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ARTICLE

Resolving complex mixtures: trilinear diffusion data

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Abstract Complex mixtures are at the heart of biology, and biomacromolecules almost always exhibit their function in a mixture, e.g., the mode of action for a spider venom is typically dependent on a cocktail of compounds, not just the protein. Information about diseases is encoded in body fluids such as urine and plasma in the form of metabolite concentrations determined by the actions of enzymes. To understand better what is happening in real living systems we urgently need better methods to characterize such mixtures. In this paper we describe a potent way to disentangle the NMR spectra of mixture components, by exploiting data that vary independently in three or more dimensions, allowing the use of powerful algorithms to decompose the data to extract the information sought. The particular focus of this paper is on NMR diffusion data, which are typically bilinear but can be extended by a third dimension to give the desired data structure.

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Introduction

NMR is a wonderfully versatile tool providing high quality information about biological systems. It is at its best with pure compounds, where all signals can safely be assumed to come from the same molecular species. Mixture analysis, however, is a much more difficult situation, and one that is commonly avoided by purifying the sample before NMR analysis. Such physical separation is often cumbersome and expensive, and can even completely defeat the purpose when it is the dynamics of the intact sample that are of interest. Mother Nature often presents her most interesting problems in the form of mixtures, and the capability of efficiently analyzing such samples is a fundamental part of biological research. One front-line technique in NMR analysis of intact mixtures is diffusion-ordered spectroscopy [DOSY (Johnson 1999; Morris 2007)], in which the signals from different compounds are distinguished by their diffusion properties (most commonly their hydrodynamic radii).

In a DOSY experiment the amplitudes of NMR signals are attenuated as described by the Stejskal–Tanner equation (Stejskal and Tanner 1965):

$$S = S_0 e^{-D\gamma^2\delta^2 g^2 \Delta'} \quad (1)$$

where S is the signal amplitude, S_0 is the signal amplitude in the absence of diffusion, D is the diffusion coefficient, δ is the gradient pulse duration, γ is the gyromagnetic ratio, g is the strength of the gradient, and Δ' is the diffusion time corrected for the effects of finite gradient pulse width. Equation 1 is appropriate for most DOSY experiments, but

when non-rectangular gradient pulses are used a modification may be necessary (Sinnaeve 2012). The decays of the various different signals of a given species in solution thus encode information about its diffusion.

The simplest way to analyze the results of such experiments is to treat each point or each peak in the NMR spectrum independently. While such basic DOSY analysis frequently provides valuable information, it is however limited by the classic difficulty of finding the constituent signals in a sum of exponential decays with different (similar) decay constants (Istratov and Vyvenko 1999; Nilsson et al. 2006). This restricts the types of problems that can be studied most productively to those where any overlapping signals come from mixture components that have relatively large differences in diffusion coefficient. For species which do not have signals that overlap in the NMR spectrum, DOSY can differentiate between molecules with as little as 1 % difference in diffusion coefficient, by using a numerically stable monoexponential fit [the High Resolution DOSY experiment (Barjat et al. 1995)]. However, in the general, and more common, case, signals do overlap, making the task of inverting a measured signal decay to give a diffusion spectrum much more difficult. This has spurred the development of various more sophisticated methods for processing DOSY data (Nilsson et al. 2006; Nilsson and Morris 2006; Nilsson and Morris 2007, 2008; Nilsson 2009; Colbourne et al. 2011; Van Gorkom and Hancewicz 1998; Windig and Antalek 1997; Stilbs and Paulsen 1996; Stilbs et al. 1996; Morris and Johnson 1993; Delsuc and Malliavin 1998; Day 2011; Stilbs 2013). They all have their pros and cons, but for overlapping signals the smallest difference in diffusion coefficient that can normally be resolved, even for very high quality data, is typically 30 %. Another limitation is that only a single separation criterion (diffusion) is used, making it impossible to separate signals from compounds of similar size, e.g., isomers. When appropriate this limitation can be overcome by adding a co-solute (a matrix) that changes the diffusion behavior of one or more of the species: matrix-assisted DOSY (Evans et al. 2009; Tormena et al. 2010; Adams et al. 2011; Rogerson et al. 2011; Cassani et al. 2012; Tormena et al. 2012; Zielinski and Morris 2009; Viel et al. 2003; Hoffman et al. 2008; Morris et al. 1994; Stilbs 1982; Kavakka et al. 2010).

