Fast, accurate 2D-MR relaxation exchange spectroscopy (REXS): Beyond compressed sensing

Ruiliang Bai, Dan Benjamini, Jian Cheng, and Peter J. Basser

Section on Quantitative Imaging and Tissue Sciences, DIBGI, NICHD, National Institutes of Health, Bethesda, Maryland 20892, USA

(Received 21 June 2016; accepted 19 September 2016; published online 20 October 2016)

Previously, we showed that compressive or compressed sensing (CS) can be used to reduce significantly the data required to obtain 2D-NMR relaxation and diffusion spectra when they are sparse or well localized. In some cases, an order of magnitude fewer uniformly sampled data were required to reconstruct 2D-MR spectra of comparable quality. Nonetheless, this acceleration may still not be sufficient to make 2D-MR spectroscopy practicable for many important applications, such as studying time-varying exchange processes in swelling gels or drying paints, in living tissue in response to various biological or biochemical challenges, and particularly for *in vivo* MRI applications. A recently introduced framework, marginal distributions constrained optimization (MADCO), tremendously accelerates such 2D acquisitions by using *a priori* obtained 1D marginal distribution as powerful constraints when 2D spectra are reconstructed. Here we exploit one important intrinsic property of the 2D-MR relaxation exchange spectra: the fact that the 1D marginal distributions of each 2D-MR relaxation exchange spectrum in both dimensions are equal and can be rapidly estimated from a single Carr–Purcell–Meiboom–Gill (CPMG) or inversion recovery prepared CPMG measurement. We extend the MADCO framework by further proposing to use the 1D marginal distributions to inform the subsequent 2D data-sampling scheme, concentrating measurements where spectral peaks are present and reducing them where they are not. In this way we achieve compression or acceleration that is an order of magnitude greater than that in our previous CS method while providing data in reconstructed 2D-MR spectral maps of comparable quality, demonstrated using several simulated and real 2D $T_2 - T_2$ experimental data. This method, which can be called “informed compressed sensing,” is extendable to other 2D- and even ND-MR exchange spectroscopy. [<http://dx.doi.org/10.1063/1.4964144>]

I. INTRODUCTION

NMR longitudinal relaxation time constants (T_1), transverse relaxation time constants (T_2), and self-diffusion constants (D) have long been used to characterize water dynamics in biological tissue, material science, porous media, etc.¹ Previous works have shown that multiple relaxation or diffusion signals might be extracted from 1D data that are relaxation time weighted or diffusion weighted via 1D numerical inverse Laplace transformation (1D ILT) or other multicomponent exponential methods.^{2–6} These signals represent different microscopic pools within heterogeneous samples that often have important physical or biological significance. In porous media, multiple signals with different relaxation time constants in rocks represent pores having different surface-to-volume ratios^{7–10} while in biological samples, such as white matter, these signals represent different microenvironments or domains, e.g., the myelin-wrapped water and intra- and extracellular water.^{11–13}

In addition to determining microscopic pools, another important question is the migration of the water molecules (or other molecules) from one pool to another, which is often referred to as a physical “exchange” process.^{8,9,14–19} In petrophysics, the frequency of this exchange can reveal

features of rock permeability, which is an important parameter in assessing the potential for extracting oil.²⁰ In biological samples, the exchange between different microscopic pools, for example, between intra- and extracellular compartments, is directly related to cell membrane permeability and active transport processes, which are important in understanding a cell’s function and viability.^{21–24} On the other hand, the observed pools’ apparent relaxation or diffusion values and sizes are strongly dependent on the exchange frequency between and among pools; this relationship also makes the quantification of the exchange processes essential for accurately determining the sizes and dynamic properties of pools.²⁵

In recent years, multidimensional MR relaxation and diffusion spectra have been proposed as a means to monitor and quantitatively measure exchange between different pools.^{14,17,19} Most notable of these methods are the 2D $T_2 - T_2$ exchange spectra obtained from the relaxation exchange spectroscopy (REXS), see Fig. 1(c) sequence first proposed by Lee *et al.*²⁶ The REXSY sequence consists of two Carr–Purcell–Meiboom–Gill (CPMG) RF pulse trains separated by a mixing time, t_m , during which the magnetization is stored along the longitudinal axis. In 2D $T_2 - T_2$ exchange spectra, spins that reside in the same pools during the two CPMG blocks will appear as peaks on

(A) CPMG

(B) IR-CPMG

(C) REXSY

FIG. 1. Pulse sequences: (a) CPMG, (b) IR-CPMG, and (c) REXSY. τ is the echo time spacing in the CPMG, n is the number of loops, IR is the inversion recovery time, and t_m is the mixing time.

the diagonal while those migrating from one relaxation pool to another will appear as off-diagonal peaks. The exchange frequency between pools can be quantitatively determined by analyzing the amplitude of the peaks with mathematical models.^{17,25} Here we use the apparent T_2 (T_2') rather than T_2 for the relaxation spectra obtained from CPMG and CPMG-based sequences since only the apparent T_2 rather than the intrinsic T_2 can be directly obtained from these types of sequences if exchange exists. In addition, $D-D$ exchange spectroscopy (DDesy) has also been proposed as a means to measure the exchange between pools with different diffusion properties.^{14,15}

These multidimensional NMR exchange spectra methods have been further advanced by the development of robust and fast 2D-ILT algorithms and data analysis methods.²⁷⁻³¹ However, the large amount of 2D-MR relaxation and diffusion spectral data and long scan times required to accurately estimate them have limited their utility in applications such as monitoring fast dynamic processes and most preclinical and clinical *in vivo* applications that require short scan times. Faster data acquisition and more efficient data reconstruction methods are required to make 2D exchange spectroscopy

practical and practicable. Several new methods were proposed recently, which include modifying the MR sequences^{25,32} and new experimental design and data analysis methods based on the REXSY sequence,^{33,34} to achieve this important goal.

These considerations have also lead us to propose novel data compression methods, like compressed sensing (CS), to reduce the amount of data that must be acquired to obtain high-quality 2D spectra.^{35,36} Still there are time-varying systems or systems requiring vast amounts of data for which even CS does not provide sufficient data compression or “acceleration.” This acceleration may still not be sufficient to make 2D spectra practicable for many applications, particularly for studying exchange in nonstationary systems (such as swelling gels, drying paints, and living tissue subjected to various stimuli). Moreover, faster data acquisition and reconstruction can always reduce the time and resource costs where 2D relaxation and diffusion spectra are used routinely, e.g., in the oil industry. It is clear that compressed sensing alone does not provide sufficient acceleration to make 2D relaxation and diffusion spectra feasible on preclinical or clinical scanners for a myriad of *in vivo* applications.

The CS acceleration is generic and can be applied to many types of multidimensional MR relaxation and diffusion correlation or exchange spectroscopies. However, it is also agnostic with respect to a particular experiment and, in our case, to the intrinsic properties of each specific MR pulse sequence, the overall experimental design, and any *a priori* information we might possess. Recently introduced, the 1D projections of the 2D-MR relaxation and diffusion spectra can be used to accelerate and improve the reconstruction of 2D-MR spectra, if these 1D projects can be rapidly estimated from independent MR measurements.³⁷ While these 1D marginal distributions provide powerful constraints when 2D spectra are reconstructed, their estimation requires an order of magnitude less data than a conventional 2D approach.³⁷ Compared with the conventional approach, this marginal distribution constrained optimization (MADCO) methodology has been shown to be highly accurate and robust, while only requiring a fraction of the data.³⁷

Here we exploit one important intrinsic property of the 2D-MR relaxation exchange spectra: the 1D marginal distributions of each 2D-MR relaxation exchange spectrum on both dimensions are equal and can be rapidly estimated from a single CPMG or inversion recovery (IR) prepared CPMG (IR-CPMG) measurement (step 1). This rapid acquisition of 1D marginal distributions of 2D $T_2' - T_2'$ spectra requires only two orders of magnitude less data than a conventional REXSY acquisition, making it a perfect application for MADCO. Rather than random sampling as proposed in MADCO (not practical in REXSY), here we propose to use the obtained 1D marginal distribution as *a priori* information to design the subsequent data-sampling scheme, concentrating measurements where spectral peaks are present and reducing them where they are not (step 2). The obtained 1D marginal distribution is further used to reconstruct the 2D-MR spectra as equality constraints as MADCO (step 3). With these three steps, this approach can achieve two orders of magnitude compression greater than conventional 2D approaches and an

order of magnitude compression greater than our previous CS method while providing comparable data quality in reconstructed 2D-MR $T_2' - T_2'$ spectral data. Here we call this extended MADCO methodology the marginal (M) distribution (D) guided (G) sampling (S) and reconstruction (R) framework (MDGSR). In this paper, we provide a proof of concept on only the 2D-MR $T_2' - T_2'$ exchange spectra, but similar principles can be applied to 2D-MR $D - D$ exchange spectra and to other 2D or higher (ND) MR relaxation and diffusion spectra in which such prior knowledge can be readily obtained.

