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The DOSY Toolbox: A new tool for processing PFG NMR diffusion data

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ABSTRACT

The DOSY Toolbox is a free programme for processing PFG NMR diffusion data (sometimes loosely referred to as DOSY data), distributed under the GNU General Public License. NMR data from three major manufacturers can be imported and all processing is done in a user-friendly graphical user interface. The Toolbox is completely free-standing in the sense that all necessary basic processing of NMR data (e.g., Fourier transformation and phasing) is catered for within the programme, as well as a number of methods specific to DOSY data (e.g., DOSY and SCORE). The programme is written in MATLAB® and as such can be run on any platform, but can also run independent of MATLAB® in a free-standing compiled version for Windows, Mac, and Linux.

1. Introduction

Pulsed field gradient (PFG) diffusion NMR, using spin or stimulated echoes(PFGS[T]E), for the study of mixtures [1] is now an important tool for many chemists, and major manufacturers of spectrometers offer different hardware and software implementations to acquire and process such data. In this publication the term DOSY data/experiments will be also be used, in its loosest and most generally accepted sense, as synonymous with PFG diffusion NMR data. Although DOSY (Diffusion-Ordered Spectroscopy [2,3]) is strictly speaking a processing and display method for PFG diffusion NMR data, it is the most commonly used scheme and the catchy name has been widely adopted in the community. Although some software to process DOSY data is supplied by all the major NMR manufacturers, they all offer different selected methods. The DOSY Toolbox offers free access to a number of important processing schemes for DOSY data on a platform that is independent of the brand of spectrometer. It is also released as open source, which gives it potential as a platform for implementation of new (and existing) methods by any user. The DOSY Toolbox has the capability to use raw data from Bruker, Jeol and Varian but is not intended to replace these manufacturers' own software; it has been developed as a complementary tool.

This publication highlights some of the important features in the DOSY Toolbox, but before that it may be useful to set the scene with a brief introduction to DOSY data and experiments. A more thorough description of PFG diffusion NMR and its importance is beyond the scope of this paper and the reader is referred to the many reviews written [2–9]. In a DOSY experiment, a series of NMR spectra is normally acquired in a spin or stimulated echo as a function of PFG amplitude, with the amplitude of each signal decaying at a rate determined by the diffusion coefficient. The ideal behavior for unrestricted diffusion is described by the Stejskal–Tanner equation [10]:

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

where S is the spin or stimulated echo signal amplitude, S_0 is the amplitude in the absence of diffusion, γ is the magnetogyric ratio, g is the gradient amplitude, and Δ' is the diffusion time corrected for the effects of the finite gradient pulse width δ. As the translational diffusion is the same for the whole molecule, the diffusion coefficient carries information that can be used to distinguish between the signals from different molecular species, and most processing of DOSY data involves fitting the experimental data to some form of the Stejskal–Tanner equation. However, processing DOSY data is often not trivial or straightforward; at the heart of it lies the classic mathematical problem of inverting exponentials (e.g., Eq. (1)) by some approximation to the inverse Laplace trans-

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form (ILT) [5]. In order to get the most out of DOSY data a number of processing methods with different assumptions and *a priori* knowledge have been developed.

The DOSY Toolbox is a freely available programme which includes a simple interface to many of these methods, some which have only recently been developed and therefore presently are only available in the software described. Selected features are illustrated here with examples using real data from a simple mixture; a more complete description of the features of the Toolbox can be found in the documentation supplied with the programme.

