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Relaxation-Assisted Separation of Overlapping Patterns in Ultra-Wideline NMR Spectra

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14 **Relaxation-Assisted Separation of**
15 **Overlapping Patterns**
16 **in Ultra-Wideline NMR Spectra**
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Abstract

Efficient acquisition of high-quality ultra-wideline (UW) solid-state NMR powder patterns in short experimental time frames is challenging. UW NMR powder patterns often possess inherently low S/N and usually overlap for samples containing two or more magnetically distinct nuclides, which obscures spectral features and drastically lowers the spectral resolution. Currently, there is no reliable method for resolving overlapping powder patterns originating from unresponsive nuclei affected by large anisotropic NMR interactions. Herein, we discuss new methods for resolving individual UW NMR spectra associated with magnetically distinct nuclei by exploiting their different relaxation characteristics using 2D relaxation-assisted separation (RAS) experiments. These experiments use a non-negative Tikhonov fitting (NNTF) routine to process high-quality T_1 and T_2^{eff} relaxation datasets in order to produce high-resolution, 2D spin-relaxation correlation spectra for both spin-1/2 and quadrupolar nuclei in organic and organometallic solids under static (*i.e.*, stationary) conditions. It is found that (i) T_2^{eff} RAS datasets can be acquired in a fraction of the time required for analogous T_1 RAS datasets, since a time-incremented 2D dataset is not required for the former; and (ii) Tikhonov regularization is superior to conventional non-negative least squares fitting, as it more reliably and robustly results in cleaner separation of patterns based on relaxation time constants.

1. Introduction

Many elements that are of great importance in chemistry, physics, biology, and materials science have isotopes that are unresponsive to the NMR experiment due to low gyromagnetic ratios (γ), low natural abundances, and/or unfavorable relaxation characteristics (*i.e.*, long longitudinal and/or short transverse relaxation

1 time constants, denoted T_1 and T_2 , respectively). For *solid-state NMR* (SSNMR), the
2 problem of sensitivity is further exacerbated by the anisotropy (*i.e.*, orientation-
3 dependence) of the NMR interactions, which give rise to inhomogeneously
4 broadened powder patterns that span wide spectral regions. So-called *ultra-wideline*
5 *NMR* (UW NMR) powder patterns are extremely broad, possess low signal-to-noise
6 ratios (S/N), and have poor resolution. Such spectra are commonly observed for
7 both spin $I = 1/2$ nuclides affected by large chemical shielding anisotropies (CSAs)
8 and quadrupolar nuclides ($I > 1/2$) influenced by both large quadrupolar coupling
9 constants (C_Q) and/or large CSAs. Enhancement of signal and improvement of
10 pattern resolution remain as prime challenges in UW NMR spectroscopy.^{1,2}

11 Several acquisition strategies have been developed to improve the low S/N
12 ratios commonly observed in UW NMR spectra. Foremost among these strategies is
13 the use of high magnetic field strengths; also common are specialized hardware and
14 pulse sequences designed for the study of unresponsive nuclides. The former is ideal
15 for half-integer quadrupolar nuclei, since the pattern breadths scale at the inverse of
16 the applied magnetic strength, but is less effective for patterns arising from spin-half
17 nuclei for which the CSA is dominant (breadths scale proportional to the field
18 strength) or integer spin nuclei (breadths do not scale with field strength). The latter
19 remain the most direct and cost effective way of enhancing the S/N. For instance,
20 WURST (Wideband, Uniform-Rate, Smooth-Truncation) pulses^{3,4} provide uniform
21 excitation of UW NMR powder patterns, through the combined modulation of their
22 amplitude and phase.^{5,6} The so-called WURST-CPMG (WCPMG) pulse sequence
23 (see Supporting Information, **SI, Figure S1a**), which uses a series of WURST
24 refocusing pulses for T_2 -dependent signal enhancement, has proven particularly
25 effective for collecting high-quality UW NMR powder patterns for both spin-1/2 and

quadrupolar nuclei.^{6–13} Cross-polarization (CP) from abundant high- γ to dilute low- γ nuclei is also extensively employed for enhancing S/N,¹⁴ and is particularly useful for studying unreceptive nuclides with long T_1 constants. Conventional CP employing monochromatic, rectangular spin-locking pulses can have limited use in the collection of UW NMR spectra due to its narrow excitation bandwidth. The *Broadband Adiabatic-Inversion Cross-Polarization* pulse sequence (BRAIN-CP, **Figure S1b**), which employs a frequency-swept WURST pulse on the low- γ nucleus during the spin locking period, provides the broad excitation bandwidth necessary for rapidly collecting distortionless, high S/N UW NMR spectra. The BRAIN-CP/WURST-CPMG pulse sequence (BCP for brevity) has been used to collect CSA-broadened UW NMR spectra for spin-1/2 nuclides in inorganic materials,¹⁵ as well as ¹⁴N NMR spectra of organic compounds, both under static conditions (*i.e.*, stationary samples).^{16,17}

More challenging remains the issue of improving site resolution in UW NMR spectra. Spectral resolution in SSNMR experiments is usually improved by magic-angle spinning (MAS), which spatially averages all anisotropic NMR interactions to first order (*e.g.*, the chemical shift and first-order quadrupolar interactions). Unfortunately, for most UW NMR applications, MAS is insufficient for efficiently averaging the anisotropic interactions, given the unrealizable spinning speeds that are needed for dealing with powder patterns that are several hundred kHz to several MHz in breadth.¹⁸ Moreover, for half-integer quadrupolar nuclides, it is not possible to completely average the inhomogeneous broadening that results from the quadrupolar interaction by spinning at any fixed rotor angle.¹⁹ In fact, it has been demonstrated for MAS NMR spectra of both spin-1/2 and half-integer quadrupolar nuclides with very broad anisotropic patterns that there are numerous challenges

1 associated with accurately extracting reliable tensor parameters, including (i) the
2 difficulty of uniformly exciting the entire spinning sideband (SSB) manifold, (ii) the
3 need for very stable MAS and an accurately set magic angle, (iii) low S/N due to the
4 wide spread of spinning sideband frequencies, (iv) the need for multiple spinning
5 speeds to accurately determine isotropic chemical shift values, and (v) residual
6 inhomogeneous broadening that results from the second-order quadrupolar
7 interaction, which is encountered even in the narrowest central-transition (CT)
8 powder patterns of half-integer quadrupolar nuclei.^{20–22} Techniques like multiple-
9 quantum MAS (MQMAS), satellite-transition MAS (STMAS) and hardware-related
10 methods (e.g., DOR and DAS) are capable of averaging second-order quadrupolar
11 anisotropies, but are only effective for quadrupolar nuclides with relatively small
12 values of C_Q .^{23–29}