II. MATERIALS AND METHODS

A. Theoretical background

Key to the new MDGSR framework is the fact that the 1D projection of the 2D $T_2' - T_2'$ spectrum reconstructed from REXSY onto either the first or second dimension is always equal to the 1D T_2' probability density function (PDF), $F(T_2')$, from CPMG (Fig. 1(a)) or T_1 -weighted inversion recovery prepared CPMG (IR-CPMG, Fig. 1(b)). Here we proved this hypothesis, in theory, by analyzing the time evolution of the magnetizations from several exchanging pools with CPMG, IR-CPMG, and REXSY sequences.

Consider Q exchanging pools with equilibrium magnetizations, M_{i0} , intrinsic longitudinal relaxation rate constants $R_{1i} = 1/T_{1i}$, and intrinsic transverse relaxation rate constants $R_{2i} = 1/T_{2i}$, where $i = 1, 2, \dots, Q$. From the Bloch-McConnell equations,^{38,39} the time evolution of the MR signal $\mathbf{M}(t)$ from the Q exchanging pools can be generally written as follows:⁴⁰

$$\frac{d}{dt} [\mathbf{M}(t) - \mathbf{M}_{eq}] = -(\mathbf{R} + \mathbf{K}) [\mathbf{M}(t) - \mathbf{M}_{eq}], \quad (1)$$

where $\mathbf{M}$ is the vector of the magnetization signals, $\mathbf{M}_{eq}$ is the $\mathbf{M}$ at equilibrium, $\mathbf{R}$ is a diagonal matrix with the corresponding relaxation rate constants on the diagonal, and $\mathbf{K}$ is the matrix of the exchange rate constants between different pools,⁴⁰

$$\mathbf{K} = \begin{bmatrix} -\sum_{i \neq 1} k_{1i} & \dots & k_{Q1} \\ \vdots & \ddots & \vdots \\ k_{1Q} & \dots & -\sum_{i \neq Q} k_{Qi} \end{bmatrix}, \quad (2)$$

where k_{ij} is the exchange rate constant from pool i to pool j . In an equilibrium system, mass balance also requires that the equilibrium magnetization in each pool remains constant,⁴⁰ i.e., $\mathbf{K}\mathbf{M}_{eq} = 0$.

The general solution for Eq. (1) is

$$\mathbf{M}(t) - \mathbf{M}_{eq} = e^{-(\mathbf{R} + \mathbf{K})t} [\mathbf{M}(0) - \mathbf{M}_{eq}]. \quad (3)$$

Let us assume that $\mathbf{A} = \mathbf{R} + \mathbf{K}$, which can be expanded in terms of eigenvalues and eigenvectors,

$$\mathbf{A} = \mathbf{U}\boldsymbol{\lambda}\mathbf{U}^{-1}, \quad (4)$$

where $\boldsymbol{\lambda}$ is a diagonal matrix with the eigenvalues of $\mathbf{A}$ on diagonal, and $\mathbf{U}$ is a matrix whose columns are the

corresponding eigenvectors. Eq. (3) can be then further rewritten as follows:

$$\mathbf{M}(t) - \mathbf{M}_{eq} = \mathbf{U}e^{-\boldsymbol{\lambda}t}\mathbf{U}^{-1} [\mathbf{M}(0) - \mathbf{M}_{eq}]. \quad (5)$$

1. CPMG

For the three terms in Eq. (3), $\mathbf{M}_{eq} = 0$, $\mathbf{M}(0) = \mathbf{M}_0$, where $\mathbf{M}_0 \equiv [M_{i0}]_{i=1,2,\dots,Q}$, and $\mathbf{R} = \mathbf{R}_2$ (transverse relaxation rate constants matrix) in the CPMG sequence. Let us assume that $\mathbf{A}_2 = \mathbf{R}_2 + \mathbf{K} = \mathbf{U}_2\boldsymbol{\lambda}_2\mathbf{U}_2^{-1}$. The detected CPMG signal, $S(\text{TE})$, is the sum of the elements of the magnetization vector $\mathbf{M}$,

$$S(\text{TE}) = \mathbf{1}_{1 \times Q} \mathbf{U}_2 e^{-\boldsymbol{\lambda}_2 \text{TE}} \mathbf{U}_2^{-1} \mathbf{M}_0, \quad (6)$$

where $\mathbf{1}_{1 \times Q}$ is a vector of ones and $\text{TE} = n\tau$ (Fig. 1(a)) is the accumulated echo time in the CPMG. In Eq. (6), $S(\text{TE})$ can still be described as the sum of several exponential items with apparent transverse relaxation rate constants determined by the diagonal elements of $\boldsymbol{\lambda}_2$. The amplitude of each exponential term (apparent pool) can be derived from Eq. (6),

$$\begin{aligned} \mathbf{P}_{\text{CPMG}} &= \mathbf{1}_{1 \times Q} \mathbf{U}_2^\circ (\mathbf{U}_2^{-1} \mathbf{M}_0)^T, \\ \mathbf{P}_{\text{CPMG},i} &= \left[(\mathbf{1}_{1 \times Q} \mathbf{U}_2) (\mathbf{U}_2^{-1} \mathbf{M}_0)^T \right]_{ii} = [\mathbf{U}_2^{-1} \mathbf{M}_0 \mathbf{1}_{1 \times Q} \mathbf{U}_2]_{ii}, \end{aligned} \quad (7)$$

where $^\circ$ represents the element-wise product operation, the superscript T represents the matrix transpose operation, and i represents the index of each exponential term.

2. T_1 -weighted CPMG

As described in Fig. 1(b), T_1 -weighted CPMG was achieved by an inversion-recovery prepared CPMG sequence, IR-CPMG. The detected signal, after being subtracted from equilibrium CPMG, can be described as

$$S(\text{IR}, t_e) = \mathbf{1}_{1 \times Q} e^{-\mathbf{A}_1 \text{IR}} \mathbf{U}_2 e^{-\boldsymbol{\lambda}_2 \text{TE}} \mathbf{U}_2^{-1} \mathbf{M}_0, \quad (8)$$

where $\mathbf{A}_1 = \mathbf{R}_1 + \mathbf{K}$ and $\mathbf{R}_1$ is the longitudinal relaxation rate constants matrix. At a fixed IR, the MR signal is still the sum of several exponential items with the same apparent transverse relaxation rate constants as in Eq. (6). The amplitude of each exponential term (apparent pool) is T_1 -weighted now and can be derived as follows:

$$\begin{aligned} \mathbf{P}_{\text{IR-CPMG}} &= \mathbf{1}_{1 \times Q} e^{-\mathbf{A}_1 \text{IR}} \mathbf{U}_2^\circ (\mathbf{U}_2^{-1} \mathbf{M}_0)^T, \\ \mathbf{P}_{\text{IR-CPMG},i} &= \left[(\mathbf{1}_{1 \times Q} e^{-\mathbf{A}_1 \text{IR}} \mathbf{U}_2) (\mathbf{U}_2^{-1} \mathbf{M}_0)^T \right]_{ii} \\ &= [\mathbf{U}_2^{-1} \mathbf{M}_0 \mathbf{1}_{1 \times Q} e^{-\mathbf{A}_1 \text{IR}} \mathbf{U}_2]_{ii} \\ &= [\mathbf{U}_2^{-1} \mathbf{M}_0 \mathbf{1}_{1 \times Q} e^{-\mathbf{R}_1 \text{IR}} \mathbf{U}_2]_{ii}. \end{aligned} \quad (9)$$

Above, the property of $\mathbf{1}_{1 \times Q} \mathbf{K} = \mathbf{0}_{1 \times Q}$ was used from line 3 to line 4. From Eqs. (9) and (7), the relative amplitude weightings for the exponential terms are equal in the CPMG and T_1 -weighted CPMG if the T_1 of each pool is equal to or much longer than IR.