Another way of looking at the task of resolving components in a DOSY data set is from a matrix algebra, or multivariate, point of view, analyzing the dataset as a whole rather than treating the diffusional attenuation of each point or peak in the NMR spectrum separately (Nilsson and Morris 2008; Windig and Antalek 1997; Stilbs and Paulsen 1996; Stilbs et al. 1996; Van Gorkom and Hancewicz 1998; Stilbs 2013, 2010). Here the structure of the DOSY data is bilinear (varying independently in two directions):

$$\mathbf{X} = \mathbf{C}^{\mathbf{T}}\mathbf{S} + \mathbf{E} \tag{2}$$

where $\mathbf{X}$ is the full data set consisting of a set of mixture NMR spectra (rows) that change in amplitude with each successive row as the pulsed field gradient amplitude is varied. The contributions of the individual mixture components can be described as a sum of the product of each spectrum, $\mathbf{S}$, with the transpose of the signal amplitude profile (here an exponential decay as a function of the square of gradient amplitude) $\mathbf{C}$, leaving the residual (or experimental noise) $\mathbf{E}$. In algebraic form this can be denoted:

$$\boldsymbol{X} = \sum_{n=1}^{N} \boldsymbol{c}_n \otimes \boldsymbol{s}_n + \boldsymbol{E} \tag{3}$$

where c_n and s_n are the signal amplitude profile and the spectrum for the nth component, $\otimes$ is the Kronecker product, and N is the number of components in the mixture.

The decomposition of $\mathbf{X}$ into $\mathbf{C}$ and $\mathbf{S}$ typically requires constraints to be imposed if it is to yield physically sensible results, because many possible linear combinations fit the data equally well (the rotational ambiguity problem). Common constraints include non-negativity, and imposing a known functional form for the signal decay.

Interestingly, when a third (or further) independent dimension is added, so that Eq. 3 becomes Eq. 4, the rotational ambiguity is broken (Cattell 1944):

$$\boldsymbol{X} = \sum_{n=1}^{N} \boldsymbol{c}_n \otimes \boldsymbol{s}_n \otimes \boldsymbol{k}_n + \boldsymbol{E} \tag{4}$$

This has two important consequences: (1) no constraints (or prior knowledge) are needed to obtain physically sensible results; (2) the combination of the variance in the $\mathbf{S}$ and $\mathbf{K}$ modes works in synergy, and much more complicated problems can be attacked than by investigating the $\mathbf{S}$ and $\mathbf{K}$ modes separately (Harshman 1970). The decomposition works best for a small number of monodisperse components (i.e., a low rank problem). The most common algorithm for decomposing multilinear data is parallel factor analysis [PARAFAC (Bro 1997)]. The bilinear case (Eq. 3) is not hard to visualize: it is intuitive that multiplying the ^{1}H spectrum with a vector containing the signal decay with increased gradient level should represent the contribution of that component to the DOSY data matrix. With that in mind it is then straightforward to extrapolate to additional dimensions. If a DOSY experiment is e.g., recorded for each time point during a chemical reaction then it is clear that the contribution of one chemical component to the whole data set is the (Kronecker) product of its ^{1}H spectrum, decay profile and concentration with time. A pictorial representation of PARAFAC is given in Fig. 1.

The PARAFAC decomposition is very powerful when the data conform to the trilinear model [e.g., it can resolve

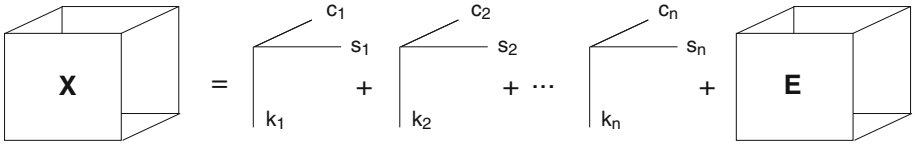

Fig. 1 A schematic representation of the PARAFAC model. In this investigation $\mathbf{c_i}$ and $\mathbf{s_i}$ represents the decay with diffusion and the ^{1}H NMR spectrum for each component respectively, while $\mathbf{k_i}$ is the independent third dimension

components from data that appear to be without signal (Khajeh et al. 2010)], but is also correspondingly sensitive so e.g., small changes in NMR peak shape and frequency will cause a failure to extract physically sensible components, if care is not taken to correct for such inconsistencies (Nilsson and Morris 2006). Interestingly, the addition of an extra dimension need not be costly in experimental time as in theory (Stegeman et al. 2006) as well as in practice (Nilsson et al. 2009a) the size in each dimension can be small.

