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### Document Version:

Accepted author manuscript (peer-reviewed)

### Citation for published version:

Jaroszewicz, MJ, Frydman, L & Schurko, RW 2017, 'Relaxation-Assisted Separation of Overlapping Patterns in Ultra-Wideline NMR Spectra', *Journal of Physical Chemistry A*, vol. 121, no. 1, pp. 51-65. <https://doi.org/10.1021/acs.jpca.6b10007>

*Total number of authors:*

3

### Digital Object Identifier (DOI):

[10.1021/acs.jpca.6b10007](https://doi.org/10.1021/acs.jpca.6b10007)

### Published In:

Journal of Physical Chemistry A

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

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## 1 **Abstract**

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

20

## 21 **1. Introduction**

22           Many elements that are of great importance in chemistry, physics, biology,  
23 and materials science have isotopes that are unresponsive to the NMR experiment  
24 due to low gyromagnetic ratios ( $\gamma$ ), low natural abundances, and/or unfavorable  
25 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.<sup>1,2</sup>

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<sup>3,4</sup> provide uniform  
21 excitation of UW NMR powder patterns, through the combined modulation of their  
22 amplitude and phase.<sup>5,6</sup> 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

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

14 More challenging remains the issue of improving site resolution in UW NMR  
15 spectra. Spectral resolution in SSNMR experiments is usually improved by magic-  
16 angle spinning (MAS), which spatially averages all anisotropic NMR interactions to  
17 first order (*e.g.*, the chemical shift and first-order quadrupolar interactions).  
18 Unfortunately, for most UW NMR applications, MAS is insufficient for efficiently  
19 averaging the anisotropic interactions, given the unrealizable spinning speeds that  
20 are needed for dealing with powder patterns that are several hundred kHz to several  
21 MHz in breadth.<sup>18</sup> Moreover, for half-integer quadrupolar nuclides, it is not possible  
22 to completely average the inhomogeneous broadening that results from the  
23 quadrupolar interaction by spinning at any fixed rotor angle.<sup>19</sup> In fact, it has been  
24 demonstrated for MAS NMR spectra of both spin-1/2 and half-integer quadrupolar  
25 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.<sup>20–22</sup> 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  $C_Q$ .<sup>23–29</sup>

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.*,<sup>30</sup> 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

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

9

## 10 **2. Theory and Numerical Methods**

11 All 2D relaxation and diffusion NMR data can be modeled according to a 2D  
 12 Fredholm integral equation of the first kind:<sup>31</sup>

$$13 \quad g(t, t) = \int_0^{\infty} \int_0^{\infty} K(s_1, t, s_2, t) f(s_1, s_2) ds_1 ds_2 + e(t, t) \quad (1)$$

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

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

$$23 \quad g(t, t) = \int_0^{\infty} \int_0^{\infty} K(R_j, t, n, t) f(R_j, n) dR_j dn + e(t, t) \quad (2)$$

