatrix} s(k_1) \\ s(k_2) \\ \vdots \\ s(k_M) \end{bmatrix}_{M \times N} = \begin{bmatrix} e^{-i2\pi k_1 x_1/M} & e^{-i2\pi k_1 x_2/M} & \dots & e^{-i2\pi k_1 x_M/M} \\ e^{-i2\pi k_2 x_1/M} & e^{-i2\pi k_2 x_2/M} & \dots & e^{-i2\pi k_2 x_M/M} \\ \vdots & \vdots & \ddots & \vdots \\ e^{-i2\pi k_M x_1/M} & e^{-i2\pi k_M x_2/M} & \dots & e^{-i2\pi k_M x_M/M} \end{bmatrix}_{M \times M} \times \begin{bmatrix} \rho(x_1) \\ \rho(x_2) \\ \vdots \\ \rho(x_M) \end{bmatrix}_{M \times N} \quad (3)$$

Each row of the known signal matrix, $\mathbf{S}_{M \times N}$, on the left side of the equation is an N -point array, where N is the number of time-domain data points. The first matrix on the right side is the phase-encoding FT operator ($\mathbf{PE}$), and each term of the unknown spectral matrix, $\mathbf{p}$, is also an N -point array. For simplicity, we write Eq. (3) as: $\mathbf{S}_{M \times N} = \mathbf{PE}_{M \times M} \times \mathbf{p}_{M \times N}$.

2.1 Localized spectroscopy using a linear algebraic model (SLAM)

The goal of the CSI experiment is to reconstruct the M unknown spectra in matrix $\mathbf{p}$ of Eq. (3), from the M known signals ($\mathbf{S}$) acquired with M different phase-encodes. However, from scout MRI we learn that $\mathbf{p}$ has just $C \ll M$ MRS compartments of interest, as well as the spatial position of each compartment. Theoretically, only C measurements with C phase-encoding steps are needed to unambiguously solve $\mathbf{p}$ and reconstruct the C spectra.

To illustrate, consider a 4-voxel 1D CSI experiment. Denoting the exponential terms by $e_{i,j}$, Eq. (3) becomes:

$$\begin{bmatrix} e_{11} & e_{12} & e_{13} & e_{14} \\ e_{21} & e_{22} & e_{23} & e_{24} \\ e_{31} & e_{32} & e_{33} & e_{34} \\ e_{41} & e_{42} & e_{43} & e_{44} \end{bmatrix} \times \begin{bmatrix} \rho_1 \\ \rho_2 \\ \rho_3 \\ \rho_4 \end{bmatrix} = \begin{bmatrix} s_1 \\ s_2 \\ s_3 \\ s_4 \end{bmatrix}. \quad (4)$$

Now suppose that from prior information, the second and third rows of $\mathbf{p}$ are the same ($\rho_2 = \rho_3$). Then we need only solve:

$$\begin{bmatrix} e_{11} & e_{12}+e_{13} & e_{14} \\ e_{21} & e_{22}+e_{23} & e_{24} \\ e_{31} & e_{32}+e_{33} & e_{34} \\ e_{41} & e_{42}+e_{43} & e_{44} \end{bmatrix} \times \begin{bmatrix} \rho_1 \\ \rho_2 \\ \rho_4 \end{bmatrix} = \begin{bmatrix} s_1 \\ s_2 \\ s_3 \\ s_4 \end{bmatrix} \quad (5)$$

Eq. (5) is now over-determined and the minimum number of phase-encoding steps required can be reduced from 4 to 3.

The same theory shows that we can reconstruct C spectra from C homogeneous compartments, with only C phase-encoding steps instead of M steps, regardless of k-space truncation. In general, prior information is incorporated via a $\mathbf{b}$ -matrix which zeros out identical rows in the $\mathbf{p}$ -matrix to retain only one spectrum for each compartment:

$$\mathbf{S}_{M \times N} = \mathbf{PE}_{M \times M} \times \mathbf{b}_{M \times M}^{-1} \times \mathbf{b}_{M \times M} \times \mathbf{p}_{M \times N} \quad (6)$$

where $\mathbf{PE}$ is the phase-encoding operator from Eq. (3). For SLAM based on the 1D CSI experiment, the $\mathbf{b}$ -matrix is an identity matrix with “-1” elements inserted to zero out identical rows in $\mathbf{p}$. For example, for an 8-voxel CSI experiment performed on a two-compartment sample in which the first compartment extends from voxels 1–3 and the second extends from voxels 4–8,

$$\mathbf{b} = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ -1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & -1 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & -1 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & -1 & 0 & 0 & 0 & 1 \end{bmatrix}. \quad (7)$$

Here, only the spectra in the compartments in voxels 1 and 4 are kept after dimensional reduction.

If we choose $M' < C$ pre-defined phase-encoding steps, and eliminate identical rows to reduce the dimension of $\mathbf{b}_{M \times M} \times \rho_{M \times N}$ from M to C , Eq. (6) shrinks to,

$$\mathbf{S}_{M' \times N} = \mathbf{PE}_{M' \times C}^r \times \rho_{C \times N}^r \quad (8)$$

where $\rho_{C \times N}^r$ is a submatrix of $\mathbf{b}_{M \times M} \times \rho_{M \times N}$ retaining the C non-eliminated rows; $\mathbf{PE}_{M' \times C}^r$ is a submatrix of $\mathbf{PE}_{M \times M} \times \mathbf{b}_{M \times M}^{-1}$ that retains the C columns corresponding to the C non-eliminated rows; and $\mathbf{S}_{M' \times N}$ is a submatrix of $\mathbf{S}_{M \times N}$ acquired from the sample using a subset of $M' \ll M$ phase-encoding steps. Solution of Eq. (8) results in a set of spectra, each of which closely approximates the average spectrum of each 1D CSI compartment.