Multilinear data analysis has been exploited in chemistry using fluorescence data since 1981 (Appellof and Davidson 1981). For diffusion NMR data, however, this application is just in its infancy (Dyrby et al. 2005; Pedersen et al. 2006). Even so, its use has already been demonstrated in a number of applications. For a set of samples containing glucose, maltose and maltotriose (Bro et al. 2010) or glucose, lactose and isoleucine (Pedersen et al. 2006) the spectra, diffusion decay and concentrations have been recovered when concentrations were set up as a fractional factorial design in order to optimize the variance. In a real application, PARAFAC was used to analyze the blood lipoprotein profile of a set of samples (Dyrby et al. 2005). PARAFAC has also been used to resolve time evolution and spectra for the acid hydrolysis of saccharides (Nilsson et al. 2009b; Khajeh et al. 2010), demonstrating the possibility of extracting kinetic information even for severely overlapped spectra, for spectra with a signal-to-noise level below the normal limit of detection, and for intermediates which may not be available in pure form. A special case is the use of relaxation as the third dimension, as this enables both the analysis of a single sample in equilibrium, and the extraction of relaxation information that can be used to understand better the dynamics of the molecules in the sample (Nilsson et al. 2009a).

In this investigation we demonstrate trilinear decomposition of NMR diffusion data on a set of samples with randomized concentrations within a narrow concentration band, a model system that more closely resembles e.g., metabolomics samples than was the case for previous studies. In addition, we show for a prototypical complex single sample that relaxation–diffusion encoded data can allow the construction of a superior DOSY representation. This is a step towards being able to analyze complex biological samples more efficiently by NMR.

Experimental

For the diffusion-concentration-NMR spectrum study, the sample set was comprised of 20 liquid samples, all containing low mM concentrations of 1-propanol (2.4–5.6 mM), 1-butanol (2.8–5.7 mM) and 1-pentanol (1.3–2.4 mM) in D_2O, with sodium 3-(trimethylsilyl)-propionate-2,2,3,3 d_4 (TSP) as a reference. All experimental measurements were carried out non-spinning at 298 K on a 500 MHz Varian Unity spectrometer using a 5 mm ^{1}H/^{13}C/^{15}N triple probe. The data were acquired using the Oneshot (Pelta et al. 2002) sequence with an imbalance factor $\alpha = 0.2$, using a diffusion delay $\Delta = 100$ ms, a diffusion-encoding pulse width $\delta = 1$ ms, and 10 nominal gradient amplitudes ranging from 3 to 27 G cm^{-1} in equal steps of gradient amplitude squared. 16,384 complex points were collected in 16 transients. The time-domain data were zero-filled once, apodized, and Fourier transformed.

For the diffusion–relaxation-NMR spectrum study, a sample was also evaluated containing the natural products camphene, geraniol and quinine, dissolved in methanol-d_4 with TMS as a chemical shift reference. Measurements were carried out without temperature regulation and non-spinning on a Varian Inova 400 MHz spectrometer in an air-conditioned room at approximately 20 °C, without spectrometer temperature regulation and with a passive probe air preconditioning system used to minimize temperature instabilities (Bowyer et al. 2001). A DRONE45 experiment, combining the decaying relaxation oneshot (DRONE) (Nilsson et al. 2009a) adaptation of the Oneshot method with the Oneshot45 variant (Botana et al. 2011), was carried out; here relaxation is encoded by incrementing the diffusion delay while keeping the diffusion encoding constant. The experiment was run with 5 gradient strength levels (ranging from 10.0 to 27.0 G cm^{-1} in equal steps of nominal gradient squared) and 5 relaxation delays (τ ranging from 0.2 to 3.2 s), making a total of 25 spectra, which were acquired with an initial delay d_1 of 5 s and with 16,384 complex data points and 16 transients. The total acquisition time was 1 h 7 min. All spectra were manually phased, reference deconvoluted with a target line shape of a 2 Hz Lorentzian (Morris et al. 1997), and baseline corrected in VnmrJ 2.2C before being exported to a text file. This file was imported into Matlab and processed by segmenting the spectrum into several regions and performing

PARAFAC analysis, with a suitable number of components, for each of them. The results were then plotted as DOSY-like spectra in which the positions of the peaks in the diffusion dimension are determined by the diffusion coefficients obtained by fitting the PARAFAC output for the diffusion-encoded dimension to Eq. 1, and the widths of the peaks are determined by the fit statistics.