13 With these sensitivity and resolution challenges in mind, this work discusses a
14 technique that can be used for resolving overlapping UW NMR powder patterns
15 arising from magnetically distinct nuclides in static NMR spectra, while endowing
16 them with enhanced S/N. As a starting point for separating overlapping powder
17 patterns, we extend the idea of relaxation-assisted separation (RAS) initially
18 proposed by Frydman *et al.*,³⁰ and exploit the different relaxation characteristics at
19 magnetically inequivalent sites to resolve their powder patterns. Non-negative
20 Tikhonov fitting (NNTF) routines are used to process both T_1 inversion recovery (IR)
21 and T_2 Carr-Purcell Meiboom-Gill (CPMG) relaxation datasets. The first part of this
22 paper introduces the key mathematical concepts used in the NNTF routine, and
23 outlines the strategy for generating the ensuing two-dimensional (2D) RAS spectra.
24 In the second part of this paper, the application of this approach is demonstrated for
25 several experimental and simulated relaxation datasets that were collected for both

spin-1/2 and half-integer quadrupolar nuclides. In particular, it is demonstrated that significant experimental time savings are afforded by collecting R_2 RAS spectra (*i.e.*, by using the NNTF routine to process one-dimensional T_2 CPMG datasets). Additionally, it is shown that using a *regularized* multi-exponential fitting procedure in the form of *non-negative Tikhonov regularization* to generate R_1 and R_2 RAS spectra (*i.e.*, by processing T_1 and T_2 datasets, respectively) allows for the separation of patterns arising from magnetically non-equivalent nuclei – even if they have similar relaxation constants.

2. Theory and Numerical Methods

All 2D relaxation and diffusion NMR data can be modeled according to a 2D Fredholm integral equation of the first kind:³¹

$$g(t, t) = \int_0^\infty \int_0^\infty K(s_1, t, s_2, t) f(s_1, s_2) ds_1 ds_2 + e(t, t) \quad (1)$$

where $g(t, t)$ is the 2D NMR signal acquired at times t and t , $K(s_1, t, s_2, t)$ is the model function known as the *kernel* that describes the 2D NMR signal, $f(s_1, s_2)$ is the *density distribution function* representing the distribution of diffusion coefficients or relaxation time constants and $e(t, t)$ represents the experimental noise.

Since the focus of this work involves collecting and processing T_1 and T_2 datasets for the purposes of separating overlapping powder patterns, the following discussion will be limited to Fredholm integral equations that describe these relaxation processes. Therefore, **Eq. 1** can be rewritten to explicitly model T_1 or T_2 relaxation behavior:

$$g(t, t) = \int_0^\infty \int_0^\infty K(R_j, t, n, t) f(R_j, n) dR_j dn + e(t, t) \quad (2)$$

where $g(t, \tau)$ is the 2D T_1 or T_2 relaxation dataset, $K(R_j, \tau, \nu, t)$ is the kernel function describing the spins' evolution frequencies and the relaxation rates R_j (where $j = 1, 2$ denote T_1^{-1} and T_2^{-1} , respectively), and $f(R_j, \nu)$ describes the distribution of NMR powder patterns separated on the basis of relaxation rate and frequency ν .

Separating overlapping powder patterns originating from magnetically distinct sites according to differences in their R_1 and R_2 relaxation rates is achieved by extracting $f(R_j, \nu)$ from $g(t, \tau)$. This in turn requires: (i) Collecting $g(t, \tau)$ using either inversion/saturation recovery or CPMG in-plane refocusing pulse sequences, which encode the relaxation behavior in a pseudo-indirect dimension (F_1) and the spins' evolution frequencies (chemical shifts, anisotropic patterns, *etc.*) in the direct dimension (F_2), as functions of τ and t , respectively. τ corresponds either to the relaxation delay time that is incremented in an inversion/saturation recovery experiment or the times at which transverse magnetization forms coherent spin-echoes during a CPMG experiment. (ii) Fourier transforming $g(t, \tau)$ along F_2 for every value of τ to extract the frequency distributions for each inequivalent site, giving the new dataset, $P(\tau, \nu)$. (iii) Subjecting $P(\tau, \nu)$ to a multi-exponential fit for each frequency point to obtain the desired $f(R_j, \nu)$ dataset, which represents a *preliminary* 2D RAS spectrum. This is accomplished by defining an appropriate kernel function that specifically describes the relaxation process encoded in F_1 ; *e.g.*, $K(R_1, \tau, \nu, t) = \exp(i\nu t) \left(1 - 2\exp(-\tau R_1) \right)$ and $K(R_2, \tau, \nu, t) = \exp(i\nu t) \left(\exp(-\tau R_2) \right)$ for T_1 IR and T_2 CPMG datasets, respectively. Fitting the distributions contained within this kernel to the measured data for each value of ν , can be formalized by the following Fredholm integral equation of the first kind:

$$P(t, n) = \int_0^\infty \int_0^\infty K(R_j, t, n, t) f(R_j, n) dt dt + e(t, t) \quad (3)$$

This step is the most challenging in this kind of analysis, as it amounts to solving an ill-posed inverse problem. These problems – which are more formally described below – may fail to produce accurate and unique solutions in general, especially for datasets contaminated with noise (*vide infra*). (iv) Assuming that **Eq. 3** has been solved, the last step in the RAS procedure involves post-processing the RAS spectrum to correct for numerical artifacts and/or the effects of anisotropic relaxation; details on how this is accomplished are also provided below.

9

2.1. Discrete Ill-Posed Inverse Problems

An inverse problem involves calculating a set of unknown input parameters, for a given set of known output data, according to a model function that describes some physical system or process.^{32,33} Inverse problems are classified as ill-posed if their solutions are either not unique or exhibit extreme sensitivity to noise (*i.e.*, if a small perturbation to the data can cause a large fluctuation in the solution). To appreciate the ill-posed nature of RAS, **Eq. 3** is rewritten in the discretized form that reflects the experimental manner in which these 2D NMR data are collected:

$$\mathbf{P}_i = \mathbf{K} \mathbf{f}_i + \mathbf{e}_i \quad (4)$$

where $\mathbf{P}_i \hat{=} \square^{m \times 1}$, $\mathbf{K} \hat{=} \square^{m \times n}$, $\mathbf{f}_i \hat{=} \square^{n \times 1}$ and $\mathbf{e}_i \hat{=} \square^{m \times 1}$ represent the discrete forms of the functions described in **Eq. 3**, and $i \in \{1, N\}$ with N representing the total number of frequency points acquired in F_2 . Notice that \mathbf{f}_i and \mathbf{P}_i in **Eq. 4** are expressed as 1D vectors, even though their functional analogues in **Eq. 3** are two-dimensional. This discretized representation is valid because **Eq. 4** is minimized for each column

belonging to $P(t, n)$ (i.e., for each frequency point, which is denoted with the index i). The resulting solution vectors \mathbf{f}_i are then assembled to form the preliminary 2D RAS spectrum. Within this formalism, it is convenient to define a new vector, $\hat{\mathbf{P}}_i$, representing the sum of the unadulterated noiseless data (\mathbf{P}_i) and the experimental noise (\mathbf{e}_i). Solutions to **Eq. 4** can then be determined by a least-squares (LS) analysis

$$\min_{\mathbf{f}_i} \left\| \mathbf{K} \mathbf{f}_i - \hat{\mathbf{P}}_i \right\|^2 \quad (5)$$

where $\left\| \cdot \right\|^2$ denotes the Euclidean norm, l_2 . A *singular value decomposition* (SVD) of the kernel matrix, \mathbf{K} , is a matrix factorization procedure that lends considerable insight into the nature of discrete ill-posed inverse problems. The SVD of the kernel matrix, \mathbf{K} , appearing in **Eqs. 4** and **5**, is defined by the factorization:

$$\mathbf{K} = \mathbf{U} \mathbf{S} \mathbf{V}^T = \sum_{j=1}^r \mathbf{u}_j \mathbf{s}_j \mathbf{v}_j^T \quad (6)$$