2.2 The SLAM recipe

In summary, the SLAM experiment is performed with Steps 1–5 as follows:

1. Acquire an MRI to extract the prior knowledge of the number of compartments ($C \ll M$), and the spatial position of each compartment for SLAM reconstruction.
2. Choose $M' < C$ phase-encoding steps. Theoretically, these can be chosen arbitrarily, but different choices will lead to different SNR and different condition numbers for the matrix $\mathbf{PE}_{M' \times C}^r$ which affect computational accuracy [23]. Of the M original CSI phase-encoding steps, selecting the M' steps that are closest to the center of k -space generally yields the best SNR. Because the set of CSI steps are discrete, fixed and finite, choosing only those from central k -space results in a SLAM phase-encoding gradient set that is determined only by the number M' or C . Moreover, because C is typically the same for a given study protocol (eg, $C=2$ to 4 in the present cardiac studies with chest muscle, heart, and/or adipose and ventricular blood compartments), the same SLAM gradient set can be used for all the studies, eliminating the need for scanner-side gradient optimization or image-based gradient prescription.
3. Apply the chosen M' encoding gradients and acquire the M' signals.
4. Determine the $\mathbf{b}$ matrix from the spatial position of each compartment identified by MRI.
5. Reduce the dimensions from M to C and compute the C spectra in the ρ^r matrix using:

$$\rho_{C \times N}^r = \mathbf{PE}_{C \times M'}^+ \times \mathbf{S}_{M' \times N} \quad (9)$$

where $\mathbf{PE}_{C \times M'}^+$ is the inverse ($M'=C$) or pseudo-inverse ($M'>C$) of $\mathbf{PE}_{M' \times C}^r$.

A flow diagram of the reconstruction algorithm appears in Fig. 1.

2.3 SLAM with fractional gradients (fSLAM)

Choice of the M' phase-encoding steps need not be limited to the original basis set of M CSI steps corresponding to integer k 's in Eq. (3). The M' phase-encoding gradients can be chosen to optimize desired properties of the reconstruction. For example as we now show, the gradients can be optimized to maximize the SNR, and/or minimize the inter-compartmental signal contamination, and/or minimize the intra-compartmental error due to nonuniform signal sources. This effectively involves allowing for fractional k 's in the CSI Eq. (3), with all other experimental parameters left unchanged. Unlike SLAM, this fractional SLAM method, denoted fSLAM, does require scanner-side gradient optimization and prescription.

2.4 fSLAM with maximum SNR

To maximize the SNR, Eq. (9) is modified to include noise terms $\mathbf{e}_{M' \times N}$ in the time-domain signal:

$$\rho_{C \times N}^r + \xi_{C \times N} = \mathbf{PE}_{C \times M'}^+ \times (\mathbf{S}_{M' \times N} + \mathbf{e}_{M' \times N}), \quad (10)$$

where $\xi_{C \times N}$ is the noise in the reconstructed spectra. The noise in the time-domain signal and the noise in the spectra are related via the linear transformation, $\xi_{C \times N} = \mathbf{PE}_{C \times M'}^+ \times \mathbf{e}_{M' \times N}$. Assuming the standard deviation (SD), σ , of $\mathbf{e}_{M' \times N}$ is constant, the SNR of the spectrum reconstructed from the i^{th} compartment is:

$$SNR_i = \frac{\rho_{C \times N}^r(i)}{\left(\sum_{m=1}^{M'} \left[|\mathbf{PE}_{C \times M'}^+(i, m)|^2 \times \sigma^2 \right] \right)^{1/2}} \quad (11)$$

where $\mathbf{PE}_{C \times M'}^+(i, m)$ is the element corresponding to the m^{th} signal. To maximize the SNR of the i^{th} spectrum in Eq. (11), we numerically minimize the cost-function

$$\Gamma_i = \sum_{m=1}^{M'} \left[|\mathbf{PE}_{C \times M'}^+(i, m)|^2 \right] / I_{cond} \quad (12)$$

where I_{cond} is '1' when the condition number [23] of $\mathbf{PE}_{C \times M'}^+$ is less than a user-predefined threshold, u , and '0' otherwise. This logic function ensures the equation system is well-conditioned. Minimization of Γ_i yields the best SNR of the i^{th} spectrum for the fSLAM experiment, or indeed the SLAM experiment when the gradients in $\mathbf{PE}_{C \times M'}^+$ are limited to integer steps.

For comparison, the SNR of the CSI experiment is given by:

$$SNR_i^{CSI} = (L_i/M)^{1/2} \cdot \rho_{C \times N}^{CSI}(i)/\sigma \quad (13)$$

where L_i is the size of the i^{th} compartment with average spectrum $\rho_{C \times N}^{CSI}(i)$. Note that the quotient of Eqs. (11) and (13) approximates Eq. (1) for SLAM and fSLAM when multiplied by $\sqrt{M/M'}$ to account for scan-time differences.

2.5 fSLAM with minimum inter-compartmental leakage

So far we have assumed that every compartment is homogeneous. However, spectra in the CSI basis set that deviate from the compartmental averages can generate signals that

propagate between and within each compartment following reconstruction. To optimize the fSLAM experiment with M' phase-encoding steps to suppress leakage, Eq. (6) is reformulated to separate the original $\mathbf{p}$ matrix into an average and an inhomogeneous part:

$$\mathbf{S}_{M' \times N} = \mathbf{PE}_{M' \times M} \times \mathbf{b}_{M \times M}^{-1} \times \mathbf{b}_{M \times M} \times (\rho_{M \times N}^{\text{avg}} + \rho_{M \times N}^{\text{inhom}}) = \mathbf{PE}_{M' \times M} \times \mathbf{b}_{M \times M}^{-1} \times \mathbf{b}_{M \times M} \times \rho_{M \times N}^{\text{avg}} + \mathbf{PE}_{M' \times M} \times \rho_{M \times N}^{\text{inhom}}.$$

where each row in $\rho_{M \times N}^{\text{avg}}$ is an average spectrum of its compartment and each row in $\rho_{M \times N}^{\text{inhom}}$ is the deviation of the true spectrum from its compartmental average. For example, assume we have a 3-voxel compartment with single-point spectra with magnitudes [1.1, 1.0, 0.9]. The average spectrum in this compartment will be '1' and the inhomogeneity will be [0.1, 0, -0.1]. Note that by definition the inhomogeneity terms for the same compartment sum to zero.