3. REXSY

The detected 2D REXSY (Fig. 1(c)) data can be written as follows:

$$\begin{aligned} S(\text{TE}_1, t_m, \text{TE}_2) &= \mathbf{1}_{1 \times Q} e^{-A_2 \text{TE}_1} e^{-A_1 t_m} e^{-A_2 \text{TE}_2} \mathbf{M}_0 \\ &= \mathbf{1}_{1 \times Q} \mathbf{U}_2 e^{-A_2 \text{TE}_1} \mathbf{U}_2^{-1} e^{-A_1 t_m} \mathbf{U}_2 e^{-A_2 \text{TE}_2} \mathbf{U}_2^{-1} \mathbf{M}_0, \end{aligned} \quad (10)$$

where t_m is the mixing time as shown in Fig. 1(c), and TE_1 and TE_2 are the effective echo times of the first and second CPMG in REXSY. By applying eigen-decomposition in λ_2 and factoring with respect to each exponential term, the amplitude of each 2D exponential term can be derived as a matrix,²⁵

$$\mathbf{P}_{\text{REXSY}} = [\mathbf{U}_2^{-1} e^{-A_1 t_m} \mathbf{U}_2] \circ [\mathbf{U}_2^{-1} \mathbf{M}_0 \mathbf{1}_{1 \times Q} \mathbf{U}_2]^T. \quad (11)$$

The projection of $\mathbf{P}_{\text{REXSY}}$ onto the second dimension is as follows:

$$\begin{aligned} \sum_{i=1}^Q \mathbf{P}_{\text{REXSY},ij} &= \sum_{i=1}^Q \left([\mathbf{U}_2^{-1} e^{-A_1 t_m} \mathbf{U}_2] \circ [\mathbf{U}_2^{-1} \mathbf{M}_0 \mathbf{1}_{1 \times Q} \mathbf{U}_2]^T \right)_{ij} \\ &= \left([\mathbf{U}_2^{-1} e^{-A_1 t_m} \mathbf{U}_2]^T [\mathbf{U}_2^{-1} \mathbf{M}_0 \mathbf{1}_{1 \times Q} \mathbf{U}_2] \right)_{jj} \\ &= [\mathbf{U}_2^{-1} \mathbf{M}_0 \mathbf{1}_{1 \times Q} e^{-A_1 t_m} \mathbf{U}_2]_{jj} \end{aligned} \quad (12)$$

which is equal to Eq. (9) if $t_m = \text{IR}$. The same case applies to the projection of $\mathbf{P}_{\text{REXSY}}$ onto the first dimension.

So far, it has been proven in theory that the 1D marginal distribution of $\mathbf{P}_{\text{REXSY}}$ is equal to the 1D T_2' PDF from a T_1 -weighted CPMG or CPMG if the T_1 of each pool is the same or much longer than t_m .

B. General 2D $T_2' - T_2'$ reconstruction with 2D ILT

From Eq. (10), the REXSY data can always be reformatted as a 2D exponentially decaying signal,

$$\begin{aligned} \mathbf{M}(\text{TE}_1, \text{TE}_2) &= \iint \mathbf{F}(T'_{2,1}, T'_{2,2}) \exp\left(-\frac{\text{TE}_1}{T'_{2,1}}\right) \\ &\quad \times \exp\left(-\frac{\text{TE}_2}{T'_{2,2}}\right) dT'_{2,1} dT'_{2,2} + \epsilon(\text{TE}_1, \text{TE}_2), \end{aligned} \quad (13)$$

where $T'_{2,1}$ and $T'_{2,2}$ are the apparent transverse relaxation time constants in the first and second dimensions, respectively; $\mathbf{F}(T'_{2,1}, T'_{2,2})$ is the 2D joint PDF of the two corresponding relaxation parameters and the numerical approximation of $\mathbf{P}_{\text{REXSY}}$, respectively; and ϵ is the noise.

Generally, the estimation of $\mathbf{F}(T'_{2,1}, T'_{2,2})$ relies on direct 2D ILT of the measured signals $\mathbf{M}(\text{TE}_1, \text{TE}_2)$, which is an ill-conditioned problem. One practical technique for obtaining a stable solution is by minimizing $\mathcal{E}$,³¹

$$\mathcal{E} \equiv \sum_{i=1}^{N_1} \sum_{j=1}^{N_2} \left[\mathbf{M}(\text{TE}_{1,i}, \text{TE}_{2,j}) - \sum_{m=1}^{N_m} \sum_{n=1}^{N_n} \mathbf{F}(T'_m, T'_n) \exp\left(-\frac{\text{TE}_{1,i}}{T'_m}\right) \exp\left(-\frac{\text{TE}_{2,j}}{T'_n}\right) \right]^2 + \alpha \sum_{m=1}^{N_m} \sum_{n=1}^{N_n} \mathbf{F}(T'_m, T'_n)^2, \quad (14)$$

where the first term is a data-quality term with nonnegative constraints on $\mathbf{F}$, and the second term is for Tikhonov regularization. Above, N_1 and N_2 are the number of measurements in the first and second dimension, respectively; N_m and N_n are the number of sampling points in the first and second T_2' dimension, respectively; and α is the regularization parameter. Here, a robust and widely used algorithm developed by Venkataramanan *et al.*^{27,28} was used to solve Eq. (14). Details about this algorithm can be found in Refs. 27, 28, and 35 and Appendix A.

C. MDGSR framework

As discussed in the Introduction, three steps are involved in this new framework, which are also illustrated in Fig. 2. The first step is to estimate the 1D marginal distribution of $\mathbf{P}_{\text{REXSY}}$ by obtaining the 1D T_2' spectrum ($\mathbf{F}(T'_2)$) from CPMG or IR-CPMG data via 1D ILT (step 1, Section II C). The obtained 1D marginal distribution is then used to guide the subsequent sampling (step 2, Section II C) and 2D-MR spectra reconstruction (step 3, Section II C).

1. Step 1: Obtain 1D T_2' spectrum, $\mathbf{F}(T'_2)$

The $\mathbf{P}_{\text{CPMG}}$ or $\mathbf{P}_{\text{IR-CPMG}}$ is estimated by obtaining the $\mathbf{F}(T'_2)$ from the CPMG or IR-CPMG with a 1D ILT algorithm described in our previous work⁵ by minimizing $\mathcal{E}1$,

$$\begin{aligned} \mathcal{E}1 &\equiv \sum_{i=1}^{N_1} \left[\mathbf{M}(\text{TE}_i) - \sum_{m=1}^{N_m} \mathbf{F}(T'_m) \exp\left(-\frac{\text{TE}_i}{T'_m}\right) \right]^2 \\ &\quad + \alpha \sum_{m=1}^{N_m} \mathbf{F}(T'_m)^2, \end{aligned} \quad (15)$$

where the regularization factor, α , is automatically chosen by using a generalized cross-validation (GCV) method.

2. Step 2: Design and perform an optimized subsampling scheme based on $\mathbf{F}(T'_2)$

In the REXSY experiment, the total acquisition time is linearly proportional to the number of measurements in the first dimension, N_1 , and independent of the number of measurements in the second dimension, N_2 , because the second CPMG can be acquired in a single scan. Therefore, in this proposed framework, subsampling is performed in

FIG. 2. The three steps in the newly proposed MDGSR framework. (a) Step 1: obtain the 1D T_2' spectrum from CPMG or IR-CPMG data using a 1D ILT. (b) Step 2: convert the 1D T_2' spectrum to a 1D TE spectrum, and design and perform the subsampling scheme based on the 1D TE spectrum. On the top panel, the green and purple color-coded regions represent the dense sampling region and the random sampling region, respectively. The bottom panel is an example of the subsampled lines (black) in the REXSY 2D space, where the smallest TE in the first dimension was always sampled (white arrow). The background color map on the bottom panel is the REXSY simulated data as described in Sections II D and III A. (c) Step 3: perform a 2D-MR $T_2' - T_2'$ spectrum reconstruction with the 1D T_2' spectrum from step 1 as equality constraints. The T_2' and $T_2' - T_2'$ spectra come from the simulation data in Sections II D and III A. In the 2D $T_2' - T_2'$ spectrum, all the other space except for the crossing area of the two 1D projections ($F(T_2')$) masked as blue were set to be 0. Unless otherwise specified, all the figure axes in the T_2' space were in logarithmic scale and those in the TE space were in linear scale, except for the top panel in Fig. 2(b), in which the axis in TE space was in logarithmic scale.

the first dimension of REXSY but complete sampling was performed in the second dimension, which is represented by black lines in Fig. 2(b) (bottom panel).