Here, $\mathbf{U} = (\mathbf{u}_1, \dots, \mathbf{u}_m) \hat{=} \mathbb{R}^{m \times m}$ and $\mathbf{V} = (\mathbf{v}_1, \dots, \mathbf{v}_n) \hat{=} \mathbb{R}^{n \times n}$ are orthogonal matrices whose columns are the left and right singular vectors of \mathbf{K} , $\mathbf{S} = \text{diag}(\mathbf{s}_1, \dots, \mathbf{s}_n) \hat{=} \mathbb{R}^{m \times n}$ is a diagonal matrix whose non-negative entries are the singular values of \mathbf{K} arranged in decreasing magnitude as the index j increases, and $r = \text{rank}(\mathbf{K})$. Two characteristic features of ill-posed inverse problems are: (i) the singular values of \mathbf{K} gradually decay to zero and (ii) the right singular vectors \mathbf{v}_j^T become more oscillatory as $j \rightarrow r$. Both of these features amplify the noise in the experimental data, thereby complicating the determination of an accurate solution. This can be visualized by

considering a generic solution to **Eq. 4**, which can be determined by using the Moore-Penrose pseudoinverse^{32,34}

$$\mathbf{K}^\dagger = \mathring{\mathbf{A}} \frac{\mathbf{v}_j \mathbf{u}_j^T}{S_j} \quad (7)$$

The resulting solution possessing the smallest l_2 norm can be represented as a sum of two components: one originating from the pure unadulterated data and the other originating from the noise. The latter can be represented as:³²

$$\mathbf{K}^\dagger \mathbf{e}_i = \mathring{\mathbf{A}} \frac{\mathbf{v}_j \mathbf{u}_j^T}{S_j} \mathbf{e}_i \quad (8)$$

As $j \rightarrow r$, the magnitude of S_j^{-1} increases, \mathbf{v}_j becomes more oscillatory, and the contributions of the noise vector \mathbf{e}_i become amplified, leading to solutions that are ultimately meaningless.

2.2. Stabilizing the Solutions of Discrete, Ill-posed Inverse Problems

Finding suitable solutions to inverse problems possessing ill-posed characteristics requires imposing additional constraints on the desired solution. Regularization refers to a variety of numerical methods that stabilize the solutions of ill-posed inverse problems, primarily by filtering out the high-frequency oscillations of the singular vectors associated with small singular values. This filtering process can take on many different forms of varying sophistication.^{35–40} The key to a successful numerical regularization scheme is to choose constraints that (i) effectively suppress the high-frequency components of the kernel matrix that amplify the noise, and (ii) return regularized solutions that are close approximations to the desired solution.

One of the most basic regularization schemes is the *non-negative least squares* (NNLS) algorithm,^{31,35} which was used to solve **Eq. 5** and generate R_1 RAS

1 spectra in ref. 30 This algorithm imposes the regularized solution $\hat{\mathbf{f}}_i^{\text{reg}}$ to be non-
 2 negative according to:

$$3 \quad \hat{\mathbf{f}}_i^{\text{reg}} = \min_{\hat{\mathbf{f}}_i \geq 0} \left\| \mathbf{K} \hat{\mathbf{f}}_i - \hat{\mathbf{P}}_i \right\|^2 \quad (9)$$

4 This non-negativity constraint is valid in this case because the desired solution
 5 represents a distribution of non-negative relaxation rates/times. However, the NNLS
 6 algorithm fails to address the problematic small singular values; therefore, $\hat{\mathbf{f}}_i^{\text{reg}}$
 7 remains sensitive to the noise.

8 *Tikhonov regularization*^{33,41} is perhaps the most popular method for stabilizing
 9 the solutions of such ill-posed inverse problems. This involves minimizing an
 10 ancillary constraint $\left\| \mathbf{L}(\hat{\mathbf{f}}_i - \hat{\mathbf{f}}_i^0) \right\|^2$ with respect to the minimization of $\left\| \mathbf{K} \hat{\mathbf{f}}_i - \hat{\mathbf{P}}_i \right\|^2$, which
 11 are commonly referred to as the solution *semi-norm* and *residual norm*, respectively,
 12 to give:

$$13 \quad \hat{\mathbf{f}}_i^{\text{reg}} = \min_{\hat{\mathbf{f}}_i} \left\{ \left\| \mathbf{K} \hat{\mathbf{f}}_i - \hat{\mathbf{P}}_i \right\|^2 + \lambda^2 \left\| \mathbf{L}(\hat{\mathbf{f}}_i - \hat{\mathbf{f}}_i^0) \right\|^2 \right\} \quad (10)$$

14 Here, \mathbf{L} is either the identity matrix \mathbf{I}_n or a discrete approximation to a derivative
 15 operator, $\hat{\mathbf{f}}_i^0$ is an initial guess of the solution, and λ is a unitless positive variable
 16 known as the *regularization parameter*, which scales the magnitude of the stabilizing
 17 solution semi-norm with respect to the residual norm.

18 It is convenient to examine the filtering effects of Tikhonov regularization
 19 when **Eq. 10** is in standard form (*i.e.*, when $\mathbf{L} = \mathbf{I}_n$ and $\hat{\mathbf{f}}_i^0 = 0$). The regularized
 20 solution can then be written as:^{32,33,42}

$$21 \quad \hat{\mathbf{f}}_i^{\text{reg}} = \hat{\mathbf{a}} \frac{\sum_{j=1}^r \frac{S_j^2}{\lambda^2 + S_j^2} \frac{\mathbf{v}_j \mathbf{u}_j^T}{S_j} \hat{\mathbf{P}}_i \quad (11)$$

1 Tikhonov regularization adds λ^2 to each of the S_j^2 so that as $j \rightarrow r$, $\frac{S_j^2}{\lambda^2 + S_j^2} \rightarrow 0$,
2 thereby effectively dampening the contributions of both the small S_j and oscillatory
3 \mathbf{v}_j on $\hat{\mathbf{f}}_i^{\text{reg}}$. Moreover, the addition of the weighted side constraint, $\lambda^2 \|\mathbf{L}(\hat{\mathbf{f}}_i - \hat{\mathbf{f}}_i^0)\|^2$,
4 produces regularized solutions possessing smaller l_2 norms. Choosing an optimal
5 value of λ is crucial and can be achieved in a number of ways; in the present study,
6 this was done by using the *L*-curve routine.⁴³