On the right side of Eq. (14), the first part ($\mathbf{PE}_{M' \times M} \times \mathbf{b}_{M \times M}^{-1} \times \mathbf{b}_{M \times M} \times \rho_{M \times N}^{\text{avg}}$) satisfies the ideal homogeneity assumption of SLAM, and the second part ($\mathbf{PE}_{M' \times M} \times \rho_{M \times N}^{\text{inhom}}$) is the source of signal leakage and errors. The solution to Eq. (14) after dimensional reduction is:

$$\mathbf{PE}_{C \times M'}^+ \times \mathbf{S}_{M' \times N} = \rho_{C \times N}^{\text{avg}} + \mathbf{PE}_{C \times M'}^+ \times \mathbf{PE}_{M' \times M} \times \rho_{M \times N}^{\text{inhom}} \quad (15)$$

Clearly, we need to minimize ($\mathbf{PE}_{C \times M'}^+ \times \mathbf{PE}_{M' \times M} \times \rho_{M \times N}^{\text{inhom}}$) to suppress leakage. In the absence of control over $\rho_{M \times N}^{\text{inhom}}$, a reasonable strategy is to minimize the coefficients in $\mathbf{PE}_{C \times M'}^l = \mathbf{PE}_{C \times M'}^+ \times \mathbf{PE}_{M' \times M}$. Because the inhomogeneity terms in the same compartment sum to zero, the mean of the coefficients can be subtracted. In the example above, if the three coefficients corresponding to inhomogeneity [0.1, 0, -0.1] are [1/2, 1/3, 1/6], they will generate the same errors as coefficients [1/6, 0, -1/6] after subtracting the mean value of 1/3. This coefficient set has a smaller sum-of-the-squares and is not affected by differences in the mean coefficient of each compartment.

Let $\mathbf{PE}_{C \times M}^{ll}(i)$ denote the new matrix of coefficients that results from subtracting the mean from $\mathbf{PE}_{C \times M}^l(i)$, for each compartment. Then, to minimize the inter-compartmental leakage into the i^{th} compartment, we minimize the sum-of-the-squares of the coefficients in $\mathbf{PE}_{C \times M}^{ll}(i)$ that derive from outside of the i^{th} compartment, analogous to SLOOP [5]:

$$\phi_i = \sum_{j \neq i}^C \sum_{m \in \text{compartment } j}^M w_{ij} \times |\mathbf{PE}_{C \times M}^{ll}(i, m)|^2 \quad (16)$$

Here, w_{ij} is the weight of inter-compartment leakage from the j^{th} compartment into the i^{th} compartment. The w_{ij} can reflect, for example, intrinsic differences in metabolite concentrations between compartments.

2.6 Minimizing intra-compartmental errors in fSLAM

To minimize the errors due to inhomogeneity within the i^{th} compartment in the fSLAM experiment, we minimize the sum-of-the-squares of the coefficients that originate from inside of the i^{th} compartment itself:

$$\varphi_i = \sum_{m \in \text{compartment } i}^M w_{ii} \times |\mathbf{PE}_{C \times M}^{ll}(i, m)|^2 \quad (17)$$

where w_{ii} is the weight of intra-compartment error in the i^{th} compartment.

To perform a numerical optimization that minimizes both the inter- and intra-compartmental errors, in practice we minimize the cost-function:

$$\Lambda_i = (\phi_i + \varphi_i) / I_{cond} \quad (18)$$

for the i^{th} compartment.

2.7 Summary of the fSLAM experiment

In summary, the fSLAM experiment is performed using the same Steps 1–5 as the SLAM protocol (Fig. 1) except that the phase-encoding gradients in Step 2 are obtained by minimizing either the SNR cost-function in Eq. (12) or the error cost-function in Eq. (18). In general, the different optimizations will result in different sets of phase-encoding gradients. If a gradient set optimized for both SNR and minimum error is being sought, minimization of the sum of the cost-functions in Eqs. (12) and (18) cannot be used because their scales differ. Instead, minimization of a weighted sum of the ratio of cost functions for fSLAM to those for SLAM can suffice. The choice of the weighting will depend on the application and error tolerance. The phase-encoding gradients in Step 2 are typically fractional.

Because $\mathbf{PE}_{\text{CXM}}^H(i)$ is derived from $\mathbf{b}$ and therefore requires knowledge of compartment location and size, and the choice of gradients is not constrained to the CSI integer gradient steps, optimization and selection of the fSLAM gradient set must be performed scanner-side as part of the MRS set-up in order to achieve any SNR advantage compared to the summed CSI spectra from the same compartment volume.

2.8 Spatial response function

In accordance with Eqs. (9) and (12) of references [13] and [24] respectively, we define a spatial response function for the heart compartment corresponding to the row $\mathbf{PE}_{\text{CXM}}^+(h)$ as:

$$SRF_h(x) = \sum_k \mathbf{PE}_{\text{CXM}}^+(h) \cdot \exp(-i2\pi kx). \quad (19)$$

The heart compartment spectrum is

$$\rho_h = \int_{FOV} SRF_h(x) \cdot f(x) dx, \quad (20)$$

where $f(x)$ is the true continuous signal. $f(x)$ can be decomposed into signals from heart, $f_h(x)$, chest, $f_c(x)$, and “other”, $f_r(x)$:

$$\rho_h = \int_{\text{heart}} SRF_h(x) \cdot f_h(x) dx + \int_{\text{chest}} SRF_h(x) \cdot f_c(x) dx + \int_{\text{other}} SRF_h(x) \cdot f_r(x) dx. \quad (21)$$

The second integral in Eq. (21) is the chest-to-heart leakage, $L_{c \rightarrow h}$.

We express $f_c(x)$ as a mean $\overline{f_c}$ plus an inhomogeneity $\Delta f_c(x)$. Then:

$$\begin{aligned}
L_{c \rightarrow h} &= \int_{chest} SRF_h(x) \cdot [\bar{f}_c + \Delta f_c(x)] dx \\
&= \bar{f}_c \cdot \int_{chest} SRF_h(x) dx \\
&\quad + \int_{chest} SRF_h(x) \cdot \Delta f_c(x) dx \leq \bar{f}_c \cdot \int_{chest} SRF_h(x) dx \\
&\quad + \int_{chest} |SRF_h(x)| \cdot |\Delta f_c(x)| dx \leq \bar{f}_c \cdot \int_{chest} SRF_h(x) dx \\
&\quad + \max(|\Delta f_c(x)|) \int_{chest} |SRF_h(x)| dx
\end{aligned} \tag{22}$$

The right hand side of the last line of Eq. (22) is the upper limit of the contamination of the heart spectrum from chest signal. The upper limit of leakage from the other compartments, $L_{r \rightarrow h}$, can be computed similarly.