2. Features

The DOSY Toolbox acts as a free-standing tool for the processing of DOSY data, and being open source serves a platform for quickly developing and implementing new methods. An important feature is therefore the range of import filters that handle raw (unprocessed) data from the major manufacturers (Bruker, Jeol and Varian); data can also be saved and recalled in the DOSY Toolbox format (*.nmr). Processing is performed in a user-friendly graphical user interface (Fig. 1) where all of the features necessary to transform raw data before submitting it to further (e.g., DOSY) processing are accessible. These include Fourier transformation, zero filling, phasing, apodisation, baseline correction and reference deconvolution [11,12]. While is convenient to be able to do this pre-processing in the DOSY Toolbox, the main justification for its existence is obviously the range of DOSY data-related processing methods. In the current version these include basic DOSY (mono [13]- and multi-exponential [13–15]), Direct Exponential Curve Resolution Algorithm (DECRA [16]), Speedy Component Resolution (SCORE [17]) and one implementation of Multivariate Curve Resolution (MCR [18,19]). In the DOSY processing section below, these and some other methods are described in more detail. The results of DOSY and SCORE analyses are shown for DOSY data collected from a simple mixture of sucrose, *n*-propanol and isopentanol.

3. Processing DOSY data

3.1. Preparing the data

This publication is mainly concerned with the processing of DOSY data, but to get the best results out of DOSY experiments it is naturally important to ascertain that good data are acquired in the first place. The many reviews on PFG diffusion NMR and DOSY [2–9] offer a good starting point for information on how to optimize DOSY experiments.

It is important to keep in mind that when processing DOSY data the result is much more strongly influenced by the quality of the input data than for 'normal' 2D NMR (e.g., COSY) processing based on the 2D Fourier transform. DOSY data processing involves a fitting or some other approximation to the ILT (which can give wildly different results depending on small differences in the input data 20]), instead of the linear, more robust and stable Fourier transform. It is therefore important to prepare the data carefully before submitting it to further (e.g., DOSY) processing. The main tools are window functions, phase correction, baseline correction, reference deconvolution [11,12], and correction for non-uniform field gradi-