7

8 2.3. Non-Negative Tikhonov Fitting Routine:

9 Multi-exponential fits of T_1 and T_2 datasets were performed using a numerical
10 algorithm combining Tikhonov regularization with non-negativity constraints. This
11 *non-negative Tikhonov fitting* (NNTF) routine uses the built-in NNLS function within
12 the MATLAB 8.1.0 environment to evaluate

$$13 \quad \hat{\mathbf{f}}_i^{\text{reg}} = \min_{\hat{\mathbf{f}}_i \geq 0} \left\| \begin{bmatrix} \mathbf{K} \\ \mathbf{L} \end{bmatrix} \hat{\mathbf{f}}_i - \begin{bmatrix} \hat{\mathbf{P}}_i \\ \mathbf{0} \end{bmatrix} \right\|^2 \quad (12)$$

14 where \mathbf{L} is the discrete second-order derivative operator that was calculated using
15 the regularization toolbox for MATLAB⁴² and $\hat{\mathbf{f}}_i^0 = 0$. The processing procedure used
16 to generate R_1 RAS spectra is similar to the method discussed in ref. 30; therefore,
17 only the processing procedure used to generate R_2 RAS spectra is discussed herein
18 (**Figure 1**). As mentioned above, WCPMG or BCP pulse sequences were used to
19 collect a 1D CPMG echo train, which was rearranged into a 2D data matrix by
20 sequentially placing each echo along the rows of the matrix with the points
21 comprising each echo occupying the columns of the matrix (**Figure 1a**). These
22 individual echoes were then apodized, zero-filled, Fourier transformed with respect

to t , and magnitude processed (**Figure 1b**). The NNTF algorithm was then used to evaluate **Eq. 12** for each frequency point using the optimal λ value^a determined from the L-curve routine⁴² and 1000 R_2 constants^b logarithmically spaced between 10 and 10000 s⁻¹. The resulting solution vectors were then assembled to form the preliminary 2D RAS spectrum (**Figure 1c**). A post-NNTF processing routine was then employed to correct for numerical artifacts and anisotropic relaxation (see Fig. 1 caption for description). The signal intensity for each frequency bin falling within this specified region was then added to form the powder pattern for each magnetically distinct site with unique relaxation characteristics (**Figure 1e, 1f**). This pattern was then positioned at the average relaxation rate determined for the corresponding site in the final *post-NNTF* 2D RAS spectrum (**Figure 1d**). The post-processed spectrum is often displayed side-by-side with the RAS spectrum that has not undergone post-NNTF processing, since the latter provides information on the relaxation behavior (*i.e.*, accurate measures of the relaxation constants and information on anisotropic relaxation), while the former provides an accurate measure of the NMR parameters for each of the overlapping spectra (*vide infra*).

3. Experimental Section

Samples. Samples of RbCH₃CO₂, RbClO₄, Ga(acac)₃ (acac = acetylacetonate), (CH₃CH₂CH₂CH₂)₂SnO (abbreviated as (*n*-Bu)₂SnO)), and SnPc (Pc = phthalocyanine) were purchased from Strem Chemicals, Inc. and used without

^a The optimal λ value was calculated for *each* frequency point, and then the average of these values was used to evaluate **Eq. 12**.

^b In general, using more R_2 values in the NNTF routine gives a better multi-exponential fit at the cost of increased computer processing time. Using 1000 R_2 values in the NNTF routine maintained a balance between accuracy and overall computational time.

further purification. GaPcCl was purchased from Sigma Aldrich and used without further purification. The following w/w mixtures were prepared: 40:1 RbCH₃CO₂:RbClO₄, 10:1 GaPcCl:Ga(acac)₃, and 1:1 (*n*-Bu)₂SnO:SnPc. These sample ratios, while not necessarily representative of ratios of sites encountered in naturally-occurring or “real world” samples, were chosen in order to produce spectra that allow for clear visualization of the powder patterns from each distinct site. All samples – whether pure chemicals or co-mixed in appropriate w/w ratios – were ground into fine powders and packed in shortened 5 mm o.d. glass NMR tubes.

Solid-State NMR Spectroscopy. NMR experiments were performed under static conditions using a Varian InfinityPlus NMR console with an Oxford 9.4 T ($\nu_0(^1\text{H}) = 400 \text{ MHz}$) wide-bore magnet operating at $\nu_0(^{87}\text{Rb}) = 130.79 \text{ MHz}$, $\nu_0(^{71}\text{Ga}) = 121.794 \text{ MHz}$, and $\nu_0(^{119}\text{Sn}) = 149.04 \text{ MHz}$. A Varian/Chemagnetics 5 mm double-resonance static wideline probe was used for all NMR experiments.

Pulse width calibrations for all nuclides were performed on their respective solution-state standards. ^{87}Rb ($I = 3/2$) and ^{71}Ga ($I = 3/2$) chemical shifts were referenced to 1.0 M solutions of RbNO₃ (aq) and Ga(NO₃)₃ (aq), respectively with $\delta_{\text{iso}} = 0.0 \text{ ppm}$ for each nuclide.^{6,44} ^{119}Sn ($I = 1/2$) chemical shifts were referenced to neat Sn(CH₃)₄ (l) with $\delta_{\text{iso}} = 0.0 \text{ ppm}$.¹⁵

All direct excitation experiments used radio-frequency (rf) field strengths (*i.e.*, $\nu_1 = \omega_1/2\pi$) between 10 and 30 kHz. Spin-locking fields ranging from 15 – 40 kHz were employed for cross-polarization experiments. WURST-80 pulses were used in all experiments, which were linearly swept over symmetric offsets with a total sweep range slightly larger than the total breadth of the powder pattern to be acquired. 15000 equally spaced points were used to define the amplitude and phase modulated waveforms for the WURST-A pulse and 900 equally spaced points were

used to define the amplitude and phase modulated waveforms for the WURST-B and WURST-C pulses (see **Figure S1** for the sequence's scheme). Spectra of compounds having protons were acquired using ^1H continuous-wave (CW) decoupling ranging between 10 and 50 kHz.

Spectral processing and simulations. All data were processed on a personal computer using custom-written code for MATLAB; this code is available from the authors upon request. Analytical simulations of NMR spectra were performed with the WSOLIDS⁴⁵ simulation package and SPINEVOLUTION⁴⁶, as noted. Further experimental and processing details are provided in the **SI** and in the text.