3. Methods

3.1 Computer simulations

Computer simulations were performed to investigate the accuracy of SLAM applied to human cardiac ^{31}P MRS, where 1D CSI has served as a work-horse in our laboratory [17–21]. Three compartments were assumed: the heart, chest skeletal muscle, and ‘other’. In practice, the ‘other’ compartment is needed because any signal generated outside of the designated compartments that is not assigned a compartment, will end up in the chest and heart, introducing errors depending on its magnitude. The chest and heart spectra are shown in Fig. 2(a, c). Signals are generated from these spectra with predefined compartment distributions using a 16-voxel 1-cm resolution 1D CSI model.

Monte Carlo simulations were done to quantify errors in SLAM arising from imperfections in the homogeneity assumption for this model. Based on experience [17–20], we assumed a metabolite-bearing chest muscle thickness of 2–3 voxels, a heart muscle thickness of 2–6 voxels, and zero or a single voxel separation between the chest and heart compartments, and zero signal in the ‘other’ compartment. This yielded 20 possible anatomical combinations. To accommodate the combined effect of differences in concentration and surface coil sensitivity, two scenarios were investigated. In the first, we assumed a constant chest to heart signal ratio of 4. In the second, we assumed a chest PCr concentration 2.5 times higher than heart [21], and scaled the result by the experimental surface coil spatial sensitivity profile as shown in Fig. 3(a). A random inhomogeneity of $\pm 15\%$ (30% total) in the resultant signal was then simulated for both scenarios. The mean signal was determined for each compartment by adding signals from the corresponding voxels of the full CSI set to serve as a reference. Then, white noise was added such that the SNR in the heart compartment was 20. The FT of the data set was used to generate a set of time-domain CSI acquisitions from which $M' = 4$ central k-space acquisitions were selected. SLAM reconstruction from these 4 phase-encoding steps was implemented, and the percentage error relative to the reference CSI value was calculated. The mean error and the SD of the error were determined after 1000 Monte Carlo simulation runs.

Monte Carlo simulations were also performed to compare the sensitivity of SLAM with SLIM [3], with respect to registration errors. A 1D cardiac ^{31}P model with chest from –60mm to –30mm, heart from –30mm to 10mm, and a chest-to-heart signal ratio of 4 was assumed as in scenario-1, above (Fig. 3a). A random segmentation error between –2 mm and +2 mm was introduced at the edges of either compartment: (i) with the chest and heart stationary (no partial volume error); and (ii) with the chest and heart also moved by $\pm 2\text{mm}$

(partial volume error). The chest was constrained never to overlap the heart. Both SLAM and SLIM were simulated with four CSI phase-encodes from central k-space. SLIM reconstruction was performed as prescribed [3], by integrating the phase-encoding coefficients over the 3-compartment model of heart, chest and 'other' and generating a 4×3 'G'-matrix [3]. The mean ($\pm$ SD) % error between the reconstructed signal and the true or the CSI result was calculated for 1000 runs.

The SNR and the root-of-the-sum-of-the-squares of the inter- and intra-compartment errors, $\sqrt{\phi_i + \varphi_i}$, were computed for the model heart, assuming 3- and 4-voxel cardiac compartments and a 2-voxel chest compartment for both SLAM and fSLAM, and that both techniques yield the same compartmental average. The SNR was measured relative to the compartment average SNR of the 16-voxel 1D CSI (Eq. (13)), using the $M' = 3$ to 16 central k-space acquisitions for SLAM, and fractional (low k-space) phase-encodes for fSLAM. fSLAM optimization was performed using the simplex method implemented via the Matlab "*fminsearch*" routine (The MathWorks, Natick, MA) on a lap-top computer with $u = 50$ in Eqs. (12) and (18), and with all the leakage weighting factors, w_{ij} set to '1' in Eqs. (16) and (17).

SRF_h was calculated from Eq. (19) for 4-step SLAM, 4-step fSLAM, 16-step CSI and 4-step CSI (zero-filled to 16 steps) for the 3-voxel chest/ 4-voxel heart model. The upper bound of chest contamination of the heart spectrum for the four cases was calculated from Eq. (22) assuming an effective chest to heart ratio of 4 and an intra-compartmental inhomogeneity of $\pm 15\%$ (30% total) for the chest.

3.2 Experiments

^{31}P 1D CSI, SLAM, and fSLAM were implemented in a 3T Philips Achieva MRI/MRS system on phantoms, the human leg, and the human heart. The phantom studies were done with a 14-cm diameter single loop transmit/receive coil, and the human studies used a 17-cm/11-cm diameter dual loop transmit and a 8-cm diameter single loop receive ^{31}P coil set described previously [22]. All human studies were approved by the Johns Hopkins Medicine Institutional Review Boards and all participants provided informed consent. The individual CSI spectra from all of the volume elements constituting each compartment were co-added post-acquisition for all comparisons of spectra from the equivalent volumes reconstructed using SLAM and fSLAM.

Phantom studies were performed on two standard Philips ^{31}P test disks 15-cm in diameter and 2.5-cm thick. One contained 300 mM H_3PO_2 , the other had 300 mM H_3PO_4 . A standard 1D CSI protocol using frequency-sweep-cycled (FSC) adiabatic half passage (AHP) pulses was applied (field-of-view, FOV = 160 mm; voxel/slice thickness, SL = 10 mm; repetition time, TR = 6 s; CSI phase-encoding steps, $k = -8, -7, -6, -5, -4, -3, -2, -1, 0, 1, 2, 3, 4, 5, 6, 7$; acquisition delay, 1.4ms) [22]. The SLAM protocol (Fig. 1) was then implemented with the same CSI parameters except for the phase-encoding gradients, which were reduced to a subset of 4 of the same steps ($-2, -1, 0, 1$). A 3-compartment model comprised of the two disks plus an 'other' compartment was assumed.

The leg was studied with the 300 mM H_3PO_4 disk phantom on top to create an additional compartment. 1D CSI was first performed with FSC AHP excitation (FOV = 160 mm; SL = 10 mm; TR = 8 s; phase-encoding steps, $k = -8, -7, \dots, 7$). This was followed by 3-compartment SLAM with the same total scan time and gradient-step increments but using only the 4 central k-space steps ($-2, -1, 0, 1$ repeated 4 times).