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

5 Separating overlapping powder patterns originating from magnetically distinct  
 6 sites according to differences in their  $R_1$  and  $R_2$  relaxation rates is achieved by  
 7 extracting  $f(R_j, \nu)$  from  $g(t, \nu)$ . This in turn requires: (i) Collecting  $g(t, \nu)$  using  
 8 either inversion/saturation recovery or CPMG in-plane refocusing pulse sequences,  
 9 which encode the relaxation behavior in a pseudo-indirect dimension ( $F_1$ ) and the  
 10 spins' evolution frequencies (chemical shifts, anisotropic patterns, *etc.*) in the direct  
 11 dimension ( $F_2$ ), as functions of  $t$  and  $\nu$ , respectively.  $t$  corresponds either to the  
 12 relaxation delay time that is incremented in an inversion/saturation recovery  
 13 experiment or the times at which transverse magnetization forms coherent spin-  
 14 echoes during a CPMG experiment. (ii) Fourier transforming  $g(t, \nu)$  along  $F_2$  for  
 15 every value of  $t$  to extract the frequency distributions for each inequivalent site,  
 16 giving the new dataset,  $P(t, \nu)$ . (iii) Subjecting  $P(t, \nu)$  to a multi-exponential fit for  
 17 each frequency point to obtain the desired  $f(R_j, \nu)$  dataset, which represents a  
 18 *preliminary* 2D RAS spectrum. This is accomplished by defining an appropriate  
 19 kernel function that specifically describes the relaxation process encoded in  $F_1$ ; e.g.,  
 20  $K(R_1, t, \nu, t) = \exp(i\nu t) \left( 1 - 2\exp(-tR_1) \right)$  and  $K(R_2, t, \nu, t) = \exp(i\nu t) \left( \exp(-tR_2) \right)$  for  $T_1$  IR  
 21 and  $T_2$  CPMG datasets, respectively. Fitting the distributions contained within this  
 22 kernel to the measured data for each value of  $\nu$ , can be formalized by the following  
 23 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.<sup>32,33</sup> 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

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

$$7 \quad \min_{\hat{\mathbf{f}}_i} \left\| \mathbf{K} \hat{\mathbf{f}}_i - \hat{\mathbf{P}}_i \right\|^2 \quad (5)$$

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

$$12 \quad \mathbf{K} = \mathbf{U} \mathbf{S} \mathbf{V}^T = \sum_{j=1}^r \mathbf{u}_j \mathbf{s}_j \mathbf{v}_j^T \quad (6)$$

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

1 considering a generic solution to **Eq. 4**, which can be determined by using the  
 2 *Moore-Penrose* pseudoinverse<sup>32,34</sup>

$$3 \quad \mathbf{K}^\dagger = \mathring{\mathbf{A}} \sum_{j=1}^r \frac{\mathbf{v}_j \mathbf{u}_j^T}{S_j} \quad (7)$$

4 The resulting solution possessing the smallest  $l_2$  norm can be represented as a sum  
 5 of two components: one originating from the pure unadulterated data and the other  
 6 originating from the noise. The latter can be represented as:<sup>32</sup>

$$7 \quad \mathbf{K}^\dagger \mathbf{e}_i = \mathring{\mathbf{A}} \sum_{j=1}^r \frac{\mathbf{v}_j \mathbf{u}_j^T}{S_j} \mathbf{e}_i \quad (8)$$

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

11

## 12 2.2. Stabilizing the Solutions of Discrete, Ill-posed Inverse Problems

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

22 One of the most basic regularization schemes is the *non-negative least*  
 23 *squares* (NNLS) algorithm,<sup>31,35</sup> 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*<sup>33,41</sup> 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  $\lambda$  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:<sup>32,33,42</sup>

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

1 Tikhonov regularization adds  $\lambda^2$  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  $v_j$  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  $\lambda$  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.<sup>43</sup>

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 MATLAB<sup>42</sup> 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

1 to  $t$ , and magnitude processed (**Figure 1b**). The NNTF algorithm was then used to  
2 evaluate **Eq. 12** for each frequency point using the optimal  $\lambda$  value<sup>a</sup> determined from  
3 the L-curve routine<sup>42</sup> and 1000  $R_2$  constants<sup>b</sup> logarithmically spaced between 10 and  
4 10000 s<sup>-1</sup>. The resulting solution vectors were then assembled to form the  
5 preliminary 2D RAS spectrum (**Figure 1c**). A post-NNTF processing routine was  
6 then employed to correct for numerical artifacts and anisotropic relaxation (see Fig. 1  
7 caption for description). The signal intensity for each frequency bin falling within this  
8 specified region was then added to form the powder pattern for each magnetically  
9 distinct site with unique relaxation characteristics (**Figure 1e, 1f**). This pattern was  
10 then positioned at the average relaxation rate determined for the corresponding site  
11 in the final *post-NNTF* 2D RAS spectrum (**Figure 1d**). The post-processed spectrum  
12 is often displayed side-by-side with the RAS spectrum that has not undergone post-  
13 NNTF processing, since the latter provides information on the relaxation behavior  
14 (*i.e.*, accurate measures of the relaxation constants and information on anisotropic  
15 relaxation), while the former provides an accurate measure of the NMR parameters  
16 for each of the overlapping spectra (*vide infra*).