For comparison with the DRONE experiment, a DOSY data set for a very similar sample (quinine, camphene and geraniol with TSP in methanol-d_4) from a previous publication (Colbourne et al. 2011) was used. This was acquired with the same spectrometer and temperature using the Oneshot (Pelta et al. 2002) sequence, with an imbalance factor $\alpha = 0.2$, together with a diffusion delay $\Delta = 200$ ms, a diffusion-encoding pulse width $\delta = 2$ ms, and 30 nominal gradient strength levels ranging from 3 to 27 G cm^{-1} in equal steps of gradient strength. 16,384 complex points were collected in 256 transients.

DOSY spectra were produced using the DOSY Toolbox (Nilsson 2009).

For the three-way decompositions, an open-source PARAFAC algorithm was used, as included in the N-way toolbox (Andersson and Bro 2000). Small changes were made to the code, but the functional part of the algorithm was used as provided.

Results and discussion

There are many situations in which the same components are present, at different concentrations, in a set of samples. Examples include a set of urine samples from different subjects in a metabolomics study, and a number of blood samples taken at different time points to follow the effects of administration of a drug to a patient. There are mixture analysis methods currently in use that are much better equipped to handle such samples, e.g., confocal microscopy on antibody-labelled samples (Barbe et al. 2008); and mass spectrometry, which in combination with chromatography has been used to identify around 10,000 different protein species in a cell line (Geiger et al. 2012), but these methods are often tedious, expensive and destructive.

The merits of NMR, in comparison, include the possibility of performing experiments under native-like conditions, and without additional labeling. However, the types of samples just mentioned are highly complex, containing hundreds of detectable compounds, and to try to determine the concentration profiles of all measurable components by multivariate means would be highly ambitious. As a first step, we need to study a far more constrained problem. A (very) simplified model of a biological study is a set of samples in which the concentrations of a small set of components are independently varied randomly to exclude complications of covariance, in a limited concentration band. Here we have chosen three simple alcohols that have too similar hydrodynamic radii to be resolved by diffusion alone (e.g., in a DOSY experiment). In Fig. 2, the spectra extracted by PARAFAC from DOSY data measured from a set of 20 mixture samples are shown to be virtually identical to those of reference spectra. In a study on real samples the likely desired outputs will be the spectra (to identify the components) and their concentrations in the respective samples. Here we show that the estimated concentrations very closely resemble those of the initial design (Fig. 3), with a substantial part of the remaining error expected to arise from uncertainties in the sample preparation (e.g., solvent and/or solute evaporation). It should also be noticed that the estimated concentration of each