Human cardiac ^{31}P MRS studies comparing SLAM and CSI were performed on 8 normal volunteers and 16 patients with non-ischemic cardiomyopathy using the same protocol

(FOV =160 mm; SL =10 mm; TR=15.7 s, cardiac triggered). For each subject, CSI data reconstructed from all 16 phase-encoding steps, was compared with SLAM reconstruction employing only the middle 4 phase-encoding steps of the same CSI data sets. This effectively reduced the scan time by 4-fold. The effect of using just 2 phase-encoding steps from central k -space corresponding to chest and heart compartments only, was also investigated. The resulting spectra were fit by the circle-fit method [25] to provide a quantitative comparison of PCr and γ -ATP peak areas measured by SLAM with those from conventional CSI co-added over the same compartment (the localization and spectral analysis method are independent). Spectra were exponential-filtered (15-Hz line-broadening) and zero-filled 4 times to 2048 points.

The performance of fSLAM with respect to SNR and compartmental leakage was compared with that of CSI and SLAM in proactive cardiac ^{31}P MRS studies of 6 additional healthy volunteers. Sequentially, a first CSI, a SLAM, an fSLAM, and a repeat last CSI scan were acquired from each subject. CSI utilized the standard 16 phase-encoding steps from -8 to 7 (FOV=160 mm; SL=10 mm; TR=15.7 s, cardiac triggered). SLAM used the same 4 middle k -space phase-encoding steps for each exam, repeated four times for the same total scan-time as CSI. fSLAM phase-encoding employed 4, typically-fractional gradient steps, specifically optimized for minimum compartmental leakage in the heart compartment for each volunteer, after manual segmentation of the scout MRI using the scanner's cursor function. As in the simulations, optimization was performed using Matlab on a lap-top computer at the scanner-side, with weighting factors set to unity. The four gradient values were manually entered as experimental parameters in the fSLAM pulse sequence on the scanner. The four steps were repeated four times for the same total scan-time as the CSI.

4. Results

4.1 Computer simulations

Fig. 2, shows that SLAM spectra of the chest and heart, reconstructed using only the three middle (k -space) phase-encoding steps of the original 16, are indistinguishable from the original simulated spectra in the absence of inhomogeneity or noise. The effect of adding noise and inhomogeneity on SLAM spectra reconstructed for a range of different chest-muscle and heart compartment distributions, is illustrated by the Monte Carlo simulations for both models of concentration and sensitivity variations in Fig. 3. These show that the accuracy of the reconstruction, as indexed by the mean of the error <10% for all chest/heart anatomical combinations. As might be expected, the higher the concentration or larger the compartment size, the smaller the error SD. For the heart, the simulations predict highest errors when the effective extent of the cardiac compartment is smallest.

The effect of small errors in the registration of compartments for CSI, SLAM and SLIM, as compared to the true value and to CSI, are summarized in Table 1. The Monte Carlo simulations show that small segmentation errors of just ± 2 mm can introduce random errors approaching 10% for SLIM when the object is stationary, while SLAM is virtually unaffected and is less sensitive to partial volume errors. SLAM's relative insensitivity to small segmentation errors is critical for real applications since perfect segmentation is rarely possible in practice—especially in cardiac ^{31}P MRS.

The results of the analysis of SNR gain and the combined inter- and intra-compartment error factor, $\sqrt{\phi_i + \varphi_i}$, for SLAM and fSLAM, as compared with 16-voxel 1D CSI spectra co-added over 3- and 4-voxel thick cardiac compartments, are shown in Fig. 4. The maximum SNR results from choosing the phase-encoding steps closest to central k -space. Because SLAM is confined to the CSI's integer phase-encoding set, its SNR advantage fades as more-and-more of the high k -space phase-encodes are used. Optimum SNR performance for SLAM

occurs when the number of phase-encodes approximates the number of compartments, wherein its performance approximates that of fSLAM. Thus for SLAM, the best strategy is to choose the $M' \approx C$ non-equal CSI phase-encoding steps at or closest to the center of k-space, and repeat or average the acquisitions up to the allotted scan time, rather than add any higher k-space phase-encodes. On the other hand, fSLAM always achieves 1.5–1.8 times the SNR of standard CSI independent of the number of phase-encoding steps that are allowed. This reflects the fact that fSLAM is free to choose an array of fractional phase-encodes that all fall close to central k-space. For fSLAM, the additional phase-encodes offer the added benefit of reduced signal bleed (Fig. 4c,d). The errors, $\sqrt{\phi_i + \varphi_i}$, for fSLAM decay faster than SLAM as phase-encodes are added, indicating better error suppression, with larger compartments generating less error than smaller ones.

Fig. 5 plots SRF_h for 16- and 4-step CSI, 4-step SLAM and 4-step fSLAM. It is important to recognize that the signal derives from the integral of the curve over each compartment, resulting in cancellation of signal outside the heart. When the chest signal is uniform, the cancellation is essentially perfect in the case of SLAM and fSLAM but not CSI (Table 2, first row). When the signal in the chest compartment varies by up to 30% peak-to-peak, the upper bound for contamination of the heart compartment from chest muscle rises to 12–14% for SLAM and fSLAM. This compares to 9% for 16-step CSI, while the 4-step CSI is basically unusable (Table 2, second row).

4.2 Experiments

Spectra from the two-disk inorganic phosphate phantom reconstructed using CSI and SLAM are shown in Fig. 6. H_3PO_4 has a single ^{31}P peak at 2.9 ppm, while the H_3PO_2 resonance is a triplet centered about 13.5 ppm (coupling constant, 545 Hz), due to heteronuclear coupling with hydrogen. Despite the 4-fold reduction in scan-time, the SLAM spectra from the two disks are very similar to the summed CSI spectrum from the same compartment volumes, with negligible leakage consistent with the simulations (Fig. 3).

Spectra from the same-sized leg compartment obtained by CSI (averaging $n=6$ voxels) and SLAM (same volume) are presented in Fig. 7(a) normalized to constant noise. The SLAM spectrum has 2.1 times better SNR than CSI, and shows negligible signal contamination or bleed from the H_3PO_4 phantom positioned above the leg. Fig. 7(b) shows ^{31}P heart spectra from a 16-step 1D CSI (averaging 4 voxels), 4-step SLAM and 2-step SLAM from the same volume. The baseline roll is due to the acquisition delay for the phase-encoding gradient. Again, negligible bleed is evident in the 4-step SLAM spectrum, either from adjacent chest skeletal muscle or from an embedded coil marker (at ~23 ppm). Importantly, while SLAM faithfully reproduces the CSI heart spectrum and the SNR of CSI and SLAM are comparable, the SLAM spectrum was acquired 4-times faster. Even with only two steps, the SLAM reconstruction remains surprisingly good as shown in Fig. 7(c). With 2 phase encodes, just two signal-generating compartments, chest muscle and heart, are allowed, resulting in some signal bleed from the external coil marker which falls outside both compartments, in a spectrum acquired 8-times faster than the CSI standard.