17

### 18 **3. Experimental Section**

19 **Samples.** Samples of RbCH<sub>3</sub>CO<sub>2</sub>, RbClO<sub>4</sub>, Ga(acac)<sub>3</sub> (acac =  
20 acetylacetonate), (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>SnO (abbreviated as (*n*-Bu)<sub>2</sub>SnO)), and SnPc  
21 (Pc = phthalocyanine) were purchased from Strem Chemicals, Inc. and used without

---

<sup>a</sup> The optimal  $\lambda$  value was calculated for *each* frequency point, and then the average of these values was used to evaluate **Eq. 12**.

<sup>b</sup> 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.

1 further purification. GaPcCl was purchased from Sigma Aldrich and used without  
2 further purification. The following w/w mixtures were prepared: 40:1  
3 RbCH<sub>3</sub>CO<sub>2</sub>:RbClO<sub>4</sub>, 10:1 GaPcCl:Ga(acac)<sub>3</sub>, and 1:1 (*n*-Bu)<sub>2</sub>SnO:SnPc. These  
4 sample ratios, while not necessarily representative of ratios of sites encountered in  
5 naturally-occurring or “real world” samples, were chosen in order to produce spectra  
6 that allow for clear visualization of the powder patterns from each distinct site. All  
7 samples – whether pure chemicals or co-mixed in appropriate w/w ratios – were  
8 ground into fine powders and packed in shortened 5 mm o.d. glass NMR tubes.

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

14 Pulse width calibrations for all nuclides were performed on their respective  
15 solution-state standards. <sup>87</sup>Rb ( $I = 3/2$ ) and <sup>71</sup>Ga ( $I = 3/2$ ) chemical shifts were  
16 referenced to 1.0 M solutions of RbNO<sub>3</sub> (aq) and Ga(NO<sub>3</sub>)<sub>3</sub> (aq), respectively with  $\delta_{\text{iso}}$   
17 = 0.0 ppm for each nuclide.<sup>6,44</sup> <sup>119</sup>Sn ( $I = 1/2$ ) chemical shifts were referenced to neat  
18 Sn(CH<sub>3</sub>)<sub>4</sub> (l) with  $\delta_{\text{iso}} = 0.0 \text{ ppm}$ .<sup>15</sup>

19 All direct excitation experiments used radio-frequency (rf) field strengths (*i.e.*,  
20  $\nu_1 = \omega_1/2\pi$ ) between 10 and 30 kHz. Spin-locking fields ranging from 15 – 40 kHz  
21 were employed for cross-polarization experiments. WURST-80 pulses were used in  
22 all experiments, which were linearly swept over symmetric offsets with a total sweep  
23 range slightly larger than the total breadth of the powder pattern to be acquired.  
24 15000 equally spaced points were used to define the amplitude and phase  
25 modulated waveforms for the WURST-A pulse and 900 equally spaced points were

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

5 **Spectral processing and simulations.** All data were processed on a personal  
6 computer using custom-written code for MATLAB; this code is available from the  
7 authors upon request. Analytical simulations of NMR spectra were performed with  
8 the WSOLIDS<sup>45</sup> simulation package and SPINEVOLUTION<sup>46</sup>, as noted. Further  
9 experimental and processing details are provided in the **SI** and in the text.