4. Results and Discussion

There are four fundamental differences distinguishing the RAS method described in this work and that of Frydman *et al.*³⁰ In the current work: (i) Pulse sequences employing broadband WURST pulses were used to collect all datasets. This is essential for efficiently collecting distortion-free UW NMR powder patterns that result from large anisotropic NMR interactions (*i.e.*, CSA and quadrupolar) with sufficient S/N.² (ii) T_1 relaxation datasets were collected using broadband IR experiments rather than SR experiments, because simulations indicate that the NNTF processing of such T_1 datasets yield RAS spectra with higher resolution (as also noted by Frydman *et al.*³⁰). (iii) All 2D RAS spectra were generated by processing relaxation datasets with a MATLAB-based algorithm that combines NNLS fitting with Tikhonov regularization (*i.e.*, NNTF). Regularization is essential for stabilizing the solutions of ill-posed inverse problems, and in this case, is crucial for obtaining accurate multi-exponential fits of decaying signals. This is especially important when processing datasets possessing limited S/N and/or multiple

overlapping patterns originating from magnetically distinct sites that have similar relaxation constants (*vide infra*). (iv) This NNTF algorithm was also applied to T_2 datasets (*i.e.*, CPMG echo trains) so that overlapping powder patterns can be separated according to differences in effective T_2 constants (*i.e.*, T_2^{eff} denotes the effective T_2 constant that results under conditions of ^1H decoupling, in which contributions to transverse relaxation from heteronuclear dipolar coupling are partially or wholly eliminated).

4.1 Theoretical Simulations of 2D RAS Datasets

There are several important factors that affect both the quality of the separations and the general applicability of the RAS technique to study challenging, “real-world” chemical systems. Some of these factors include the number of magnetically distinct sites (herein, only systems containing up to two magnetically distinct sites are discussed) and the difference in their relaxation constants, the S/N ratio of the relaxation datasets, the number of F_1 points (*e.g.*, the number of CPMG echoes in a T_2 dataset), and the presence of spectral artifacts (*e.g.*, DC offsets). To begin to address some of the issues that affect the success of a 2D RAS-based strategy for resolving inequivalent chemical sites, several T_2 relaxation datasets were simulated in which the aforementioned factors were independently manipulated or controlled. Subsequently, each dataset was processed with the NNTF routine in order to observe the influences of these factors on the 2D R_2 RAS spectra, and to determine how the acquisition or processing routines could be modified to produce spectra with optimal resolution and minimal distortion.

Figure 2 shows nine simulated R_2 RAS spectra, which were generated by applying the NNTF routine on simulated ^{35}Cl CPMG datasets, each composed of

1 120 echoes (or equivalently each possessing 120 points in F_1) for two equally
 2 populated chlorine sites with overlapping CT spectra. White noise was added to
 3 each CPMG dataset prior to Tikhonov fitting to give desired S/N ratios of 100, 500,
 4 and 1000 for the spectra shown in the first, second, and third column, respectively.
 5 The $T_2(^{35}\text{Cl})$ constants for these two sites differ by a factor of 10, 4, and 2 for the
 6 spectra shown in the top, middle, and bottom row, respectively. **Figure 2**
 7 demonstrates how the NNTF algorithm separates the overlapping ^{35}Cl powder
 8 patterns, for a given pair of $T_2(^{35}\text{Cl})$ constants as a function of the S/N ratio. The
 9 best separation is achieved when the T_2 constants differ by a factor of 10 or more
 10 (*i.e.*, $T_{2,A} = 1.0$ ms and $T_{2,B} = 10.0$ ms for site A and site B, **Figure 2a-2c**). The
 11 separation between the patterns increases as the S/N ratio of the R_2 RAS spectrum
 12 increases, from left to right across each row. When the T_2 constants differ by a
 13 factor of 4 ($T_{2,A} = 2.5$ ms and $T_{2,B} = 10.0$ ms), which is the case presented in the
 14 middle row, a S/N ratio of 100 is too low for the overlapped patterns to be clearly
 15 separated (**Figure 2d**). Even so, the co-added projections of both patterns can still
 16 be accurately extracted and fitted (**Figure S2**) by using the post-NNTF processing
 17 procedure in this case. However, poor separation is achieved when the T_2 constants
 18 differ by a factor of only 2 ($T_{2,A} = 5.0$ ms and $T_{2,B} = 10.0$ ms), as can be seen in the
 19 bottom row for all three S/N ratios (**Figure 2g-2i**). Interestingly, with *a priori*
 20 knowledge of the quadrupolar parameters for both sites, it is possible to resolve the
 21 overlapping patterns using the post-NNTF processing procedure (**Figure S3**). It
 22 should be noted that better separation might be possible when the T_2 constants for
 23 the magnetically distinct nuclides differ by the same ratio, but have different
 24 magnitudes (*i.e.*, 5 ms vs. 10 ms and 50 ms vs. 100 ms). However, this is an issue
 25 that will have to be resolved by conducting several new series of experiments, and is

not discussed further in this section. For these three simulated R_2 RAS spectra, better separation is possible if more R_2 relaxation constants are used in the NNTF algorithm (100 potential R_2 constants were used to process all nine spectra) and/or when more echoes are collected (*vide infra*). In general, using more potential relaxation constants in the multi-exponential fitting of relaxation data produces better quality RAS spectra, with the only disadvantage being an increase in the computational time. Furthermore, using a larger value of λ than the one provided by the L-curve routine, in combination with post-NNTF processing, could potentially isolate each individual pattern (as was done for several of the experimental datasets presented below). One caveat at this juncture is that there is not an accurate means of evaluating the experimental errors in the T_2 values within the current numerical regularization routine; rather, the 1D T_2 CPMG dataset can be fit using a multi-exponential analysis and the resulting values can be compared against those determined from the corresponding R_2 RAS spectrum. A full consideration of a statistical analysis that separates experimental from processing uncertainties is currently under consideration and beyond the scope of the current work.

Another parameter that influences the quality of R_2 RAS spectra is the number of echoes collected in F_1 (*i.e.*, the number of F_1 points). **Figure 3** shows that increasing the number of echoes leads to better separation of the powder patterns in the R_2 RAS spectrum (due to increased resolution in the indirect dimension), which may be especially useful for resolving inequivalent sites with very similar relaxation constants (120, 240, and 480 echoes were simulated in **Figure 3a**, **3b**, and **3c**, respectively). This is analogous to the collection of additional increments in standard 2D NMR experiments. The T_2 dataset simulated with 480 echoes gives an R_2 RAS spectrum (**Figure 3c**) with the best separation between the overlapping patterns,

which makes it easier for the post-NNTF processing procedure to accurately extract the projections for both site A and site B (**Figure 3e** and **3f**, respectively). Experimentally, however, it may not be feasible to collect so many echoes because of either hardware limitations (e.g., a high duty cycle) and/or short T_2^{eff} constants. In general, it is desirable to collect as many CPMG echoes as possible, which can be achieved by simply increasing the number of CPMG loops in the pulse sequence. One can also use techniques that increase the value of T_2^{eff} , by attenuating heteronuclear dipolar couplings, such as high-power ^1H decoupling or isotopic substitution of ^1H with ^2H . Another possibility is the use of variable-temperature NMR to exploit temperature dependencies of the T_2^{eff} constants (where these exist).⁴⁷