The comparison of fitting results from the cardiac 4-step SLAM and 16-step CSI spectra from 8 healthy subjects and 16 patients and co-added over the same compartments, are presented in Fig. 8. In these data sets, the ratio of PCr signal in chest to that in heart compartments was at or below ~5. The PCr and γ -ATP peak areas from the SLAM reconstruction agree with those from CSI reconstruction (Fig. 8 a,b). The myocardial PCr/ATP ratio for the pooled patients and healthy subjects was the same (1.94 ± 0.60 in CSI vs. 1.90 ± 0.67 in SLAM; $p=0.42$, paired t-test), consistent with negligible contamination from chest muscle with its much higher PCr/ATP ratio of ~4 [19]. In addition, Fig. 8(c) shows

that the total PCr in the chest-plus-heart compartments measured by SLAM, is the same as that measured by CSI, indicating that the total signal is conserved. Because the fraction of cardiac PCr to the total chest-plus-heart PCr measured by SLAM is also equal to that measured by CSI (Fig. 8d), the contamination of heart spectra from chest muscle in SLAM is indistinguishable from that in CSI. This result is consistent with Table 2. Importantly, all these SLAM results correspond to acquisitions effectively taking $1/4^{\text{th}}$ of the scan-time of CSI.

Fig. 9 compares CSI, SLAM and fSLAM ^{31}P cardiac spectra proactively acquired in the same total scan-time from the same volume size in the same healthy volunteer. The time taken to implement fSLAM scanner-side was 1–2min to manually segment the scout MRI, plus several seconds to optimize the gradient set on the lap-top computer. The SLAM and fSLAM spectra both have higher SNR than CSI from the same volume, while a possible bleed signal from the coil marker in the SLAM spectrum (black) is eliminated by either designating a separate compartment for the coil phantom (Fig. 9b, top blue spectrum), or using fSLAM (Fig. 9c). There is no obvious chest muscle contamination of either the SLAM or fSLAM spectra. The PCr/ATP ratio for SLAM and fSLAM was not significantly different from that measured in either the first or the repeated last CSI scans, and the absolute metabolite signal levels do not change (Fig. 9d).

Table 3 lists the SNR of human cardiac PCr in same-sized voxels for CSI, SLAM and fSLAM proactively performed in 6 volunteers in the same scan-time. The mean SNR improvement for SLAM vs CSI for the six studies is 1.45 ± 0.25 . The mean SNR improvement for fSLAM vs CSI for the six studies is 1.36 ± 0.24 . According to Eq. (1), this SNR gain would be consistent with a cardiac compartment equivalent to two of the 1-cm CSI voxels even though the reconstruction assumed a 4-voxel cardiac compartment. This likely reflects the combined effect of the decline in surface coil sensitivity with depth, and the 1–2 cm actual thickness of the anterior myocardial wall.

5. Discussion

Single voxel methods such as PRESS [26], STEAM [27] or ISIS [28] are good localization choices for performing MRS of a single compartment, but do not offer optimum SNR for a fixed scan time for MRS of multiple compartments. In addition, their sensitivity to relaxation effects (both T_1 and T_2) and motion, presents real problems for quantification, especially in ^{31}P MRS [1, 26]. CSI, being a simple pulse-and-acquire experiment that collects all-of-the-signal from all-of-the-sample, all-of-the-time, currently offers the cleanest approach to quantitative MRS, with potentially the highest SNR efficiency. It is however, limited by the minimum scan-time required to encode the entire sensitive volume or FOV of the detector coil. This can limit the direct translation of SNR gains, such as those afforded by higher B_0 magnetic field strengths, to reductions in scan-time. In addition, the highest SNR efficiency of CSI is only realized when the spatial resolution imposed at the time of acquisition, matches the desired compartment size [1]. Unfortunately, CSI's spatial resolution is usually set not by the size of the desired compartment, but by the geometry of the tissue that it must be distinguished from (eg, the chest in heart or liver studies, the scalp in brain studies).

Alternative approaches that localize spectra to pre-selected compartments based on anatomical MRI information, are not new. The SLIM, GSLIM and SLOOP methods were originally proposed some 20 years ago [3–5], but see little use today compared to CSI or even PRESS, STEAM or ISIS. When SLIM, GSLIM and SLOOP are applied to regular CSI acquisitions, without pro-active implementation or gradient selection criteria that place a premium on SNR—as is most often the case [3, 4, 6–16], they cannot deliver the highest SNR

achieved by matching the resolution to the compartment, *a priori*. Although not previously documented, the difference would be significantly higher than the SNR gained from summing signals from the constituent CSI voxels—by a factor of $\sim g$ (Eq. 1). Similarly, a many-fold speed-up in the minimum CSI scan-time could result if the phase-encoding gradient set were cut.

Here for the first time we have exploited differences in volume sizes between desired MRS compartments and CSI resolution, to realize and document a g -fold SNR gain consistent with Eq. (1), using a new MRS localization method, SLAM. SLAM differs from SLIM, GSLIM and SLOOP in both the pulse sequence that is applied, and in MRS reconstruction. Simply put and unlike other methods, the SLAM pulse sequence is based on a CSI sequence from which essentially all of the high-order gradient phase-encoding steps are eliminated except for the $\sim C$ phase-encoding steps closest to central k -space. Because the CSI gradient set is discretized, this means that the only *a priori* information needed to run the sequence is the number C , which is generally fixed for a given study protocol. Compared to pro-active implementation of SLOOP [5], this has the advantage of avoiding image-guided gradient optimization, prescription, and implementation at the scanner-side prior to acquisition, whereas SLIM and GSLIM utilize standard CSI sequences [3, 4, 6, 11, 12].