10

#### 11 **4. Results and Discussion**

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



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

8

#### 9 4.1 Theoretical Simulations of 2D RAS Datasets

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

24 **Figure 2** shows nine simulated  $R_2$  RAS spectra, which were generated by  
25 applying the NNTF routine on simulated  $^{35}\text{Cl}$  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  $^{35}\text{Cl}$  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

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

17 Another parameter that influences the quality of  $R_2$  RAS spectra is the  
18 number of echoes collected in  $F_1$  (*i.e.*, the number of  $F_1$  points). **Figure 3** shows that  
19 increasing the number of echoes leads to better separation of the powder patterns in  
20 the  $R_2$  RAS spectrum (due to increased resolution in the indirect dimension), which  
21 may be especially useful for resolving inequivalent sites with very similar relaxation  
22 constants (120, 240, and 480 echoes were simulated in **Figure 3a**, **3b**, and **3c**,  
23 respectively). This is analogous to the collection of additional increments in standard  
24 2D NMR experiments. The  $T_2$  dataset simulated with 480 echoes gives an  $R_2$  RAS  
25 spectrum (**Figure 3c**) with the best separation between the overlapping patterns,

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

#### 13 4.2. $^{87}\text{Rb}$ SSNMR of a 40:1 $\text{RbCH}_3\text{CO}_2:\text{RbClO}_4$ w/w mixture

14  $^{87}\text{Rb}$  possesses several favorable NMR properties such as a high  
15 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),  
16 desirable relaxation characteristics (*i.e.*, long  $T_2^{\text{eff}}$  and/or short  $T_1$  relaxation time  
17 constants), and a moderate nuclear quadrupole moment (NQM) of 133.5(5) millibarn.  
18  $^{87}\text{Rb}$   $T_1$  and  $T_2^{\text{eff}}$  relaxation datasets were collected for the model compounds  
19  $\text{RbCH}_3\text{CO}_2$  and  $\text{RbClO}_4$ , as well as their mixture (*vide infra*). Each compound  
20 possesses a single rubidium site (**Figure S4a, S4b**)<sup>44</sup> with very different  $^{87}\text{Rb}$   
21 second-order CT powder patterns (quadrupolar NMR parameters have been  
22 previously reported).<sup>44</sup>

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

1 five evenly spaced frequency points across the powder pattern; the five partially  
2 recovered powder patterns were then fit to standard formulas<sup>48</sup> for each compound.  
3 This led to average  $T_1(^{87}\text{Rb})$  values of *ca.* 109 ms and *ca.* 213 ms for  $\text{RbCH}_3\text{CO}_2$   
4 and  $\text{RbClO}_4$  at room temperature, respectively (**Table S3, S4**). The  $T_2^{\text{eff}}(^{87}\text{Rb})$  time  
5 constants were measured using the WCPMG echo trains (**Figures 4a, 4b**);  
6 exponential fitting of the resulting  $T_2^{\text{eff}}$  decay curves<sup>48</sup> led to average  $T_2^{\text{eff}}(^{87}\text{Rb})$  of  
7 1.16(7) ms and 14(1) ms for  $\text{RbCH}_3\text{CO}_2$  and  $\text{RbClO}_4$ , respectively (**Table S1**). The  
8 details of collecting, processing, and analyzing the  $R_1$  and  $R_2^{\text{eff}}$  RAS spectra are  
9 explicitly described for these first two samples; similar methods were used for the  
10 remainder of the samples.

11  $T_2^{\text{eff}}(^{87}\text{Rb})$  echo trains were collected for  $\text{RbCH}_3\text{CO}_2$  and  $\text{RbClO}_4$  using the  
12 WCPMG sequence (**Figures 4a and 4b**, respectively) and processed as described in  
13 the SI. **Figure 4d** and **Figure 4e** show the WCPMG spectra of  $\text{RbCH}_3\text{CO}_2$  and  
14  $\text{RbClO}_4$ , respectively. **Figure 4c** shows the echo train of a 40:1  $\text{RbCH}_3\text{CO}_2$ : $\text{RbClO}_4$   
15 w/w mixture acquired with the WCPMG pulse sequence in *ca.* 40 minutes of  
16 acquisition time, and **Figure 4f** shows the resulting  $^{87}\text{Rb}$  WCPMG 1D spectrum of  
17 the overlapping CT powder patterns. The 40:1 w/w ratio of this mixture was chosen  
18 due to the much stronger signal intensity of  $\text{RbClO}_4$  in comparison to  $\text{RbCH}_3\text{CO}_2$ ,  
19 resulting primarily from a  $T_2^{\text{eff}}(^{87}\text{Rb})$  constant that is ten times longer and CT powder  
20 pattern that is six times narrower.