4.2. ^{87}Rb SSNMR of a 40:1 $\text{RbCH}_3\text{CO}_2\text{:RbClO}_4$ w/w mixture

^{87}Rb possesses several favorable NMR properties such as a high gyromagnetic ratio ($\gamma = 8.78640 \times 10^7 \text{ rad T}^{-1} \text{ s}^{-1}$, $\nu_0 = 130.79 \text{ MHz}$ at 9.4 T), desirable relaxation characteristics (i.e., long T_2^{eff} and/or short T_1 relaxation time constants), and a moderate nuclear quadrupole moment (NQM) of 133.5(5) millibarn. ^{87}Rb T_1 and T_2^{eff} relaxation datasets were collected for the model compounds RbCH_3CO_2 and RbClO_4 , as well as their mixture (*vide infra*). Each compound possesses a single rubidium site (**Figure S4a, S4b**)⁴⁴ with very different ^{87}Rb second-order CT powder patterns (quadrupolar NMR parameters have been previously reported).⁴⁴

The $T_1(^{87}\text{Rb})$ and $T_2^{\text{eff}}(^{87}\text{Rb})$ relaxation time constants were measured for each of the pure compounds. T_1 relaxation times were measured using a WURST-CPMG IR sequence (**Figure S1c**), and T_1 constants were determined by sampling

five evenly spaced frequency points across the powder pattern; the five partially recovered powder patterns were then fit to standard formulas⁴⁸ for each compound. This led to average $T_1(^{87}\text{Rb})$ values of *ca.* 109 ms and *ca.* 213 ms for RbCH_3CO_2 and RbClO_4 at room temperature, respectively (**Table S3, S4**). The $T_2^{\text{eff}}(^{87}\text{Rb})$ time constants were measured using the WCPMG echo trains (**Figures 4a, 4b**); exponential fitting of the resulting T_2^{eff} decay curves⁴⁸ led to average $T_2^{\text{eff}}(^{87}\text{Rb})$ of 1.16(7) ms and 14(1) ms for RbCH_3CO_2 and RbClO_4 , respectively (**Table S1**). The details of collecting, processing, and analyzing the R_1 and R_2^{eff} RAS spectra are explicitly described for these first two samples; similar methods were used for the remainder of the samples.

$T_2^{\text{eff}}(^{87}\text{Rb})$ echo trains were collected for RbCH_3CO_2 and RbClO_4 using the WCPMG sequence (**Figures 4a and 4b**, respectively) and processed as described in the SI. **Figure 4d** and **Figure 4e** show the WCPMG spectra of RbCH_3CO_2 and RbClO_4 , respectively. **Figure 4c** shows the echo train of a 40:1 RbCH_3CO_2 : RbClO_4 w/w mixture acquired with the WCPMG pulse sequence in *ca.* 40 minutes of acquisition time, and **Figure 4f** shows the resulting ^{87}Rb WCPMG 1D spectrum of the overlapping CT powder patterns. The 40:1 w/w ratio of this mixture was chosen due to the much stronger signal intensity of RbClO_4 in comparison to RbCH_3CO_2 , resulting primarily from a $T_2^{\text{eff}}(^{87}\text{Rb})$ constant that is ten times longer and CT powder pattern that is six times narrower.

A T_1 dataset was collected for this mixture using the WCPMG IR pulse sequence (**Figure 5a**). The NNTF routine was then used to determine the distribution of R_1 relaxation rates (*i.e.*, $R_1 = T_1^{-1}$) for each spectral frequency point. 1000 potential relaxation constants were used in all NNTFs (unless stated otherwise); the resulting 2D RAS spectrum (**Figure 5b**) separates the overlapping

resonances on the basis of frequency (direct dimension, F_2) and R_1 (indirect dimension, F_1).

It is clear from the contour plot in **Figure 5c** that the $T_1(^{87}\text{Rb})$ constants are too similar to produce a well-resolved R_1 RAS spectrum. The appearance of this spectrum is a consequence of the Tikhonov regularization used in the NNTF routine, which has the effect of broadening the powder patterns in the indirect dimension. This loss in resolving power – which is akin to imposing a “line broadening” in the relaxation rate distribution – is primarily controlled by the magnitude of the regularization parameter λ (see **Figure S7**). The optimal degree of regularization (*i.e.*, the value of λ) was determined by using the L-curve routine (see **SI**).⁴³ While this allows one to discriminate overlapping patterns originating from inequivalent sites that possess similar relaxation time constants (*vide infra*), such regularization-imposed broadening often masks the differences arising from anisotropic relaxation.

Despite the very similar relaxation characteristics of the two sites, the 2D contour plot in **Figure 5c** displays regions in which the RbClO_4 or RbCH_3CO_2 powder patterns can be clearly identified (i) at points of maximum signal intensity (as indicated by the arrows) or (ii) best separation of the patterns (as indicated by the blue highlighted areas). At the points indicated by the arrows, R_1 (T_1) values of *ca.* 6.14 s^{-1} (0.16 s) and *ca.* 17.84 s^{-1} (0.056 s) are measured for RbClO_4 and RbCH_3CO_2 , respectively. These values are slightly different than the ones that were measured by fitting the T_1 datasets for each of the individual compounds, primarily because of the large value of λ employed in the NNTF, which causes a broadening of the powder patterns in F_1 , thereby complicating an accurate measurement of the relaxation rates from the R_1 RAS spectrum. This dataset demonstrates, that in some cases, the areas of the RAS spectrum that give the best separation of the

overlapping powder patterns may be distinct from the areas that give increasingly accurate values of the relaxation constants for each of the sites.

The post-NNTF processing procedure discussed in the Theory Section was used to further refine the separation of these patterns. In this case, average R_1 values and co-added projections were calculated for each inequivalent chemical site by considering only the regions along F_1 that are highlighted in **Figure 5c**. The post-NNTF processed R_1 RAS spectrum (**Figure 5d**) clearly shows the separated ^{87}Rb CT powder patterns, even though the $T_1(^{87}\text{Rb})$ constants for these compounds differ only by a factor of ca. 2 (**Table S3, S4**). These 1D projections of RbCH_3CO_2 and RbClO_4 can then be imported into an appropriate fitting program and their NMR parameters determined (**Figures 5e, 5f**); the resulting quadrupolar parameters are similar to those reported in the literature for both compounds.⁴⁴

An added advantage for using the NNTF routine over a basic NNLS algorithm to generate RAS spectra is the ability to apply the post-NNTF processing procedure over *specific* regions along the indirect dimension (*i.e.*, in a “row-by-row” fashion along F_1), whereby the powder patterns may be partially or completely separated from one another. The post-NNTF processing procedure does not work properly for RAS spectra that were produced with an NNLS algorithm, since NNLS fitting is sensitive to the noise contained within relaxation datasets, which ultimately leads to distorted spectra for datasets having low S/N and/or for chemical sites having very similar relaxation constants (see **Figure S8**). Additionally, a *priori* knowledge of the NMR parameters (*e.g.*, the EFG and CS tensor parameters) for at least one of the overlapping patterns can greatly aid in defining the regions over which to apply the post-NNTF processing procedure.