Like prior methods, reconstruction of SLAM spectra *does* require a scout MRI to identify and segment the compartments which are assumed uniform. However, SLAM reconstruction *differs* from SLIM, GSLIM and SLOOP in that it solves a set of C linear simultaneous equations by eliminating un-needed phase-encoding steps from the standard CSI algorithm. SLAM aims to generate spectra that are at best equal to the compartmental average CSI spectra, whereas SLIM, GSLIM and SLOOP use MRI-based constrained reconstruction or SRF optimization to obtain optimally-localized compartment spectra. Because of the relatively coarse resolution of CSI, this renders SLAM relatively insensitive to registration errors in segmenting the compartments—compared to SLIM for example (Table 1), where problems were noted previously [11, 29].

With SLAM, we demonstrate many-fold reductions in the minimum scan-time compared to CSI in theory (Fig. 4) and in practice (Fig. 7, 8), and substantial SNR gains in human *in vivo* studies on a standard clinical MRI/MRS scanner at 3T (Fig. 9, Table 3). Importantly, in 1D ^{31}P human cardiac applications, SLAM delivers qualitative and quantitative results (Fig. 9) that are practically indistinguishable from results obtained from conventional CSI, other than being 4-times faster or higher in SNR (Figs 2, 6–9). Even so, significant inter-compartmental contamination may arise when signals from adjacent compartments differ greatly or are not segmented. This can occur in ^{31}P MRS heart studies, for example, when chest skeletal muscle compartment signals are many-fold higher (eg >5-fold) than cardiac signals due to the higher muscle metabolite concentrations, and/or its thickness, and/or proximity to surface coil detectors with nonuniform sensitivity. Conventional CSI, used here as a standard, is not immune from this problem [30] (Table 2). Despite the uniform compartment assumption, both the numerical results (Fig. 3, Tables 1, 2) and the experiments (Figs. 6–9) suggest that SLAM is relatively robust to the variations in signal that arise in practical applications such as cardiac surface-coil MRS.

The SLAM acquisition pulse sequence with integer k -space phase-encodes was surprisingly simple to implement, at least for the 1D case. For our cardiac ^{31}P MRS studies, we chose the same 4 central gradient steps to provide a fixed SLAM acquisition sequence suitable for up to 4 compartments, extracted from a standard 16-step CSI sequence with the other 12 steps discarded. Further reductions in C and the number of phase-encodes, to 2 for example (Fig. 7c), risk leakage from unaccounted-for signal sources that lie outside of any designated compartment. This may be tolerable if the leakage does not interfere with the spectral region

of interest. For validation or test purposes, SLAM can be performed retroactively on raw data sets that are accompanied by a scout MRI, simply by applying the algorithm to a subset of frames in each CSI data set. The result can be compared with the summed CSI from the same-sized compartments analogous to Fig. 8.

fSLAM extends SLAM by removing the limitation that the phase-encodes be selected from the set of integer-stepped CSI gradients. Instead, they are adjusted to minimize leakage or errors due to inhomogeneity and/or maximize SNR. We observed that maximizing SNR alone can produce unacceptable error if the clustering of phase-encodes at the center of k -space is unchecked (Fig. 4). Minimization of inter- and intra-compartmental errors alone yields acceptable results, albeit at the expense of a small reduction in SNR (Fig. 9; Table 3). Thus, inter- and intra-compartmental error was substantially eliminated with fSLAM, also using only four phase-encoding gradient steps. When SNR is low also, inter-compartmental leakage could become problematic relative to the compartment signal. Adjustment of the weighting factors in Eq. (18) from the values of unity used herein may help attenuate bleed from specific adjacent compartments, depending on the particular application. The gradient optimization in fSLAM derives from tracking errors through the reconstruction process and includes those due to both inter- and intra-compartmental signal inhomogeneity. This differs from SLOOP's use of the SRF to minimize only the inter-compartmental leakage [5], while SLIM and GSLIM do not use optimized gradients.

Note also that the SRF is not global but is specific to the cardiac model. Inter- and intra-compartmental leakage occurs only when the integral over the entire compartment is non-zero or in the presence of significant heterogeneity. Compartmental segmentation in SLAM ensures that the integral of the SRF vanishes over other compartments, while fSLAM minimizes the effect of heterogeneity within the compartment of interest as well. Ultimately however, the spatial responses for SLAM and fSLAM and their compartmental contamination are fully characterized by determining the accuracy of the solutions and leakage errors, for which CSI is used as the standard in the current work (Figs 4, 6–9, Tables 1, 2).

In conclusion, the SLAM and fSLAM methods yield spectra comparable to the average of same-sized CSI compartments but with large scan-time reductions, SNR gains, and manageable, if not insignificant, bleed artifacts. The SNR gains predicted by Eq. (1) will be moderated in practice by the depth-dependence of the surface coil sensitivity, as well as the actual metabolite distribution (in our case, the myocardial wall thickness). Independent of the SNR gain, SLAM and fSLAM reduce the minimum scan-time required for localization from M acquisitions in CSI, to C or $M' \ll M$. We believe that this efficiency advantage alone can dramatically reduce MRS scan-times for patient MRS studies employing CSI in global disease such as cardiomyopathies [15–20], large lesions, or where single voxel methods are limited by relaxation, motion or other considerations [21]. In addition, the significant reductions in minimum scan time provided by the SLAM and fSLAM methods compared to CSI, provides a practical pathway for translating the higher SNR afforded by increases in magnetic field strength, into faster MRS exams. We are currently investigating extension of the techniques to higher dimensions [31].

- SLAM is a new method of localizing spectra to C anatomic compartments located by MRI.
- C phase-encoding gradients are selected from central k -space to maximize SNR.
- Compartment-average spectra are reconstructed from a reduced CSI equation set.

- Application to 24 ^{31}P heart MRS studies yields same quantitative results 4-times faster.
- Proactive application in 6 hearts yields 30–40% ^{31}P MRS SNR gain in same time and volume.

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Figure 1.
Flow chart depicting implementation of SLAM (left pathway) or fSLAM (right pathway).

Figure 2. Simulated 16-step ^{31}P 1D CSI spectra of a model chest with 3 skeletal muscle voxels (a) and 4 heart voxels (c). The reconstructed SLAM chest (b) and heart (d) spectra are indistinguishable from the originals.

Figure 3.