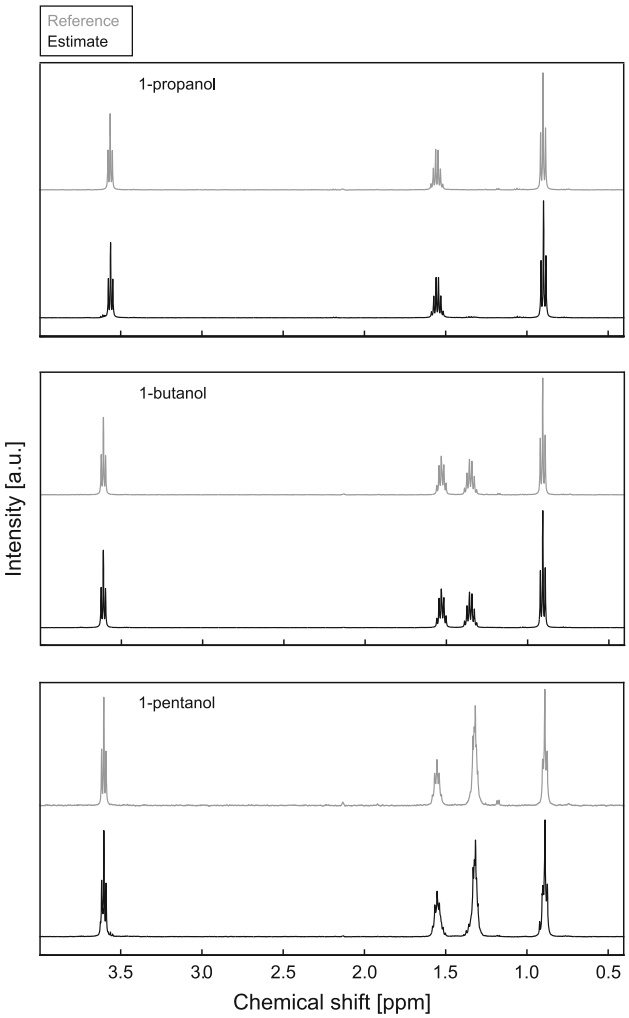

Fig. 2 Component spectra (*bottom*) obtained from a 3-component PARAFAC fit of diffusion NMR data from 20 samples containing randomized mixtures of propan-1-ol, butan-1-ol, and pentan-1-ol, and reference spectra (*top*)

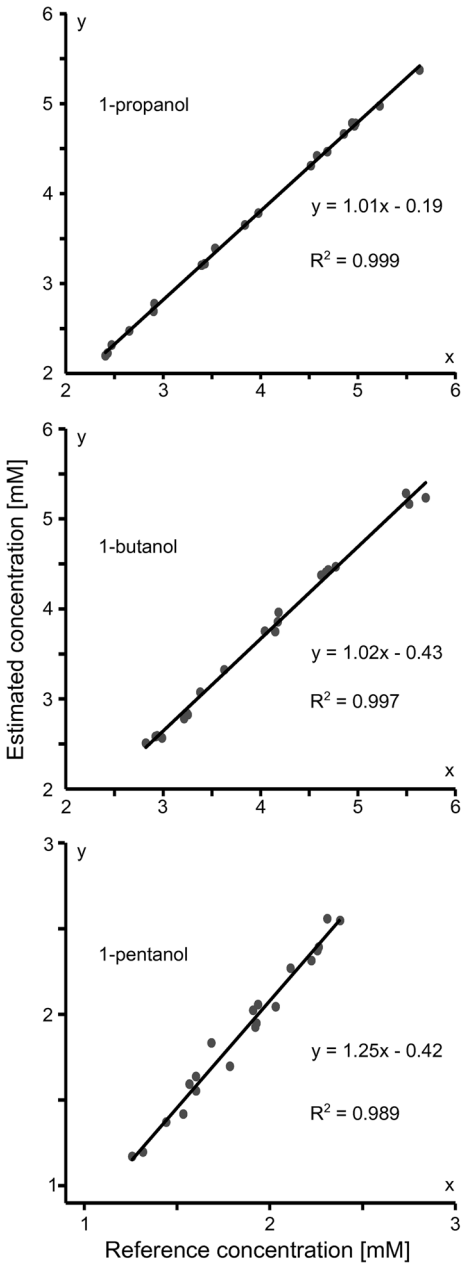

Fig. 3 Estimated concentration plotted against known concentration for 20 samples containing randomized mixtures of propan-1-ol, butan-1-ol, and pentan-1-ol

component may be arbitrarily rescaled as long as the product remains constant. This means that some sort of reference—e.g., a compound of known concentration in the mixture—is required if absolute amplitudes of the factors are required.

Mixture analysis in a set of samples is very important, and lends itself well to trilinear analysis. However, in many cases it is the composition of a single, intact, sample that is of interest. Now we are much more limited in the third dimension, but T_1 relaxation has previously been shown to help disentangle the spectra of a two-component system (Nilsson et al. 2009a). As relaxation differs for nuclei in chemically-distinct sites in a molecule, the resulting diffusion–relaxation encoding data (Fig. 4) is only locally, not globally, trilinear. However, as each multiplet shows, to a good approximation in practical experiments using full excitation, the same T_1 relaxation, the spectrum can be divided into regions that each contain only signal from one multiplet per component, and a local PARAFAC decomposition can be performed on each region independently. The results can then be merged into a composite data set in which the diffusion mode is the same for each component. A good way to display such data is in a DOSY plot, as in Fig. 5, where the DOSY plots from a standard HR-DOSY and a "T_1-DOSY" plot from a 5 component mixture (quinine, camphene, geraniol, and residual OH signals from methanol and water [from the solvent]) are shown. Spectral overlap causes signals to appear at misleading apparent diffusion coefficients in the HR-DOSY spectrum, complicating its interpretation. In the T_1-DOSY spectrum, in contrast, interpretation is much more straightforward. A method that is globally, rather than merely locally, linear for a single sample would be a substantial improvement; investigations are under way into averaging out effective relaxation rates within a spin system by magnetization transfer techniques.