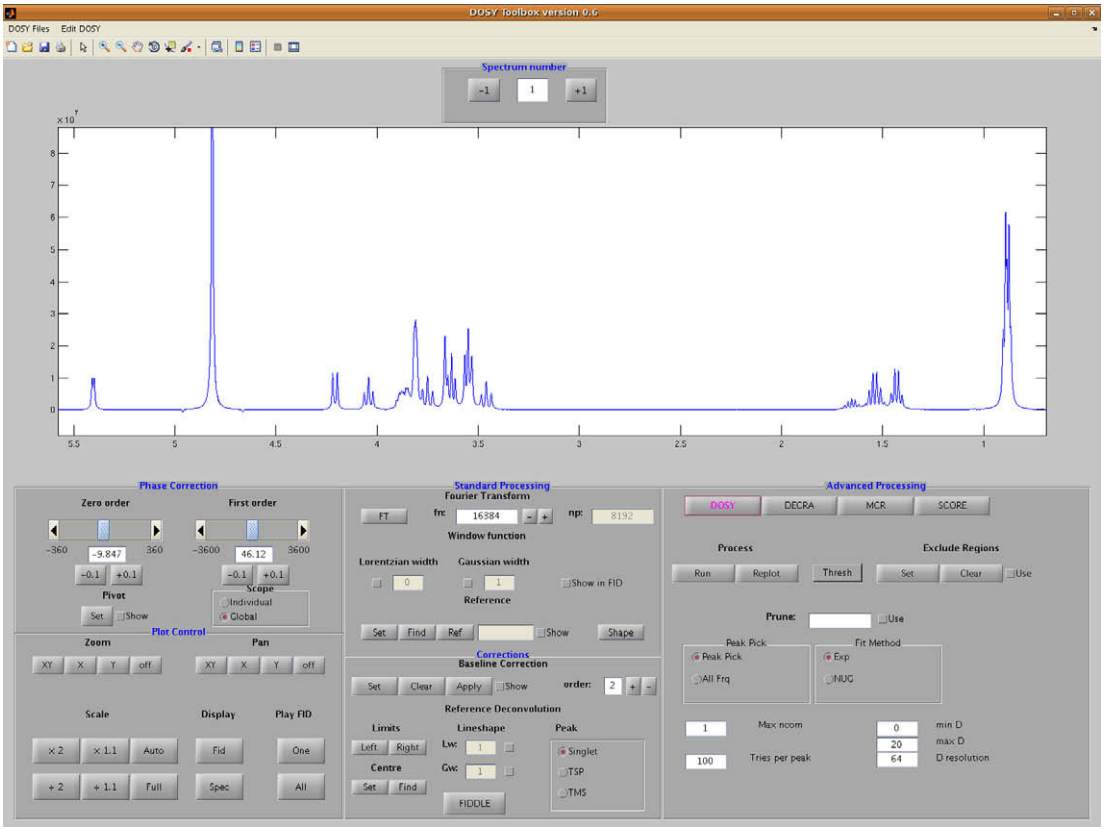

Fig. 1. The main window of the graphical user interface of the DOSY Toolbox. Most of the functionality is easily accessible from here. The spectrum shown is the least attenuated spectrum from the DOSY data set for the demonstration sample. The HOD peak at 4.8 ppm is removed from further analysis (i.e., the DOSY and SCORE processing in Figs. 2–4) by setting all points to zero.

ents (NUG [21]). When applying a window function, a compromise has to be made between maximizing signal-to-noise ratio and minimizing spectral overlap. The optimal choice is dependent on the DOSY processing methods to be used. For High Resolution DOSY [13], described in detail below, it is vital to minimize signal overlap and here some resolution enhancement may be in order; a sensible choice is often a Lorentz-to-Gauss transformation [22]. For multivariate methods such as SCORE [17], the optimal strategy is less obvious and is often found by trial and error. Generally, careful correction of the signal phase is important to minimize spectral overlap. In DOSY data it is also not uncommon to have a zeroth order phase error that depends on the amplitude of the diffusion-encoding gradients. In the Toolbox this can be corrected for by adjusting the phases of spectra from different gradient increments individually; this is particularly useful when it is not possible to use reference deconvolution (*vide infra*), which will generally correct for such phase errors.

Baseline correction should normally be used. The major reasons are that most DOSY data processing schemes assume that the signal decays to zero and not to a constant value, and that the baseline offset varies with gradient amplitude. In the DOSY Toolbox, baseline correction is performed by subtracting a polynomial that has been fitted to signal-free regions of the spectrum. Many significant sources of systematic error in DOSY data (and in NMR data generally) can be corrected for by reference deconvolution, where prior knowledge about a reference signal is used to remove systematic errors that affect all peaks in a spectrum in the same way (e.g., lineshape errors, phase errors and frequency drifts). This approximately linear process relies on having a well-resolved reference singlet present at a significant amplitude in all gradient increments; for small to medium molecules, TMS (tetramethylsilane) and TSP (sodium 3-(trimethylsilyl)-propionate-2,2,3,3-d_4) are sensible choices as reference compounds. In this laboratory reference deconvolution is used routinely, and has been shown to offer significant improvements for DOSY data [15,17,23]. In PFG diffusion NMR experiments, a major source of systematic error that cannot be corrected for by reference deconvolution is the effect of non-uniformity of the field gradients used for diffusion-encoding. This causes signal decay to deviate from the ideal Stejskal–Tanner behavior of Eq. 1, and can have a profound effect on the results on the processing of DOSY data [15,17,23–25]. Fortunately, the (non-)uniformity of the field gradients can be mapped and then corrected for by using an alternative equation to describe the signal decay [26,21]. Such an approach, using an equation based on the exponential of a power series, has been used for a decade in this laboratory:

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

where the coefficients c_i depends on the probe and pulse sequence. The DOSY Toolbox allows the use of pure exponential (Eq. 1) or the NUG corrected Stejskal–Tanner equation (Eq. 2) for relevant processing methods.