The obtained 1D marginal distribution reveals the location of peaks in the 2D $T_2' - T_2'$ spectra; this information can be used to optimize the sampling scheme to increase efficiency. When the location of the relaxation peaks was unknown, uniform sampling or random sampling in a large dynamic range was commonly used.^{25,35} However, in a system where its T_2' is known (single relaxation pool), Jones *et al.* suggested that the sampling pattern in T_2' measurement with 22% of the sampling points at TE = 0 or smallest TE and the remaining 78% at TE = $1.28 \times T_2'$ is more efficient.^{41,42} Here, in the system where a distribution of T_2' rather than a single relaxation pool exists, our conjecture is that by randomly sampling spectral data with a frequency proportional to the known 1D T_2' spectrum, we can concentrate the sampled points at TE = $1.28 \times T_2'$ in the first dimension of REXSY data and vastly reduce the data required to obtain a robust estimate of the underlying 2D distribution.

To implement this scheme, the first step is to map $F(T_2')$ to the sampling space, echo time (TE) space, by a linear transform: $F_{\text{TE}}(\text{TE}) = F(T_2' = \text{TE}/1.28)$. Then we construct the cumulative density function (CDF) of the obtained $F_{\text{TE}}(\text{TE})$ (Fig. 2(b), top panel). We chose values of the CDF from a uniform random number distribution between 0 and 1,

from which we determine the corresponding TE value of the sampled random point on the CDF, using the inverse probability integral transform (IPIT). In practice, when the spectrum was sparse, the TE space was divided into two regions: a dense sampling region (DSR, green in Fig. 2(b), top panel), in which $F_{\text{TE}}(\text{TE})$ is greater than the threshold, and a random sampling region (RSR, purple in Fig. 2(b), top panel), in which $F_{\text{TE}}(\text{TE})$ is less than or equal to the threshold and its CDF is almost a flat line. In this work, the threshold was set to be 1% of the amplitude of the highest peak in $F_{\text{TE}}(\text{TE})$. If the number of subsampling points was equal to or larger than the size of the DSR, the entire DSR would be sampled, and the other sampling points were randomly picked from the RSR. In the other cases, no points would be picked from the RSR, and random sampling that is based on uniformly sampling the CDF of $F_{\text{TE}}(\text{TE})$ would be performed on the DSR. In both cases, the point with the smallest TE was always kept (white arrow in Fig. 2(b), bottom panel).

3. Step 3: Reconstruct 2D $T_2' - T_2'$ map with equality constraints

In Section II A, it was shown that the marginal PDFs of the $T_2' - T_2'$ exchange map in both dimensions were the same as the $F(T_2')$ estimated from the CPMG or IR-CPMG. On the basis of this finding, the $T_2' - T_2'$ space was reduced so that

only the crossing areas of the regions of $F(T'_2)$ greater than the threshold were kept (blue regions in Fig. 2(c)) while the other regions were set to zero. In this work, the threshold was set to be 1% of the amplitude of the highest peak in $F(T'_2)$. Then, the same 2D-ILT method described in Section II B was applied to the subsampled measurement data set and the reduced $T'_2 - T'_2$ space. During the 2D ILT, equality constraints forcing the marginal PDFs of the reconstructed $T'_2 - T'_2$ map to be equal to $F(T'_2)$ in both dimensions⁴³ were added to Eq. (14), which were written as

$$\begin{aligned} \sum_{m=1}^{N_m} \mathbf{F}(T'_m, T'_n) &= F(T'_2), \\ \sum_{n=1}^{N_n} \mathbf{F}(T'_m, T'_n) &= F(T'_2). \end{aligned} \quad (16)$$

It is worth noting that this strategy was originally developed and applied by Benjamini and Basser⁴³ to measure the joint radius-length distribution of capped cylindrical pores from an underdetermined system.

D. Simulations

Here a two-pool exchanging equilibrium system was used for simulation purposes. Unless otherwise specified, the following parameters were used for simulations: pool a, $M_{a0} = 0.55$, $T_{2a} = 40$ ms, $k_{ab} = 1$ s⁻¹; pool b, $M_{b0} = 0.45$, $T_{2b} = 300$ ms, $k_{ba} = M_{b0} k_{ab}/M_{a0} = 1.22$ s⁻¹. T_1 values were defined as infinitely large in all of the simulations except for the studies on the T_1 effect described in Section III E. For a two-pool exchange system, analytical solutions for the apparent relaxation time constants and pool volume fractions are also available and can be found in Ref. 19.

The CPMG, IR-CPMG, and REXSY data were generated with Eqs. (6), (8), and (10), respectively, with Gaussian noise at various signal-to-noise ratios (SNRs). Here the SNR was defined as the ratio between the amplitude of the first data point and the standard deviation of noise. In the CPMG and IR-CPMG, 300 echoes with echo spacing $\tau = 1$ ms were simulated in each echo train. The same simulation parameters were set for each dimension of REXSY. The $T'_2 - T'_2$ space ranged from 10 ms to 1000 ms in each dimension with $N_m = N_n = 100$. The same parameters were applied in the T'_2 space for the 1D ILT. Monte Carlo simulations with 100 realizations were performed for each condition to obtain stable estimates.

E. Experiments with urea-water phantom

The two-pool aqueous urea model system was chosen for this study.^{25,35,44} A urea solution was made by dissolving 0.714 mg urea powder (Sigma-Aldrich, Inc., USA) into 1 mL phosphate buffered saline (PBS, pH = 7.4) at room temperature, resulting in a urea-water proton ratio of 30%/70%. Then, 0.2 mM Gd-DTPA (Magnevist®; Berlex, Inc.) and 0.025 μ M MnCl₂ were added to the urea solution to reduce relaxation time constants. The pH of the urea solution

was titrated to 8.0 with NaOH. All NMR experiments were completed within 4 h after the solution was prepared to ensure stability of the phantom.^{25,35,44} All the experiments were performed on a 7T Bruker vertical-bore microimaging μ MRI scanner (Bruker BioSpin, Billerica, MA) at a bore temperature ($\approx 16^\circ\text{C}$). Three NMR pulse sequences were acquired on the phantom: CPMG (Fig. 1(a)), IR-CPMG (Fig. 1(b)), and REXSY (Fig. 1(c)).

In the IR-CPMG pulse sequence, a single IR point (IR = 1000 ms) was acquired with 300 echoes in the CPMG pulse trains with a temporal spacing of $\tau = 1.5$ ms. The pre-scan delay was set to 10 s to ensure full inversion recovery. A two-step phase cycling scheme was used (Fig. 1(a)) with 32 repetitions. An equilibrium CPMG echo train was also acquired with an IR of 10 s and 4 repetitions. In the REXSY experiments, the same parameters were used as in the IR-CPMG experiments, with the mixing time, $t_m = 1000$ ms. The repetition time (TR) was 10 s. Two-step phase cycling was applied with a single repetition. A gradient spoiler was placed after the IR pulse in the IR-CPMG sequence and during the mixing period in the REXSY sequence to “crush” any remaining magnetization in the transverse plane.

F. Data analysis and comparison

All simulations and data processing were performed with MATLAB® (R2015b, the MathWorks, Natick, MA). All the REXSY data were processed with two pipelines: (1) the MDGSR framework as described above and (2) a control, which consisted of random sampling in the first dimension of REXSY and direct reconstruction with the 2D ILT algorithm as described in Section II B. In the urea-water NMR experiments, the IR-CPMG data (IR = 1 s) were subtracted from the equilibrium CPMG data (IR-CPMG at IR = 10 s) to conform to the formula in Eq. (8). In the 2D $T'_2 - T'_2$ reconstruction, the IR-CPMG data were randomly selected from the 32 repetitions.