21 A  $T_1$  dataset was collected for this mixture using the WCPMG IR pulse  
22 sequence (**Figure 5a**). The NNTF routine was then used to determine the  
23 distribution of  $R_1$  relaxation rates (*i.e.*,  $R_1 = T_1^{-1}$ ) for each spectral frequency point.  
24 1000 potential relaxation constants were used in all NNTFs (unless stated  
25 otherwise); the resulting 2D RAS spectrum (**Figure 5b**) separates the overlapping

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

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

14 Despite the very similar relaxation characteristics of the two sites, the 2D  
15 contour plot in **Figure 5c** displays regions in which the  $\text{RbClO}_4$  or  $\text{RbCH}_3\text{CO}_2$   
16 powder patterns can be clearly identified (i) at points of maximum signal intensity (as  
17 indicated by the arrows) or (ii) best separation of the patterns (as indicated by the  
18 blue highlighted areas). At the points indicated by the arrows,  $R_1$  ( $T_1$ ) values of *ca.*  
19  $6.14 \text{ s}^{-1}$  (0.16 s) and *ca.*  $17.84 \text{ s}^{-1}$  (0.056 s) are measured for  $\text{RbClO}_4$  and  
20  $\text{RbCH}_3\text{CO}_2$ , respectively. These values are slightly different than the ones that were  
21 measured by fitting the  $T_1$  datasets for each of the individual compounds, primarily  
22 because of the large value of  $\lambda$  employed in the NNTF, which causes a broadening  
23 of the powder patterns in  $F_1$ , thereby complicating an accurate measurement of the  
24 relaxation rates from the  $R_1$  RAS spectrum. This dataset demonstrates, that in some  
25 cases, the areas of the RAS spectrum that give the best separation of the

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

3 The post-NNTF processing procedure discussed in the Theory Section was  
4 used to further refine the separation of these patterns. In this case, average  $R_1$   
5 values and co-added projections were calculated for each inequivalent chemical site  
6 by considering only the regions along  $F_1$  that are highlighted in **Figure 5c**. The post-  
7 NNTF processed  $R_1$  RAS spectrum (**Figure 5d**) clearly shows the separated  $^{87}\text{Rb}$   
8 CT powder patterns, even though the  $T_1(^{87}\text{Rb})$  constants for these compounds differ  
9 only by a factor of *ca.* 2 (**Table S3, S4**). These 1D projections of  $\text{RbCH}_3\text{CO}_2$  and  
10  $\text{RbClO}_4$  can then be imported into an appropriate fitting program and their NMR  
11 parameters determined (**Figures 5e, 5f**); the resulting quadrupolar parameters are  
12 similar to those reported in the literature for both compounds.<sup>44</sup>

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

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

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



1 relies essentially on an optimized radio-frequency (rf) field and a long enough  $T_2^{\text{eff}}$   
2 constant to permit proper encoding of the transverse relaxation behavior.  $R_1$  RAS,  
3 by contrast, is a 2D arrayed experiment requiring careful setting of the rf field and  
4 sweep rate of the WURST-A pulse (*i.e.*, to ensure the entire powder pattern is  
5 uniformly inverted). Missets in these parameters can not only drastically increase  
6 the overall experimental time, but can also affect the quality of the separations (*vide*  
7 *infra*). The projections of  $\text{Rb}_2\text{CH}_3\text{CO}_2$  (**Figure 6c**) and  $\text{RbClO}_4$  (**Figure 6d**) were fit  
8 with NMR parameters similar to the ones reported in the literature. The approximate  
9 values of the  $R_1(^{87}\text{Rb})$  and  $R_2^{\text{eff}}(^{87}\text{Rb})$  constants as determined from the RAS spectra  
10 are shown in **Table S2**.