3.2. Processing methods for DOSY data

It is assumed here that the pre-processed DOSY data set can be described as signal $S(f, g)$ as a function of frequency (f) and pulsed field gradient amplitude (g). This assumption holds for most experimental data sets (exceptions include when attenuation is achieved by incrementing the gradient pulse width δ). It is also assumed that the sample contains only monodisperse components; this more restrictive assumption will be returned to when the effects of polydispersity are discussed later. To demonstrate the functionality of the DOSY Toolbox, an example data set for a simple mixture containing sucrose, *n*-propanol and isopentanol will be used. The data were corrected by reference deconvolution using the TSP signal to a target line shape of a 3 Hz Lorentzian, giving a signal-to-noise ratio of approximately 20,000:1 in the least attenuated spectrum. The region containing the HOD resonance (4.6–5.1 ppm) was excluded from analysis by setting all points to zero. In this paper, the Stejskal–Tanner equation corrected for non-uniform gradients (Eq. 2) was used throughout.

There are two main classes of DOSY data processing: univariate [13–15,27–34] and multivariate [16–19,23,35–37]. In the former, each signal is processed individually, and in the latter whole spectra (or parts of spectra) are processed simultaneously. The familiar pseudo-2D DOSY plot is mainly used to display results from univariate processing, while the norm for multivariate processing is to display fitted spectra for individual components.

The most basic (and often most effective) way to process DOSY data is by the High Resolution DOSY approach [13]. Here, the decay of each signal is fitted to a single exponential decay (e.g., Eqs. 1 or 2) and the data are presented in a pseudo-2D DOSY plot. Each peak is, in the diffusion dimension, a Gaussian centered on the fitted diffusion coefficient with a width determined by the statistics of the fit. In HR-DOSY the primary assumption is that each signal arises from one species in the mixture. The HR-DOSY spectrum of the demonstration data set (Fig. 2) immediately reveals both the strengths and weaknesses of the method: the well-resolved peaks in the region between 0.75 and 1.75 ppm (originating from *n*-propanol and isopentanol) show unambiguous separation in the diffusion dimension, despite relatively similar diffusion coefficients; where the signals overlap, as in the region around 3.5 ppm, the fitted diffusion coefficient does not correspond to that of a single molecular species (see below) and it is much more difficult to assign the peaks based on diffusion data.

When the primary assumption of HR-DOSY holds, it offers excellent resolution in the diffusion dimension. Differences as small as 0.5% in diffusion coefficient can be detected. When, however, signals do overlap (as is the norm for all but the simplest mixtures), the decay of a given signal contains contributions from more than one mixture component. Monoexponential fitting then leads to apparent diffusion coefficients that are a compromise value between those of the species involved, severely complicating the interpretation of spectra. It is not straightforward to determine when a signal decay contains contributions from more than one species, as a sum of two exponentials with similar decay constants is almost indistinguishable from that of a single exponential with an intermediate decay constant. Fitting to a single exponential therefore often gives good fit statistics. Close examination of the residuals may indicate where there are superimposed exponentials, but the effect can be easily confounded with the effect of systematic errors such as non-uniform gradients [15]. The very good resolution in the diffusion domain generally makes HR-DOSY the first choice for processing, and even when some overlap is present a skilled user can often interpret the HR-DOSY plot to good effect.

When signal overlap is severe in the ^{1}H spectrum, one of the many more sophisticated 2D [13,24,38–43] or 3D [39,44–55] DOSY experiments available will often allow individual peaks to be resolved, allowing the HR-DOSY approach to be used. It is however not always desirable or even possible (e.g., due to restrictions in time, signal-to-noise ratio etc.) to use such experiments. The DOSY Toolbox therefore provides a number of more advanced processing methods, to aid in the extraction of useful information from data in which signals from different species overlap. A seemingly straightforward way of resolving the diffusion data from overlapped peaks is to fit each decay to a bi- or even multi-exponential decay. This can be very effective when data are of high quality and high signal-to-noise ratio, as in the demonstration data set used here (Fig. 3). The multi-exponential approach puts very high demands