The results were quantitatively compared by calculating the relative geometric volume fraction (f) and the geometric mean T'_2 (gm T'_2 , the probability-weighted mean T'_2 in the selected volume) of each peak in each 2D-relaxation spectrum. The results of each 100 realizations were displayed as Tukey box plots, in which the notch is the median, the edges of the box are the 25th and 75th percentiles, the whisker length is 1.5, and the outliers are plotted separately. Unless otherwise specified, the displayed 2D $T'_2 - T'_2$ and 1D T'_2 spectra are the average of the 100 repetitions, and the statistical bias shown in f and gm T'_2 was normalized by the total geometric volume ($\sum f = 1$) and the analytical gm T'_2 of each peak, respectively, as the format of the median $\pm$ interquartile range (IQR).

III. RESULTS

A. Two-pool system simulations at SNR = 2000

The results of the two-pool system simulations at SNR = 2000 with the MDGSR framework and the control

FIG. 3. Simulations of the two-pool system at SNR = 2000. (a) 2D $T_2' - T_2'$ spectra from the MDGSR framework (top) and the control framework (bottom, see details in Section II F) with various N_1 . (b) Statistical results of the estimated parameters f_{aa} , $f_{ab} + f_{ba}$ and the first dimension gmT_2' of peak aa at various N_1 with the MDGSR framework and the control framework.

framework are displayed in Fig. 3. The T_2' and its relative geometric area fraction for each pool in the CPMG sequence can be analytically calculated from Eq. (7);¹⁰ these values were 38.4 ms and 49.9% for pool a, and 222.3 ms and 50.1% for pool b. In the REXSY sequence, at mixing time, $t_m = 500$ ms, Eq. (12) indicates that the relative geometric volume fractions of the molecules staying in pools a (f_{aa}) and b (f_{bb}) were 33.1% and 33.4%, respectively, and both the relative geometric volume fractions of the molecules that moved from pool a to b (f_{ab}) and from pool b to a (f_{ba}) were 16.8%.

With full data (Fig. 3(a)), both the control and the MDGSR framework resulted in four symmetric, sharp peaks that were very close to the ground truth (analytical solutions). The biases in the estimate of f of each peak compared with the ground truth were less than 0.25% (median) in the control framework and 0.14% (median) for the MDGSR framework. As for the estimate of gmT_2' , the bias was less than 0.16% (median) for the control and 0.12% (median) for the MDGSR framework (Fig. 3(b)). As the number of data points in the first dimension was reduced, the 2D $T_2' - T_2'$ spectra from the control became blurred and biased, while the estimates using the MDGSR framework did not change (Fig. 3(a)). In estimating f and gmT_2' , the MDGSR framework also showed greater accuracy and consistency than the control

(Fig. 3(b)) and maintained the quality of the 2D $T_2' - T_2'$ spectra up to $N_1 = 2$. For example, at $N_1 < 20$, large outliers and symmetrical biases started to show up in both the f estimation, e.g., f_{aa} and $f_{ab} + f_{ba}$, and the gmT_2' , e.g., the first dimension gmT_2' of peak aa, as shown in Fig. 3(b). At $N_1 = 5$, the f_{aa} was underestimated $11.6\% \pm 10.2\%$ by the control while the bias in the MDGSR framework was still in the range of $0.15\% \pm 0.08\%$. Even at $N_1 = 3$ and $N_1 = 2$, the bias of f_{aa} with the MDGSR framework was still less than $0.23\% \pm 0.13\%$ and $0.38\% \pm 0.29\%$, respectively.

B. Effects of each step

To study the effects of each step in the MDGSR framework, another set of simulations was performed in which step 2 was replaced with random sampling in the first dimension, or step 3 was replaced with normal 2D-ILT reconstruction as described in Section II B. The other simulation setup parameters were the same as those described in Section III A except that only $N_1 = 3$ was performed here. Parts of the statistical results of the simulation data are shown in Fig. 4. The major effect of the optimized subsampling pattern here was to stabilize the results and reduce variance. For example, in the estimation of f_{aa} and $f_{ab} + f_{ba}$, normal 2D ILT with optimized sampling

FIG. 4. The effect of each step in the new framework: statistical results of the parameters f_{aa} , $f_{ab} + f_{ba}$ and the first dimension gmT'_2 of peak aa with the control and the MDGSR framework with and without step 2 or step 3.

as step 2 reduced the IQR from 17.2% to 0.48% and from 7.3% to 2.9%, respectively, while the median of bias stayed fairly consistent (from -18.4% to -18.5% and from -17.2% to -14.2% , respectively), compared with random sampling in the first dimension. With step 3 reserved, step 2 also reduced the IQR from 0.42% to 0.13% and 0.75% to 0.29% in the estimate of f_{aa} and $f_{ab} + f_{ba}$, respectively, compared with random sampling in the first dimension. The correction of the

systematic bias mainly relied on step 3. After step 3 replaced the normal 2D ILT reconstruction, the systematic biases were successfully corrected in all the statistical parameters (Fig. 4).

C. SNR dependence

The effect of the SNR was studied by performing the same two-pool system simulations as those described in

FIG. 5. SNR dependence. (a) 2D $T'_2 - T'_2$ spectra from the full data with normal 2D ILT at SNR = 200 (left) and 500 (middle), and 1D T'_2 spectra from CPMG data with 1D ILT at various SNRs (right). ((b) and (c)) 2D $T'_2 - T'_2$ spectra (b) and statistical results of the parameters f_{aa} , $f_{ab} + f_{ba}$ and the first dimension gmT'_2 of peak aa from subsampled data ($N_1 = 3$) (c) with the MDGSR framework and various numbers of averages in the CPMG in the 1D T'_2 spectra estimation.

Section III A with the SNR varying from 100 to 2000. The blurring artifacts from noise showed up in both the 2D $T_2' - T_2'$ spectra from the full data with normal 2D ILT and 1D T_2' spectra from the CPMG data with 1D ILT as the noise level increased (Fig. 5(a)). The inaccurate estimation of the 1D T_2' spectra also resulted in blurring of the 2D $T_2' - T_2'$ spectra (Fig. 5(b)) and biased estimation of f of each magnetization pool (Fig. 5(c)), when the results were obtained with the MDGSR framework ($N_1 = 3$). One strategy to overcome the errors caused by the inaccurate estimation of 1D T_2' spectra is to improve the SNR of the CPMG signal by averaging more CPMG repetitions. As shown in Fig. 5(b), the blurring artifacts in the 2D $T_2' - T_2'$ spectra with the MDGSR framework at SNR = 200 were corrected step by step as the number of the averages in the CPMG increased from 1 to 16. Furthermore, the biases in the estimate of f were largely corrected at SNR ≥ 200 , e.g., at SNR = 300, the bias of $f_{ab} + f_{ba}$ was corrected from $8.5\% \pm 5.7\%$ to $1.1\% \pm 0.9\%$ with the number of averages in the CPMG increased from 1 to 16. The biases in the gmT_2' estimation were relatively small, but the addition of the averages in the CPMG still improved the accuracy, e.g., at SNR = 300, the biases in the 1D gmT_2' of peak aa

were changed from $-0.3\% \pm 1.2\%$ to $-0.2\% \pm 0.4\%$ with the number of averages in the CPMG increased from 1 to 16.

D. Mixing-time dependence

The MDGSR framework showed consistently good performance at various mixing times (10 ms, 100 ms to 2000 ms with a step of 100 ms) in simulation data (SNR = 2000). As shown in Figs. 6(a) and 6(b), the reconstructed 2D $T_2' - T_2'$ spectra from the subsampled data ($N_1 = 3$) with the MDGSR framework showed good matching with those reconstructed from the full data with normal 2D ILT. The essential parameters, f and gmT_2' , also showed consistency with the ground truth and stability at various mixing times (Fig. 6(c)), although small biases in f were observed at extremely short mixing times when the off-diagonal peaks were nearly 0, e.g., the biases in f_{aa} were $0.02\% \pm 0.10\%$ at $t_m = 2000$ ms, $-0.53\% \pm 0.28\%$ at $t_m = 100$ ms, and $-0.82\% \pm 0.47\%$ at $t_m = 10$ ms. However, these biases are negligible compared with the large dynamic range of f_{aa} from $t_m = 10$ ms to $t_m = 2000$ ms.

FIG. 6. Mixing-time dependence. 2D $T_2' - T_2'$ spectra from the full data with normal 2D ILT (a) and from the subsampled data ($N_1 = 3$) with the MDGSR framework (b) at various mixing times. (c) Statistical results of the parameters f_{aa} , $f_{ab} + f_{ba}$ and the first dimension gmT_2' of peak aa from subsampled data ($N_1 = 3$) with the MDGSR framework at various mixing times.