11

#### 12 4.3. $^{71}\text{Ga}$ SSNMR of a 10:1 $\text{GaPcCl}:\text{Ga}(\text{acac})_3$ w/w mixture

13  $^{71}\text{Ga}$  is a receptive half-integer ( $I = 3/2$ ) quadrupolar nuclide, owing to its high  
14  $Q$  ratio ( $\gamma = 8.18117 \times 10^7 \text{ rad T}^{-1} \text{ s}^{-1}$ ,  $\nu_0 = 121.794 \text{ MHz}$  at 9.4 T)  
15 and high natural abundance (39.89%). The moderate NQM of  $^{71}\text{Ga}$  (107(1)  
16 millibarn) most often results in broadened second-order CT powder patterns that can  
17 span hundreds of kHz. These broad patterns often have inherently low S/N,  
18 resulting in lengthy experimental times, and making it challenging to resolve multiple  
19 overlapping patterns.

20 The  $R_1$  and  $R_2^{\text{eff}}$  RAS protocols were used to try to resolve the overlapping  
21  $^{71}\text{Ga}$  CT powder patterns resulting from a 10:1 gallium phthalocyanine chloride  
22 ( $\text{GaPcCl}$ ):gallium acetylacetonate ( $\text{Ga}(\text{acac})_3$ ) w/w mixture. The WCPMG spectrum  
23 of this mixture (**Figure 7c**) shows the overlapped  $^{71}\text{Ga}$  powder patterns; the one with  
24 a breadth of ca. 500 kHz corresponds to  $\text{GaPcCl}$  (**Figure 7a**) and the other (75 kHz  
25 in breadth) corresponds to  $\text{Ga}(\text{acac})_3$  (**Figure 7b**). Applying the NNTF routine to the

1  $T_2^{\text{eff}}$  dataset of the 10:1 GaPcCl:Ga(acac)<sub>3</sub> mixture (**Figure S5c**), which was  
2 collected in ca. 47 minutes of acquisition time using WCPMG, yields a high-quality,  
3 post-NNTF processed  $R_2^{\text{eff}}$  RAS spectrum (**Figure 7d**) in which the powder patterns  
4 corresponding to GaPcCl and Ga(acac)<sub>3</sub> are clearly separated. The 1D co-added  
5 projections for Ga(acac)<sub>3</sub> and GaPcCl are shown in **Figure 7e** and **7f**, respectively.  
6 Both of these projections were fit with NMR parameters similar to the ones reported  
7 in the literature<sup>6</sup>, which reinforces the fact that RAS is a suitable technique for not  
8 only identifying and separating overlapping powder patterns, but also useful for  
9 accurately obtaining the NMR tensor parameters that reveal detailed chemical  
10 information.

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

20

#### 21 4.4. <sup>119</sup>Sn SSNMR of a 1:1 SnPc:(n-Bu)<sub>2</sub>SnO w/w mixture

22 Tin possesses three NMR-active isotopes, with <sup>119</sup>Sn being the preferred  
23 isotope for NMR experimentation due to its high receptivity resulting from a large  
24 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  
25 higher natural abundance (8.58%). Despite these relatively favorable NMR