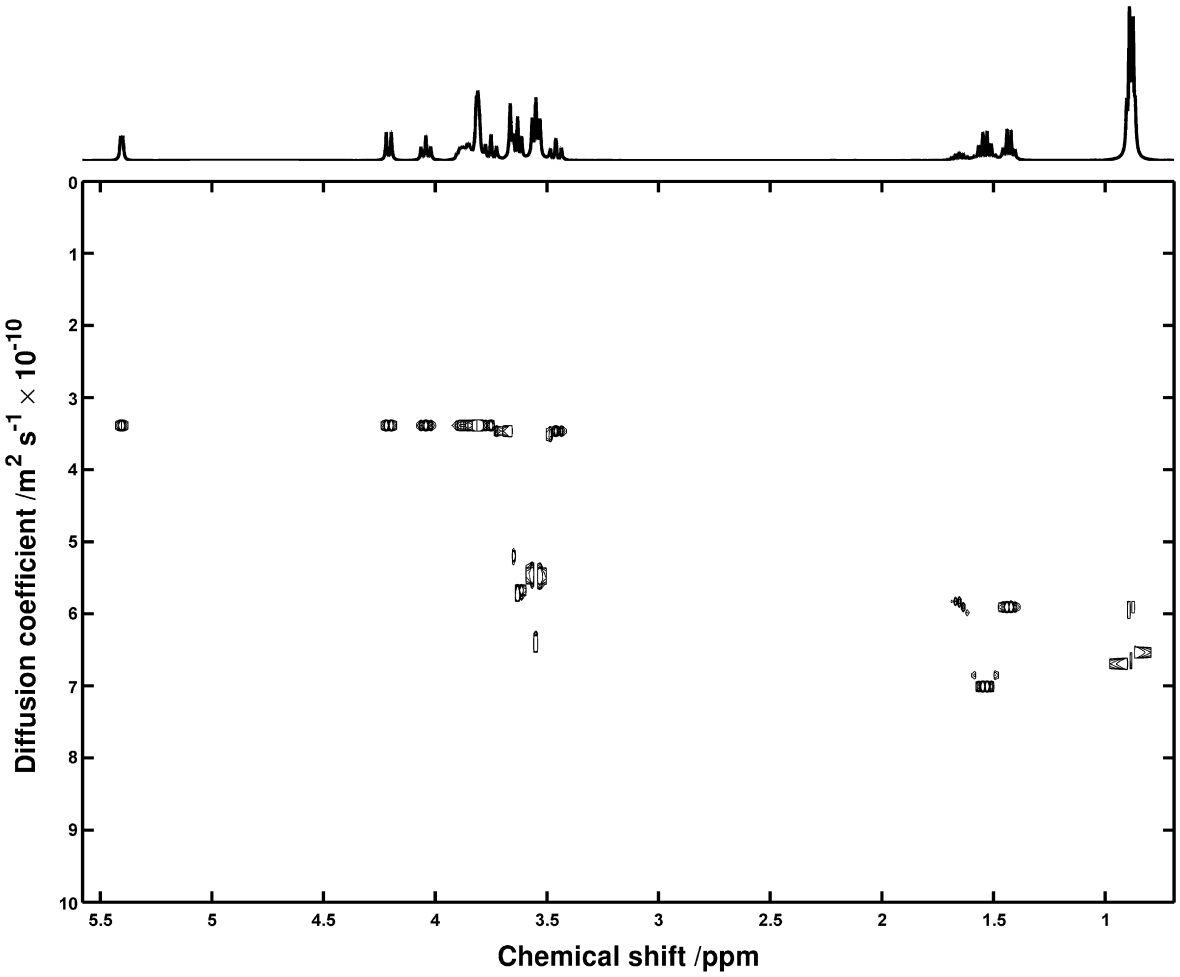

Fig. 2. High Resolution DOSY spectrum of the demonstration data. Signals originate from sucrose (diffusion coefficient 3.4×10^{-10} m^2 s^{-1}), isopentanol (diffusion coefficient 5.9×10^{-10} m^2 s^{-1}), and *n*-propanol (diffusion coefficient 7.0×10^{-10} m^2 s^{-1}). Where signals overlap, the apparent diffusion coefficient is a compromise between the coefficients of involved species. The most obvious example is around 3.6 ppm, where signals from all three species overlap and the assignments are difficult; the subtle effects of more limited overlap can be seen for the multiplets around 0.9 and 1.5 ppm (e.g., the smallest multiplet components from the *n*-propanol signal at 1.5 ppm are dragged towards the isopentanol signals). The region containing the HOD resonance (4.6–5.1 ppm) was excluded from the analysis.