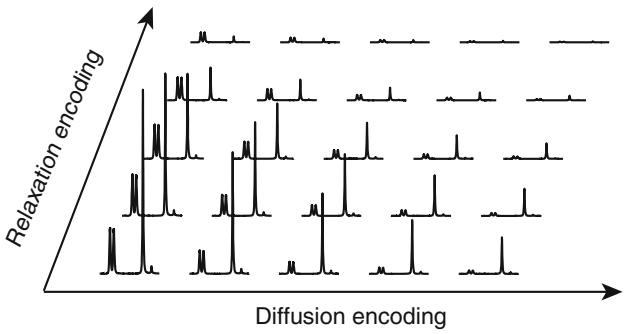

Fig. 4 Raw experimental data from the T_1-DOSY experiment. Relaxation and diffusion encoding are shown for representative signals originating from quinine and camphene between 3.9 and 4.1 ppm

Although this study was focused on extracting the spectra of individual compounds by exploiting differences in their diffusion coefficients, similar analyses can be performed using differences in both diffusion and relaxation. In macromolecules this would not only allow molecules aggregated to different extents to be distinguished, but would also allow different regions of a single macromolecule with different local dynamics to be identified using relaxation information.

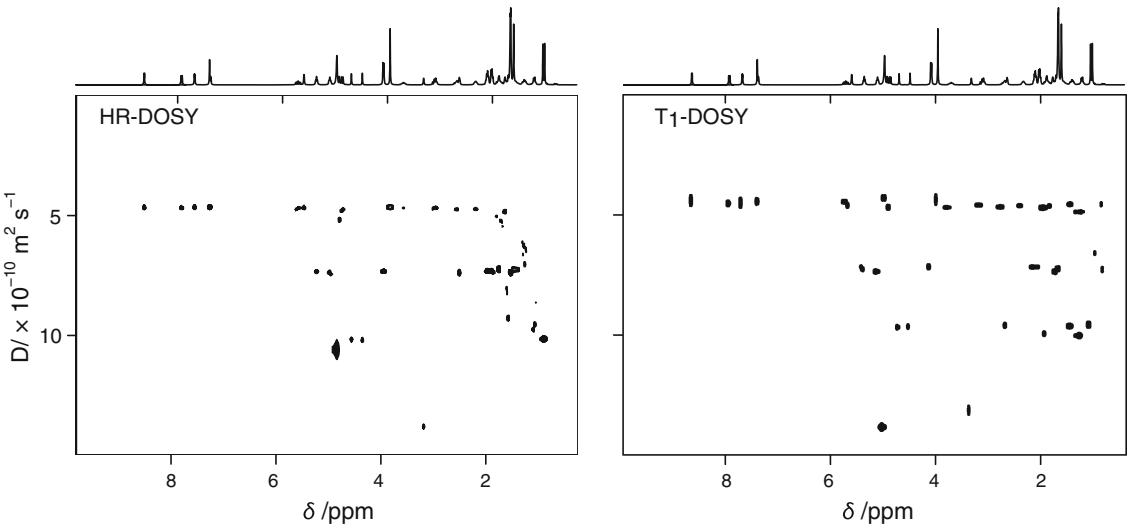

Fig. 5 HR-DOSY (*left*) and T_1-DOSY (*right*) spectra for a mixture of quinine, camphene and geraniol in methanol d_4. Overlap in the chemical shift domain causes signals to appear at erroneous apparent diffusion coefficients in the HR-DOSY spectrum, while in the T_1-DOSY it is clear that there are only three components between 4 and 10×10^{-10} m^2 s^{-1}

Conclusions

The ability to characterize complex mixtures is important to anyone working with biological systems. Unfortunately NMR, one of our most powerful spectroscopic tools, often struggles when applied to mixtures. New and better methods of analyzing biological samples by NMR would be very welcome. Here we illustrate the use of NMR diffusion data in combination with powerful multi-way decompositions as a promising route to a better understanding of mixture spectra. Clearly there is a lot of work to be done before we can attack more complex problems, but it is already evident that this method can help unravel problems with limited numbers of components that were previously inaccessible to NMR analysis.

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