The ability to resolve overlapped patterns according to differences in the $T_2^{\text{eff}}(^{87}\text{Rb})$ constants was also tested on this mixture by applying the NNTF routine to a 2D dataset generated by chronologically rearranging the 1D WCPMG train of echoes (**Figure 4c**). The reader is reminded that this 2D matrix is constructed from a 1D WCPMG T_2 dataset by sequentially placing each of the spin echoes along the rows of the matrix (e.g., a WCPMG echo train composed of 50 echoes with 100 points defined for each echo would form a 2D matrix of size 50x100). This 2D data matrix was Fourier transformed along the “direct” dimension (i.e., down each of the rows), magnitude processed, and then the NNTF routine was used to extract the distribution of $T_2^{\text{eff}}(^{87}\text{Rb})$ constants for each frequency point (i.e., down each of the columns). The ensuing R_2^{eff} ($1/T_2^{\text{eff}}$) RAS spectrum (**Figure 6a**) leads to two well-separated ridges – even if these show a substantial anisotropic T_2 dependence. The post-NNTF processing procedure was then used to calculate the co-added projections for each unique chemical site by adding up the *total* signal intensity pertaining to each of the well-separated patterns; when placed at their corresponding average R_2^{eff} values, clear post-NNTF processed R_2^{eff} separations are achieved (**Figure 6b**). Notice that for this mixture, the R_2^{eff} RAS analysis is much better at separating the overlapped spectra than the R_1 RAS analysis, largely because the $T_2^{\text{eff}}(^{87}\text{Rb})$ constants for these two rubidium sites differ by a factor of ca. 10. Also, the S/N ratio in the R_2^{eff} RAS spectrum (acquired with WCPMG) is higher than that observed in the R_1 RAS spectrum (acquired with WCPMG IR) for each increment in F_1 . Additionally, more points could be collected in F_1 for the R_2^{eff} dataset than that for R_1 .

In general, the R_2^{eff} RAS analysis is more robust than the R_1 RAS analysis, since the former simply requires a high-quality 1D CPMG dataset, which in turn

relies essentially on an optimized radio-frequency (rf) field and a long enough T_2^{eff} constant to permit proper encoding of the transverse relaxation behavior. R_1 RAS, by contrast, is a 2D arrayed experiment requiring careful setting of the rf field and sweep rate of the WURST-A pulse (*i.e.*, to ensure the entire powder pattern is uniformly inverted). Misses in these parameters can not only drastically increase the overall experimental time, but can also affect the quality of the separations (*vide infra*). The projections of $\text{Rb}_2\text{CH}_3\text{CO}_2$ (**Figure 6c**) and RbClO_4 (**Figure 6d**) were fit with NMR parameters similar to the ones reported in the literature. The approximate values of the $R_1(^{87}\text{Rb})$ and $R_2^{\text{eff}}(^{87}\text{Rb})$ constants as determined from the RAS spectra are shown in **Table S2**.

4.3. ^{71}Ga SSNMR of a 10:1 $\text{GaPcCl}:\text{Ga}(\text{acac})_3$ w/w mixture

^{71}Ga is a receptive half-integer ($I = 3/2$) quadrupolar nuclide, owing to its high γ ratio ($\gamma = 8.18117 \times 10^7 \text{ rad T}^{-1} \text{ s}^{-1}$, $\nu_0 = 121.794 \text{ MHz}$ at 9.4 T) and high natural abundance (39.89%). The moderate NQM of ^{71}Ga (107(1) millibarn) most often results in broadened second-order CT powder patterns that can span hundreds of kHz. These broad patterns often have inherently low S/N, resulting in lengthy experimental times, and making it challenging to resolve multiple overlapping patterns.

The R_1 and R_2^{eff} RAS protocols were used to try to resolve the overlapping ^{71}Ga CT powder patterns resulting from a 10:1 gallium phthalocyanine chloride (GaPcCl):gallium acetylacetonate ($\text{Ga}(\text{acac})_3$) w/w mixture. The WCPMG spectrum of this mixture (**Figure 7c**) shows the overlapped ^{71}Ga powder patterns; the one with a breadth of ca. 500 kHz corresponds to GaPcCl (**Figure 7a**) and the other (75 kHz in breadth) corresponds to $\text{Ga}(\text{acac})_3$ (**Figure 7b**). Applying the NNTF routine to the

T_2^{eff} dataset of the 10:1 GaPcCl:Ga(acac)₃ mixture (**Figure S5c**), which was collected in ca. 47 minutes of acquisition time using WCPMG, yields a high-quality, post-NNTF processed R_2^{eff} RAS spectrum (**Figure 7d**) in which the powder patterns corresponding to GaPcCl and Ga(acac)₃ are clearly separated. The 1D co-added projections for Ga(acac)₃ and GaPcCl are shown in **Figure 7e** and **7f**, respectively. Both of these projections were fit with NMR parameters similar to the ones reported in the literature⁶, which reinforces the fact that RAS is a suitable technique for not only identifying and separating overlapping powder patterns, but also useful for accurately obtaining the NMR tensor parameters that reveal detailed chemical information.

The NNTF routine was also applied to a T_1 dataset (**Figure S6**) for this mixture, which required ca. 13 hours of acquisition time using WCPMG IR. The resulting post-NNTF processed R_1 RAS spectrum is shown in **Figure 7g**. Comparison of the spectra in **Figures 7d** and **7g** clearly reveals higher S/N and better spectral resolution in the former, despite the fact that the R_2^{eff} RAS spectrum was acquired ca. 16 times faster than its R_1 counterpart. Thus, while it is clearly advantageous to have the option to separate overlapping patterns based on either R_1 or R_2 , it seems that the latter is preferable, since it only requires the acquisition of a single WCPMG spectrum.