FIG. 7. T_1 correction. (a) 1D $F(T_2')$ of IR-CPMG data at various IR. (b) The relative geometric area fraction of the peak with small T_2' peak in $F(T_2')$ at various IR. (c) Statistical results of the parameters f_{aa} , $f_{ab} + f_{ba}$, and the first dimension gmT_2' of peak aa from 2D $T_2' - T_2'$ spectra reconstructed from subsampled data ($N_1 = 3$) via the MDGSR framework with IR-CPMG data or CPMG data. (d) 2D $T_2' - T_2'$ spectra from the full data with normal 2D ILT (left) and from the subsampled data ($N_1 = 3$) via the MDGSR framework with the CPMG data (middle) and the IR-CPMG data (right).

E. T_1 correction

When the T_1 effect cannot be ignored in REXSY, the CPMG signal should be replaced by the IR-CPMG signal, that is, $IR = t_m$. This approach was validated by performing simulations with $T_1 = 500$ ms for pool a and $T_1 = 2000$ ms for pool b. As shown in Fig. 7(a), the 1D $F(T_2')$ of IR-CPMG showed continuous changes in the amplitudes rather than in the position of the two peaks in the T_2' dimension as the IR increased. The relative geometric area fraction of the peak with small T_2' , $f(a)$, from the 1D $F(T_2')$ of IR-CPMG also agreed with the analytical solutions (Eq. (12), Fig. 7(b)). With CPMG data, the reconstructed 2D $T_2' - T_2'$ spectra showed strong bias from the ground truth (Fig. 7(d)) with an overestimation of f_{aa} by $19.5\% \pm 1.4\%$ and an underestimation of $f_{ab} + f_{ba}$ by $16.5\% \pm 2.7\%$ (Fig. 7(c)). With IR-CPMG data, more accurate 2D $T_2' - T_2'$ spectra were achieved (Fig. 7(d)) with the biases in f_{aa} and $f_{ab} + f_{ba}$ corrected back to $-0.3\% \pm 0.2\%$ and $0.3\% \pm 0.4\%$, respectively (Fig. 7(c)). The biases in the gmT_2' were small and comparable in both cases, which agreed with the theory.

F. Urea-water phantom

With the full data set, the control and MDGSR framework closely estimated the 2D $T_2' - T_2'$ spectra, but the MDGSR framework showed sharper peaks that were closer to being delta functions (Figs. 8(a) and 8(b)). In the control, 2D $T_2' - T_2'$ spectra started to blur as N_1 decreased, while the results from the MDGSR framework were consistent until $N_1 \geq 3$. The essential parameters, f and gmT_2' , also showed consistency in the MDGSR framework as N_1 decreased, e.g., at $N_1 = 3$, the

biases in the f_{aa} , $f_{ab} + f_{ba}$ and the first dimension gmT_2' of peak aa were $0.0\% \pm 0.2\%$, $0.0\% \pm 0.4\%$, and $-0.6\% \pm 0.3\%$, respectively, while those in the control were $-5.0\% \pm 1.3\%$, $-14.9\% \pm 6.2\%$, and $-7.7\% \pm 6.6\%$, respectively.

G. Comparison with CS

This new approach was compared with the CS framework (see Appendix B) proposed previously,³⁵ by testing the simulation data in Section III A and the urea-water phantom experimental data in Section III F with the CS framework with the same acceleration factors ($R \equiv N_1$ in the full sampling/ N_1 in the subsampling) as those in Sections III A and III F. In the simulation results from the CS framework, systematic bias with increasing variance appeared at $R \geq 15$ (corresponding to $N_1 \leq 20$, Fig. 9(c)) with blurring in the average 2D $T_2' - T_2'$ spectra (Fig. 9(a)), where the MDGSR framework can reach $R = 150$ (corresponding to $N_1 = 2$). In the urea-water phantom results from the CS framework, the quality of the 2D $T_2' - T_2'$ spectra declined quickly at $R \geq 12$ (corresponding to $N_1 \leq 25$, Figs. 9(b) and 9(c)), where the MDGSR framework can reach $R = 99$ (corresponding to $N_1 = 3$).

IV. DISCUSSION

In this work, our main objective was to further accelerate the data acquisition and reconstruction of a specific subgroup of the multidimensional MR relaxation and diffusion spectra, the 2D-MR $T_2' - T_2'$ exchange spectra, by taking full advantages of one important property of the 2D-MR $T_2' - T_2'$ exchange spectrum obtained from REXSY: its marginal distribution in

FIG. 8. Urea-water phantom NMR experiments. (a) 2D $T_2' - T_2'$ spectra from the MDGSR framework (top) and the control (bottom) with various N_1 . (b) Statistical results of the parameters f_{aa} , $f_{ab} + f_{ba}$, and the 1D gmT_2' of peak aa from 2D $T_2' - T_2'$ spectra reconstructed with the control pipeline and MDGSR framework at various N_1 .

both dimensions are equal and can be quickly and accurately estimated from a single CPMG or IR-CPMG measurement. First, we extended a recently proposed experimental and processing framework (MADCO³⁷) to include judicious informed data sampling of the 2D space, the obtained marginal distribution. The 1D T_2' PDF was used as *a priori* knowledge to both optimize the subsampling scheme and provide constraint in the reconstruction of the 2D $T_2' - T_2'$ spectra. The efficiency of the proposed framework, MDGSR, in maintaining the quality of the 2D-MR $T_2' - T_2'$ exchange spectra was validated with both numerical simulations and NMR experiments on a urea-water phantom.

Compared with the CS framework we proposed previously,^{35,36} the MDGSR framework shows at least two obvious advantages. First, the MDGSR framework achieves a much higher acceleration factor (almost an order of magnitude) than the previous CS method. In the two-pool exchange simulations, the MDGSR framework can still estimate the 2D $T_2' - T_2'$ spectra at $N_1 = 2$ or 3 (the corresponding acceleration factor $R = 150$ or 100) with very high quality, while the CS method can achieve $R \sim 10$ only. The performance of the MDGSR framework is equally good across a large dynamic range with mixing times ranging from 10 ms to 2000 ms (Section III D). In the urea-water phantom NMR experiments, the MDGSR framework can achieve $R = 99$ ($N_1 = 3$) and reduce the scan time for a single 2D $T_2' - T_2'$ spectrum from 100 min to 1 min, while

the CS method can achieve $R \sim 12$ ($N_1 = 25$) and reduce the scan time to 8 min only. Second, the MDGSR framework is more practical than the CS framework in the applications of REXSY. In most applications on porous media, the second CPMG in REXSY is collected in a single scan, and the number of echoes in the first CPMG is changed step by step. The MDGSR framework takes into account the nature of this sequence and applies acceleration on the first CPMG only, while the CS framework needs subsampling in both dimensions.

This new experimental design and processing framework has three steps: (1) obtaining the correct $F(T_2')$ from the CPMG or IR-CPMG; (2) subsampling in the first dimension of REXSY based on $F(T_2')$ while the whole acquisition in second dimension is kept, and the subsequent REXSY 2D data are acquired; and (3) performing 2D $T_2' - T_2'$ spectral reconstruction with $F(T_2')$ as equality constraints. Steps 2 and 3 strongly depend on the accuracy of step 1, which means that the quality of the final reconstructed 2D $T_2' - T_2'$ spectra requires accurate 1D $F(T_2')$ estimation. In the low SNR regime, the CPMG or IR-CPMG can be averaged to improve the accuracy of the $F(T_2')$ estimation. In Section III C, we demonstrated that by increasing the number of the averages in the CPMG, the quality of the 2D $T_2' - T_2'$ spectra via this MDGSR framework was significantly improved; therefore, this MDGSR framework is practical in the low SNR regime. In cases in which the T_1 plays an important role during the

FIG. 9. ((a) and (b)) 2D $T_2' - T_2'$ spectra from the CS framework from the simulation data (a) and urea-water phantom data (b) at various R . (c) and (d) Statistical results of the parameters $f_{ab} + f_{ba}$ from 2D $T_2' - T_2'$ spectra reconstructed from the simulation data (c) and urea-water phantom data (d) with the CS framework and the MDGSR framework at various R . At (c) and (d), some data from CS framework are out of range and not fully displayed for display purpose.

mixing time in REXSY, the incorrectly estimated $F(T_2')$ from the CPMG induced a strong bias in the 2D $T_2' - T_2'$ spectra (Fig. 7). With a correct estimation of $F(T_2')$ from the IR-CPMG, the quality of the 2D $T_2' - T_2'$ spectra was maintained. Step 2 provides an optimized subsampling scheme that stabilizes the results compared with results from random sampling. Step 3 is essential to ensure that the peaks are located in the right position with the correct amplitude in the reconstructed 2D $T_2' - T_2'$ spectra.