on the data, and is most effective where diffusion coefficients are rather different and concentrations similar [20]. As a rule of thumb for data with a signal-to-noise ratio of 10000:1, the lower limit for the detection of differences in diffusion coefficients is around 30% for a biexponential fit, and a factor of two for tri-exponential. Tri-exponential analysis is probably the practical limit for univariate methods.

In univariate processing, each signal is treated as independent, although in a DOSY experiment all signals of a given component should, in the absence of exchange [56,57], show identical diffusion behavior. Multivariate methods exploit this covariance by fitting the entire spectra (or chosen parts thereof) simultaneously, with the aim of increasing the probability of successfully extracting component spectra. The contribution of a single compound to the DOSY data set, represented as a matrix $\boldsymbol{D}$, is the outer product of two row vectors:

$$\boldsymbol{D} = \boldsymbol{c}\boldsymbol{s}^{\mathrm{T}} \tag{3}$$

where $\boldsymbol{s}$ is the unattenuated spectrum, $\boldsymbol{c}$ is the decay profile, and T denote the transpose. When the data set contains more than one component, the vectors become matrices $\boldsymbol{S}$ and $\boldsymbol{C}$ with the number of rows equal to the number of components, and in experimental data there is a further contribution $\boldsymbol{E}$ from random and systematic error.

$$\boldsymbol{D} = \boldsymbol{C}\boldsymbol{S}^{\mathrm{T}} + \boldsymbol{E} \tag{4}$$

Multivariate methods are concerned with finding the matrices $\boldsymbol{S}$ and $\boldsymbol{C}$ that best represent component spectra and decays.

Methods used for the multivariate analysis of DOSY data include DECRA [16], MCR [19] and (S)CORE [17,35,36]; they all have pros and cons as described previously [17]. For example, DECRA is very fast, but relies on experimental data conforming to pure exponential decays; MCR makes no assumptions on the decay shape but is very reliant on good starting guesses and constraints; and for SCORE a known/assumed decay shape is a prerequisite. SCORE [17] is based on the COmponent REsolved NMR [35,36] (CORE) algorithm but uses a faster, linear, kernel. In all of these methods the number of components must be specified by the user. Such multivariate data processing can give excellent estimates of the component spectra, as exemplified by a three-component SCORE fit of the demonstration data (Fig. 4); the spectra of all three-components, sucrose, *n*-propanol and isopentanol, are in essence identical to the reference spectra.

Fitting data where the mixture contains polydisperse components is even more challenging than when discrete (monodisperse)