Cardiac model (a) and Monte Carlo simulation of the effect of noise and 30% ($\pm 15\%$) inhomogeneity on the accuracy of SLAM signal reconstruction vs. CSI (b–e). The chest-to-heart signal ratio is held constant at 4 in (b,c) depicted by the dark continuous curve in (a). In (d,e) the ratio is 2.5 scaled by the experimental surface coil sensitivity profile depicted by the blue dashed curve in (a). The horizontal axis in parts (b–e) denotes a numeric index corresponding to one of the 20 cardiac configurations of chest and heart thickness (see text). Errors are mean $\pm$ SD in the chest (b,d) and heart (c,e), calculated with cardiac SNR=20. The largest errors in the heart correspond to configurations #1 (2cm chest, 2cm heart, no

separation between chest and heart), #6 (2cm chest, 2cm heart, 1cm gap), #11 (3cm, 2cm, 0cm), and #16 (3cm, 2cm, 1cm).

Figure 4.

The SNR gain for the same volume (a, b), and the total inter- and intra-compartment error factor, $\sqrt{\phi_i + \varphi_i}$, (c, d) for SLAM and fSLAM in the heart as a function of the number of phase encodes, M' , of the original $M=16$ that are allowed. For comparison, CSI has an SNR = 1 with zero error assumed. Points depict results for three sets of gradients (square points, fSLAM with maximum SNR; stars, fSLAM with minimized inter/intra-compartmental errors; circles, SLAM). Here, (a) and (c) are for a 4-voxel thick heart; (b) and (d) are for a 3-voxel-thick heart compartment, all with a 2-voxel thick chest compartment.

Figure 5. SNR_h for (a) 16- and (b) 4- step CSI (zero-filled to 16 steps), (c) 4-step SLAM and (d) 4-step fSLAM, computed for a model comprised of three 10mm-thick chest voxels adjoining four 10mm heart voxels as a function of depth (black lines, real part; dashed red, imaginary component). Vertical dashed lines delineate the chest and heart compartments, as labeled. The signal contribution from each compartment derives from the integral of the curve over that compartment.

Figure 6.

CSI and SLAM spectra reconstructed from the standard Philips ^{31}P test phantom comprised of a H_3PO_4 disk on the bottom (a, c), and a H_3PO_2 disk on top (b, d), as shown in the image (e). The CSI spectra (a, b) are the sum of the spectra from the voxels (red horizontal lines) containing the disks and were acquired with 16 phase-encoding gradients ($-8 \dots +7$). The SLAM spectra (c, d) were acquired 4-times faster with just 4 phase-encodes ($-2, -1, 0, 1$). The SNR for the CSI spectra are 660 (a) and 638 (b), compared to 528 (c) and 482 (d) for SLAM. The signal at ~ 0 ppm is a contaminant present only in the H_3PO_2 disk. Vertical axes denote spectral amplitudes in arbitrary units.

Figure 7.

(a) Human leg ^{31}P spectrum acquired by SLAM (red, top) and CSI (blue, lower) from the same 6-voxel volume in the same scan time (2.1 min) normalized to constant noise. (b) ^{31}P spectra acquired from a normal human heart from the same 4-voxel volume, using 1D CSI (blue) in 8.4 min, and SLAM spectra reconstructed with a subset of 4 central k -space phase-encodes and a 3-compartment model, (red spectrum). (c) Spectra acquired with just two phase-encodes (green) and a 2-compartment model (chest and heart). The effective SLAM acquisition times were $1/4^{\text{th}}$ and $1/8^{\text{th}}$ of CSI in (b) and (c) respectively.

Figure 8.

Fitting results reconstructed by SLAM from a subset of 4 of the 16 CSI phase encoding steps acquired from the 24 heart patients and control subjects, as compared to the CSI results. (a) PCr and (b) γ -ATP peak areas (arbitrary units) quantified in the cardiac compartment. (c) The total PCr peak areas from both heart and chest compartments. (d) The ratio of heart PCr to the total PCr from both chest and heart compartments. The correlation coefficients are $r > 0.97$ in all cases, and the solid line is the identity line.

Figure 9.

(a) CSI, (b) 4(top, blue)- and 3(bottom, black)-compartment SLAM and (c) error-minimized 3-compartment fSLAM spectra, plotted with amplitudes all normalized to constant noise from the same volunteer with the same total scan time and total voxel volume. Gradient encoding steps of -8 to $+7$ (integer) were used for standard CSI; integer steps $-2, -1, 0, 1$ repeated 4 times were used for SLAM; and fSLAM used non-integer steps $-2.13, -0.73, +0.73, +2.13$ repeated 4 times. (d) Cardiac PCr peak area (arbitrary units) from proactive ^{31}P MRS studies of all 6 subjects in the first CSI, the SLAM, the fSLAM and the repeated CSI scan as labeled (no significant difference between exams at paired t-testing; lines connect measurements from the same subjects).

Table 1

Monte Carlo analysis of the effect of ± 2 mm misregistration on accuracy of cardiac PCr measurements for a 30mm chest/40mm heart model.

Simulation (1000 runs)	Error (mean $\pm$ SD), %		
	CSI	SLAM	SLIM
With model fixed on CSI grid, error vs. true	2.7 ± 0.0	0.7 ± 0.0	1.1 ± 8.4
With ± 2 mm partial volume shift, error vs. CSI	0.0 ± 0.0	-2.2 ± 5.1	-1.1 ± 9.8
With ± 2 mm partial volume shift, error vs. true	2.4 ± 5.2	0.3 ± 8.2	1.1 ± 8.7

Table 2Integral of SRF_h and upper bound of chest contamination for CSI, SLAM and fSLAM^a

	16-step CSI	4-step CSI	SLAM	fSLAM
Integral of SRF_h over chest	0.0138	0.1654	0.0045	0.0073
Upper bound of $L_{c \rightarrow h}$ ^b	9.0%	77.3%	13.9%	12.0%

^aComputed for 3-slice chest/ 4-slice heart model.^bComputed with chest/heart signal ratio of 4 and $\pm 15\%$ (total 30%) chest inhomogeneity.

Table 3

The cardiac ³¹P MRS SNR of PCr for the same cardiac voxel volumes and scan time using CSI, SLAM, and fSLAM in n = 6 healthy volunteers (left-to-right).

	Vol 1	Vol 2	Vol 3	Vol 4	Vol 5	Vol 6	Average
CSI	61	30	33	18	18	26	31 ± 16
SLAM	86	53	41	30	20	39	45 ± 23 ^a
fSLAM	71	45	44	32	21	31	41 ± 17 ^b

^a p<0.01 vs. CSI, paired t-test.

^b p<0.002 vs. CSI, paired t-test.