In this paper, we demonstrated that this MDGSR framework performed well in a large range of SNRs and mixing times, making it practical for many applications in NMR spectroscopy from low to high field, e.g., the NMR analysis of materials and specimen. It also has the potential to be used to obtain 2D $T_2' - T_2'$ spectra in biological samples when there are many detectable water exchange processes.^{23,24,45} Some modifications might be needed in specific implementations of this method. For example, in the low-field regime, such as in one-sided NMR applications, in which the SNR is also low, more averages can be added to improve the accuracy of the $F(T_2')$ estimation. When the specimen is strongly heterogeneous and its $F(T_2')$ is very broad and cannot be accurately estimated from 1D CPMG or IR-CPMG, the 1D marginal distribution of the 2D $T_2' - T_2'$ spectrum result from a single REXSY experiment with enough data sampled at a fixed mixing time can be used as $F(T_2')$.

Because the same $F(T_2')$ is used for all the 2D $T_2' - T_2'$ spectra with different mixing times, the total scan time can still be significantly reduced though the maximum acceleration factor can be smaller than the results presented in this paper.

Another potential application of this MDGSR framework is to make the 2D-MR exchange spectra fast enough and practical for MRI studies on biological samples, preclinically and clinically. Living tissue is naturally heterogeneous; the water inside is distributed among different compartments, such as intracellular water, interstitial water, and vascular water. The water exchange frequency between these compartments characterizes the integrity of cell membranes or vascular walls and may be a useful new biomarker in development, degeneration, aging, and disease. In most MRI applications, only the magnitude data are collected. Therefore, Rician noise correction will be needed in both the estimation of $F(T_2')$ and 2D $T_2' - T_2'$ spectral reconstruction to avoid systemic biases.^{5,35} Additionally, obtaining $F(T_2')$ from the whole volume rather than from a single voxel should be used in step 2.

The first potential MRI application of this framework can be quantitatively mapping the amount of myelin water (MW) and its exchange frequency or rate with the intracellular/extracellular water. The water molecules trapped in the space between the lipid membranes in the myelin sheath have a shorter T_2 than that of intracellular/extracellular

water naturally.⁴⁶ Based on this contrast, the multiple spin-echo MRI sequence has already been used to obtain the 1D T_2' spectrum for each imaging voxel and characterize the myelin water fraction (MWF) from this 1D T_2' spectrum, both preclinically and clinically.^{5,46–48} However, the MWF obtained from this 1D T_2' spectrum can be underestimated due to the intercompartment water exchange.⁴⁹ By implementing this new framework and modifying the 1D multiple spin-echo MRI sequence to a 2D MRI $T_2 - T_2$ sequence (e.g., adding a T_2 -preparation module in front of the 1D multiple spin-echo MRI sequence), both the MWF and the water exchange between MW and other compartments can be accurately determined in a practical amount of time. For a typical case within reasonable SNR, a matrix size of 32×32 in the $T_2 - T_2$ encoding is required to get a good 2D $T_2 - T_2$ reconstruction via 2D ILT. If we assume that the other imaging parameters are spatial matrix size 64×64 , TR 5 s, two-step phase cycling, single repetition, and the total scan time of the full data set would be 5.7 h for a single mixing time. While our previous CS framework might reduce the scan time to 4.4 h ($N_1 = 25$, from urea phantom data), the newly proposed framework can reduce scan time to 0.5 h ($N_1 = 3$), which is more practical for most preclinical and clinical studies.

With the exception of 2D $T_2 - T_2$ exchange spectra, this framework can also be easily adapted and applied to other types of 2D-MR exchange spectral acquisitions, e.g., $D - D$, $T_2^* - T_2^*$ exchange spectra. In addition, any multidimensional (3D or greater) experiment for which 1D marginal distributions can be readily obtained would provide sufficient *a priori* information for the design of subsequent secondary experiments and reconstruction of the multidimensional spectra that use this *a priori* information.

V. CONCLUSION

A recently introduced experimental and analytical framework was expended and validated to significantly reduce the amount of data and MR scan time required for obtaining high-quality 2D-MR exchange spectra. This framework takes advantage of one intrinsic property of 2D-MR exchange spectra: the fact that their 1D marginal distributions can be obtained rapidly and accurately. This 1D marginal distribution is then used as *a priori* information to design the subsampling scheme and reconstruct the resulting 2D spectra. The efficiency of this framework has been validated in both simulations and NMR spectroscopy experiments. We expect that this 2D [and higher (ND)] MR sampling and reconstruction scheme will facilitate data collection and reconstruction in systems for which it is currently not possible to estimate robust and reliable 2D spectra or spectra of higher dimensions.

ACKNOWLEDGMENTS

This work was supported by the Intramural Research Program (IRP) of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH.

We thank our colleague, Dr. Alexandru Avram, for helpful discussions. We are also grateful to our colleagues Dr. Michal Komlosh and Dr. Elizabeth Hutchinson for assistance with NMR experiments.

APPENDIX A: 2D ILT

The essential step of the 2D ILT developed by Venkataramanan *et al.*^{27,28} is to rewrite Eq. (14) into the form of a kernel matrix and reduce the size of the 2D matrices associated with the measurement data by singular value decomposition (SVD),

$$\begin{aligned}\hat{\mathbf{F}} &= \arg \min_{\mathbf{F} \geq 0} \|\mathbf{M} - \mathbf{K}_1 \mathbf{F} \mathbf{K}_2^T\|^2 + \alpha \|\mathbf{F}\|^2 \\ &= \arg \min_{\mathbf{F} \geq 0} \|\mathbf{U}_1 \hat{\mathbf{M}} \mathbf{U}_2^T - \mathbf{U}_1 \mathbf{U}_1^T \mathbf{K}_1 \mathbf{F} \mathbf{K}_2^T \mathbf{U}_2 \mathbf{U}_2^T\|^2 \\ &\quad + \|\mathbf{M}\|^2 - \|\mathbf{U}_1 \hat{\mathbf{M}} \mathbf{U}_2^T\|^2 + \alpha \|\mathbf{F}\|^2 \\ &= \arg \min_{\mathbf{F} \geq 0} \|\hat{\mathbf{M}} - (\mathbf{S}_1 \mathbf{V}_1^T) \mathbf{F} (\mathbf{S}_2 \mathbf{V}_2^T)^T\|^2 + \alpha \|\mathbf{F}\|^2, \quad (\text{A1})\end{aligned}$$

where $\|\cdot\|$ is the Frobenius norm of a matrix; $\mathbf{K}_1$ and $\mathbf{K}_2$ are the kernels of the first and second dimension with the matrix size $N_1 \times N_m$ and $N_2 \times N_n$; and the SVD of $\mathbf{K}_i$ ($i \in \{1, 2\}$) is $\mathbf{K}_i = \mathbf{U}_i \mathbf{S}_i \mathbf{V}_i^T$. By truncating the small singular values with a threshold, $\mathbf{S}_i$ can be reduced to a much smaller matrix with dimensions $N_i \times s_i$. Then, the data matrix $\mathbf{M}$ can be projected onto the column space of $\mathbf{K}_1$ and the row space of $\mathbf{K}_2$ with a much smaller dimension: $\hat{\mathbf{M}} = \mathbf{U}_1^T \mathbf{M} \mathbf{U}_2$ with the new matrix size $s_1 \times s_2$.^{27,28} The third line in Eq. (A1) comes from $\mathbf{U}_1$ and $\mathbf{U}_2$ having orthogonal columns; the second and third terms in the second line drop out because they are independent of $\mathbf{F}$. A method based on generalized cross validation (GCV) was used to determine the regularization parameter, α .³¹

APPENDIX B: CS

In our previous work,^{35,36} a CS method was developed and implemented to reduce the number of measurements required to reconstruct 2D-MR relaxation spectra. Here we provide a brief summary. Subsampling was achieved by randomly sampling the 2D-relaxometry data matrix. Then, the compressed data, $\hat{\mathbf{M}}$, were reconstructed from the subsamples based on the fact that $\hat{\mathbf{M}}$ has rapidly decaying singular values with a singular value threshold algorithm.³⁶ This algorithm searches for the matrix $\mathbf{X}$ that minimizes the sum of the singular values, while matching the measurements $\mathbf{M} = \mathbf{U}_1 \mathbf{X} \mathbf{U}_2^T$. The solution to this optimization problem, then, has a high probability, close to $\hat{\mathbf{M}}$, of being up to a constant factor of the noise.³⁶ Then the 2D-relaxation spectra were calculated from the reconstructed data with the 2D ILT as described in Section II B.