4.4. ^{119}Sn SSNMR of a 1:1 SnPc:(*n*-Bu)₂SnO w/w mixture

Tin possesses three NMR-active isotopes, with ^{119}Sn being the preferred isotope for NMR experimentation due to its high receptivity resulting from a large gyromagnetic ratio ($\gamma = 10.03170 \times 10^7 \text{ rad T}^{-1} \text{ s}^{-1}$, $\nu_0 = 149.04 \text{ MHz}$ at 9.4 T) and higher natural abundance (8.58%). Despite these relatively favorable NMR

characteristics, ^{119}Sn SSNMR spectra can be challenging to acquire since tin CSAs often broaden spectral breadths beyond both the excitation bandwidth of conventional monochromatic rf pulses, as well as the detection bandwidth of the probe. Furthermore, it is common for many tin-containing compounds to possess extremely long $T_1(^{119}\text{Sn})$ constants, necessitating recycle delays on the order of tens to hundreds of seconds in between scans, which prevent the retrieval of high-quality spectra in reasonable experimental timeframes.^{7,49,50} ^{119}Sn MAS experiments, which are used more often than static experiments, are subject to some of the experimental difficulties described in the Theory Section. ^1H - ^{119}Sn CP/MAS experiments are often employed to collect ^{119}Sn powder patterns, exploiting the usually shorter recycle delays which depend on the $T_1(^1\text{H})$ constants.^{51–53} However, since the excitation bandwidth over which CP is efficient is effectively determined by the length and power of the contact pulses, frequency-stepped acquisition must also be used to acquire these powder patterns, which in turn can lead to lengthy experimental times.^{17,18,20,54} The recently developed broadband adiabatic inversion cross polarization (BRAIN-CP) pulse sequence effectively addresses the limited excitation bandwidths associated with so-called conventional CP experiments by using a frequency-swept WURST pulse as the X-channel spin-lock pulse (**Figure S1b**), which allows for the collection of high-quality UW NMR spectra under static conditions.¹⁵

The BRAIN-CP/WCPMG (BCP for brevity) pulse sequence, which uses a train of WURST-CPMG pulses for refocusing (**Figure S1b**), was used to collect ^{119}Sn spectra of $(\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2)_2\text{SnO}$ (dibutyltin(IV) oxide, abbreviated as $(n\text{-Bu})_2\text{SnO}$) and tin phthalocyanine chloride (SnPc), which are shown in **Figures 8a** and **8b**, respectively. The BCP pulse sequence uniformly excites the entire breadth of both

1 CSA-dominated powder patterns using relatively low-power spin-locking pulses (ca.
2 18 kHz and ca. 42 kHz on the ^{119}Sn and ^1H channels, respectively) and a contact
3 time of 30.0 ms. The corresponding experimental times to collect both ^{119}Sn spectra
4 were ca. 10 minutes and ca. 30 minutes for $(n\text{-Bu})_2\text{SnO}$ oxide and SnPc,
5 respectively, which is a significant time savings over direct excitation (DE)
6 experiments (e.g., the $T_1(^{119}\text{Sn})$ constant for $(n\text{-Bu})_2\text{SnO}$ is on the order of 100 s).
7 The BCP spectrum of a 1:1 w/w mixture of these two tin compounds (**Figure 8c**)
8 does not clearly reveal each of the unique ^{119}Sn powder patterns that originate from
9 each compound in the mixture. In this case, identifying and deconvoluting the
10 contribution of each individual powder pattern may be difficult, making this mixture a
11 good test case for 2D RAS.

12 R_1 RAS analyses would be impractical for separating the individual ^{119}Sn
13 powder patterns, as the τ increments used in the collection of a T_1 relaxation dataset
14 would have to be quite long in order to ensure a proper encoding of the T_1 relaxation
15 behavior. A R_2^{eff} RAS analysis was therefore attempted by applying the NNTF
16 routine to the WCPMG T_2^{eff} dataset (**Figure S5f**) acquired with the BCP pulse
17 sequence using 100 CPMG loops, a recycle delay of 10.0 s, and 4096 scans (total
18 acquisition time of ca. 11 hours). The resulting 2D R_2^{eff} RAS spectrum of this 1:1
19 mixture (**Figure 8d**) easily resolves the ^{119}Sn powder patterns. The $R_2^{\text{eff}}(^{119}\text{Sn})$
20 constants determined from the R_2^{eff} RAS spectrum are tabulated in **Table S2**. The
21 projections of both powder patterns (**Figure 8f** and **8g**, SnPc and $(n\text{-Bu})_2\text{SnO}$,
22 respectively) were fit with similar NMR parameters to the ones used to fit each of the
23 individual patterns collected with the BCP pulse sequence. This example illustrates
24 that the BCP pulse sequence can be used to collect high-quality T_2^{eff} datasets that
25 can then be processed using the NNTF algorithm to yield high-quality RAS spectra,

which is extremely useful when dealing with unreceptive nuclei (*i.e.*, nuclei associated with broad CSA-dominated patterns, long T_1 constants and/or low values of γ).

5. Conclusions

2D R_1 and R_2 relaxation-assisted separation (RAS) analyses can be used to separate overlapping UW NMR powder patterns originating from magnetically distinct sites for both spin-1/2 and quadrupolar nuclei, provided that their relaxation characteristics are distinct. The WCPMG and BCP pulse sequences are robust and can be easily used to collect T_1 and T_2 datasets, which can then be imported into MATLAB and processed with the NNTF routine to give the corresponding RAS spectra. The NNTF routine is easily implemented within MATLAB and is straightforward to use. NNTF effectively addresses the problematic small singular values that are characteristic of ill-posed inverse problems. This is especially useful when processing T_1 and T_2 relaxation datasets having low S/N and when attempting to resolve overlapping patterns originating from sites having similar relaxation time constants. The combined use of NNTF with post-processing of R_1 or R_2 RAS spectra can greatly aid in achieving clear separation of powder patterns for instances where the separation is poor due to either (i) low S/N, (ii) similar relaxation constants among magnetically distinct nuclei, (iii) multiple inequivalent sites (each of which gives rise to a unique powder pattern, which may overlap with one another), and/or (iv) combinations of these factors. Moreover, *a priori* knowledge of the relaxation constants and/or the NMR parameters is beneficial when defining the range of relaxation rates in the NNTF routine and when using the post-NNTF processing procedure; however, this information is not required in order to collect and process

R_1 and R_2 RAS spectra. The experiments and simulations presented in this work demonstrate that in order to successfully resolve patterns originating from magnetically distinct sites in 2D RAS spectra, high-quality T_1 and T_2 relaxation datasets are essential. The WCPMG and BCP pulse sequences are indispensable to this end, since they can provide the necessary high-quality relaxation datasets in reasonable experimental timeframes. Moreover, the combined use of these pulse sequences with other sensitivity-enhancing techniques (e.g., the use of high magnetic fields, dynamic nuclear polarization, low-temperature NMR, etc.) is likely to open up larger swaths of the periodic table to routine analysis with R_1 and R_2 RAS methods. We hope that the ease with which T_1 and T_2 datasets can be collected and then processed with the NNTF routine will make RAS-based strategies effective methods for increasing spectral resolution. Our future work will include the continued development of the NNTF routine and related post-processing protocols, so that higher-quality RAS spectra can be produced. We will also investigate systems with two or more magnetically distinct sites in the unit cell, as well as those with very similar T_2^{eff} values.

6. Supporting Information

Also included in the supporting information: (i) information on the L-curve routine and how the optimal regularization parameter is chosen, (ii) details on spectral processing of 1D NMR spectra, (iii) figures of the 1D NMR spectra and associated analytical simulations for all compounds, as well as their 2D T_1 relaxation datasets, (iv) schemes of pulse sequences used to collect T_1 and T_2 datasets, (v) tables of the experimental NMR parameters, and (vi) figures of the separated and individual patterns obtained from the ^{71}Ga RAS experiments and simulated T_2 RAS spectra.

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