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

21 The BRAIN-CP/WCPMG (BCP for brevity) pulse sequence, which uses a train  
22 of WURST-CPMG pulses for refocusing (**Figure S1b**), was used to collect  $^{119}\text{Sn}$   
23 spectra of  $(\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2)_2\text{SnO}$  (dibutyltin(IV) oxide, abbreviated as  $(n\text{-Bu})_2\text{SnO}$ )  
24 and tin phthalocyanine chloride (SnPc), which are shown in **Figures 8a** and **8b**,  
25 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  $^{119}\text{Sn}$  and  $^1\text{H}$  channels, respectively) and a contact  
3 time of 30.0 ms. The corresponding experimental times to collect both  $^{119}\text{Sn}$  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  $^{119}\text{Sn}$  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  $^{119}\text{Sn}$   
13 powder patterns, as the  $\tau$  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  $R_2^{\text{eff}}$  RAS analysis was therefore attempted by applying the NNTF  
16 routine to the WCPMG  $T_2^{\text{eff}}$  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  $R_2^{\text{eff}}$  RAS spectrum of this 1:1  
19 mixture (**Figure 8d**) easily resolves the  $^{119}\text{Sn}$  powder patterns. The  $R_2^{\text{eff}}(^{119}\text{Sn})$   
20 constants determined from the  $R_2^{\text{eff}}$  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  $T_2^{\text{eff}}$  datasets that  
25 can then be processed using the NNTF algorithm to yield high-quality RAS spectra,

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

4

## 5 **5. Conclusions**

6       2D  $R_1$  and  $R_2$  relaxation-assisted separation (RAS) analyses can be used to  
7 separate overlapping UW NMR powder patterns originating from magnetically  
8 distinct sites for both spin-1/2 and quadrupolar nuclei, provided that their relaxation  
9 characteristics are distinct. The WCPMG and BCP pulse sequences are robust and  
10 can be easily used to collect  $T_1$  and  $T_2$  datasets, which can then be imported into  
11 MATLAB and processed with the NNTF routine to give the corresponding RAS  
12 spectra. The NNTF routine is easily implemented within MATLAB and is  
13 straightforward to use. NNTF effectively addresses the problematic small singular  
14 values that are characteristic of ill-posed inverse problems. This is especially useful  
15 when processing  $T_1$  and  $T_2$  relaxation datasets having low S/N and when attempting  
16 to resolve overlapping patterns originating from sites having similar relaxation time  
17 constants. The combined use of NNTF with post-processing of  $R_1$  or  $R_2$  RAS  
18 spectra can greatly aid in achieving clear separation of powder patterns for instances  
19 where the separation is poor due to either (i) low S/N, (ii) similar relaxation constants  
20 among magnetically distinct nuclei, (iii) multiple inequivalent sites (each of which  
21 gives rise to a unique powder pattern, which may overlap with one another), and/or  
22 (iv) combinations of these factors. Moreover, *a priori* knowledge of the relaxation  
23 constants and/or the NMR parameters is beneficial when defining the range of  
24 relaxation rates in the NNTF routine and when using the post-NNTF processing  
25 procedure; however, this information is not required in order to collect and process

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

17

## 18 **6. Supporting Information**

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

## 1 **7. Acknowledgments**

2 M.J.J. thanks the Ontario Ministry of Training, Colleges, and Universities for  
3 an Ontario Graduate Scholarship. R.W.S. thanks NSERC for funding this research  
4 in the form of a Discovery Grant and Discovery Accelerator Supplement. R.W.S. is  
5 also grateful for an Early Researcher Award from the Ontario Ministry of Research  
6 and Innovation and for a 50<sup>th</sup> Anniversary Golden Jubilee Chair from the University  
7 of Windsor. L.F. also acknowledges support from the Israel Science Foundation  
8 (grant 795/13), the ITN Marie Curie program 642773 “Europol”, the Kimmel Institute  
9 for Magnetic Resonance (Weizmann Institute), and from the generosity of the  
10 Perlman Family Foundation. We are also grateful for the funding of the Laboratories  
11 for Solid-State Characterization at the University of Windsor from the Canadian  
12 Foundation for Innovation, the Ontario Innovation Trust, and the University of  
13 Windsor.

14

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