¹P. T. Callaghan, *Principles of Nuclear Magnetic Resonance Microscopy* (Oxford University Press, New York, 1991).

²A. MacKay, C. Laule, I. Vavasour, T. Bjarnason, S. Kolind, and B. Mädler, *Magn. Reson. Imaging* **24**, 515 (2006).

³S. Peled, D. G. Cory, S. A. Raymond, D. A. Kirschner, and A. Jolesz, *Magn. Reson. Med.* **42**, 911 (1999).

⁴E. J. Fordham, A. Sezginer, and L. D. Hall, *J. Magn. Reson., Ser. A* **113**, 139 (1995).

- ⁵R. Bai, C. G. Koay, E. Hutchinson, and P. J. Basser, *J. Magn. Reson.* **244**, 53 (2014).
- ⁶N. Wang and Y. Xia, *J. Magn. Reson.* **212**, 124 (2011).
- ⁷Y.-Q. Song, *New J. Phys.* **14**, 055017 (2012).
- ⁸Y.-Q. Song, H. Cho, T. Hopper, A. E. Pomerantz, and P. Z. Sun, *J. Chem. Phys.* **128**, 052212 (2008).
- ⁹P. McDonald, J.-P. Korb, J. Mitchell, and L. Monteilhet, *Phys. Rev. E* **72**, 011409 (2005).
- ¹⁰P. J. McDonald, J. Mitchell, M. Mulheron, P. S. Aptaker, J.-P. Korb, and L. Monteilhet, *Cem. Concr. Res.* **37**, 303 (2007).
- ¹¹M. D. Does and R. E. Snyder, *Magn. Reson. Imaging* **13**, 575 (1995).
- ¹²M. D. Does, C. Beaulieu, P. S. Allen, R. E. Snyder, and R. I. E. S. Nyder, *Magn. Reson. Imaging* **16**, 1033 (1998).
- ¹³R. Harrison, M. J. Bronskill, and R. M. Henkelman, *Magn. Reson. Med.* **33**, 490 (1995).
- ¹⁴P. T. Callaghan, C. H. Arns, P. Galvosas, M. W. Hunter, Y. Qiao, and K. E. Washburn, *Magn. Reson. Imaging* **25**, 441 (2007).
- ¹⁵P. T. Callaghan and I. Furó, *J. Chem. Phys.* **120**, 4032 (2004).
- ¹⁶Y. Qiao, P. Galvosas, T. Adalsteinsson, M. Schönhoff, and P. T. Callaghan, *J. Chem. Phys.* **122**, 214912 (2005).
- ¹⁷K. Washburn and P. Callaghan, *Phys. Rev. Lett.* **97**, 175502 (2006).
- ¹⁸P. Galvosas, Y. Qiao, M. Schönhoff, and P. T. Callaghan, *Magn. Reson. Imaging* **25**, 497 (2007).
- ¹⁹L. Monteilhet, J.-P. Korb, J. Mitchell, and P. McDonald, *Phys. Rev. E* **74**, 061404 (2006).
- ²⁰L. M. Burcaw and P. T. Callaghan, *J. Magn. Reson.* **198**, 167 (2009).
- ²¹G. Benga, *Prog. Biophys. Mol. Biol.* **51**, 193 (1988).
- ²²Y. Zhang, M. Poirier-Quinot, C. S. Springer, and J. A. Balschi, *Biophys. J.* **101**, 2833 (2011).
- ²³W. D. Rooney, X. Li, M. K. Sammi, D. N. Bourdette, E. A. Neuwelt, and C. S. Springer, *NMR Biomed.* **28**, 607 (2015).
- ²⁴J. D. Quirk, G. L. Bretthorst, T. Q. Duong, A. Z. Snyder, C. S. Springer, J. J. H. Ackerman, and J. J. Neil, *Magn. Reson. Med.* **50**, 493 (2003).
- ²⁵R. D. Dortch, R. A. Horch, and M. D. Does, *J. Chem. Phys.* **131**, 164502 (2009).
- ²⁶J. H. Lee, C. Labadie, C. S. Springer, and G. S. Harbison, *J. Am. Chem. Soc.* **115**, 7761 (1993).
- ²⁷Y.-Q. Song, L. Venkataramanan, M. D. Hürlimann, M. Flaum, P. Frulla, and C. Straley, *J. Magn. Reson.* **154**, 261 (2002).
- ²⁸L. Venkataramanan, Y. Song, and M. D. Hürlimann, *IEEE Trans. Signal Process.* **50**, 1017 (2002).
- ²⁹N. Marigheto, L. Venturi, D. Hibberd, K. M. Wright, G. Ferrante, and B. P. Hills, *J. Magn. Reson.* **187**, 327 (2007).
- ³⁰E. W. Abel, T. P. J. Coston, K. G. Orrell, V. Sik, and D. Stephenson, *J. Magn. Reson.* **70**, 34 (1986).
- ³¹J. Mitchell, T. C. Chandrasekera, and L. F. Gladden, *Prog. Nucl. Magn. Reson. Spectrosc.* **62**, 34 (2012).
- ³²R. D. Dortch, K. D. Harkins, M. R. Juttukonda, J. C. Gore, and M. D. Does, *Magn. Reson. Med.* **70**, 1450 (2013).
- ³³M. N. d'Eurydice, E. T. Montrazi, C. A. Fortulan, and T. J. Bonagamba, *J. Chem. Phys.* **144**, 204201 (2016).
- ³⁴R. Song, Y.-Q. Song, M. Vembusubramanian, and J. L. Paulsen, *J. Magn. Reson.* **265**, 164 (2016).
- ³⁵R. Bai, A. Cloninger, W. Czaja, and P. J. Basser, *J. Magn. Reson.* **255**, 88 (2015).
- ³⁶A. Cloninger, W. Czaja, R. Bai, and P. J. Basser, *SIAM J. Imaging Sci.* **7**, 1775 (2014).
- ³⁷D. Benjamini and P. J. Basser, *J. Magn. Reson.* **271**, 40 (2016).
- ³⁸F. Bloch, *Phys. Rev.* **70**, 460 (1946).
- ³⁹H. M. McConnell, *J. Chem. Phys.* **28**, 430 (1958).
- ⁴⁰M. V. Landeghem and A. Haber, *Concepts Magn. Reson., Part A* **36A**, 153 (2010).
- ⁴¹J. A. Jones, *J. Magn. Reson.* **126**, 283 (1997).
- ⁴²J. A. Jones, P. Hodgkinson, A. L. Barker, and P. J. Hore, *J. Magn. Reson., Ser. B* **113**, 25 (1996).
- ⁴³D. Benjamini and P. J. Basser, *J. Chem. Phys.* **141**, 214202 (2014).
- ⁴⁴R. A. Horch and M. D. Does, *Magn. Reson. Mater. Phys., Biol. Med.* **20**, 51 (2007).
- ⁴⁵C. S. Landis, X. Li, F. W. Telang, P. E. Molina, I. Palyka, G. Vetek, and C. S. Springer, *Magn. Reson. Med.* **42**, 467 (1999).
- ⁴⁶C. Laule, I. M. Vavasour, S. H. Kolind, D. K. B. Li, T. L. Traboulsee, G. R. W. Moore, and A. L. MacKay, *Neurotherapeutics* **4**, 460 (2007).
- ⁴⁷A. Mackay, K. Whittall, J. Adler, D. Li, D. Paty, and D. Graeb, *Magn. Reson. Med.* **31**, 673 (1994).
- ⁴⁸E. P. Minty, T. A. Bjarnason, C. Laule, and A. L. MacKay, *Magn. Reson. Med.* **61**, 883 (2009).
- ⁴⁹K. D. Harkins, A. N. Dula, and M. D. Does, *Magn. Reson. Med.* **67**, 793 (2012).