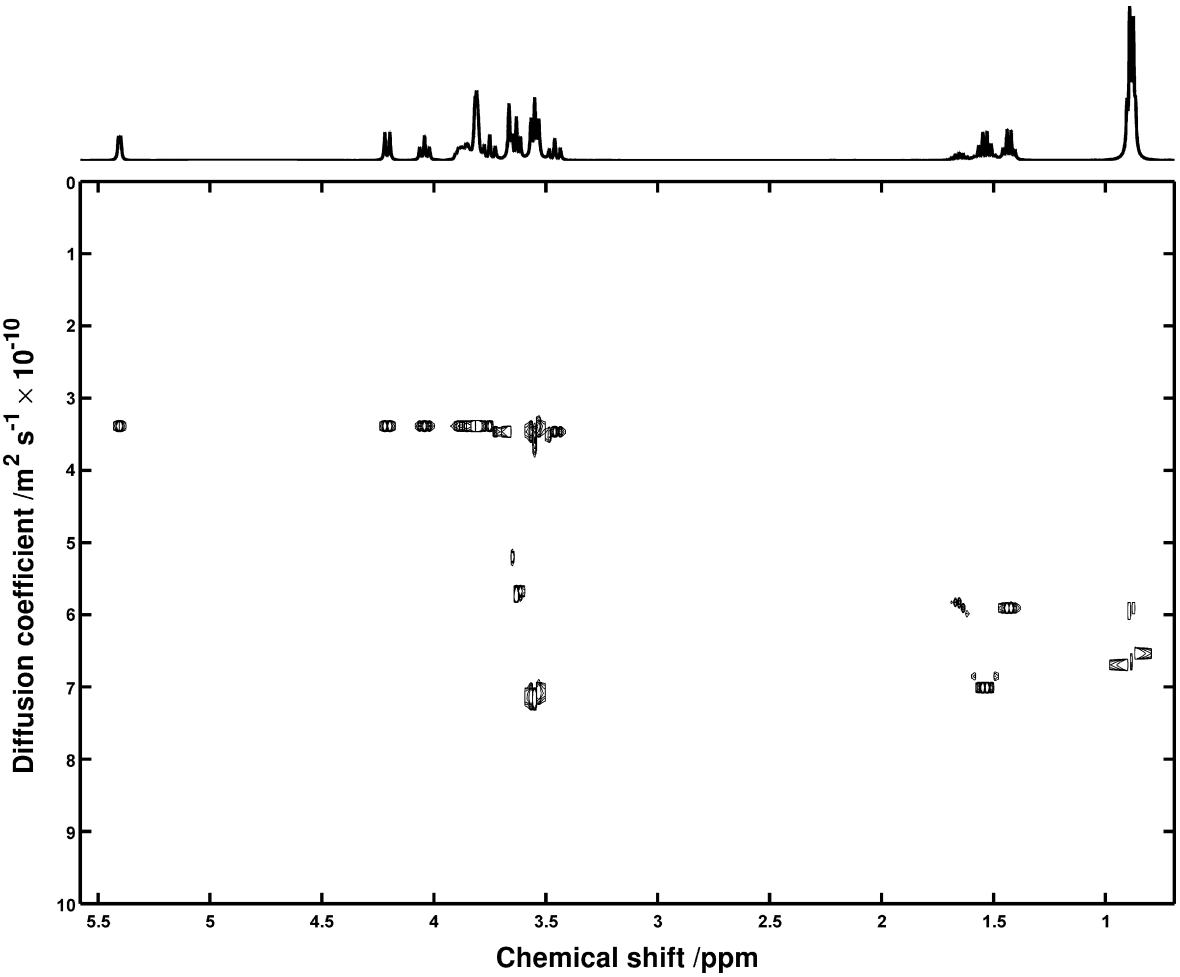

Fig. 3. DOSYspectrum resulting from biexponential fitting of the demonstration data. The signals originate from sucrose (diffusion coefficient 3.4×10^{-10} m^2 s^{-1}), isopentanol (diffusion coefficient 5.9×10^{-10} m^2 s^{-1}), and *n*-propanol (diffusion coefficient 7.0×10^{-10} m^2 s^{-1}). The overlaping signals around 3.6 ppm, where the assignments were ambiguous in the HR-DOSY (Fig. 2), can now easily be assigned. The region containing the HOD resonance (4.6–5.1 ppm) was again excluded from the analysis.

data can be assumed. Here it is common to use regularized ILT methods incorporating constraints such as non-negativity and smoothness. Univariate methods used for fitting DOSY data of polydisperse samples include CONTIN [31], MaxEnt [28] and neural networks [33]; these are not currently implemented in the DOSY Toolbox. When it comes to the multivariate methods, MCR should in principle be able to accommodate polydispersity; in (S)CORE the decay function can be chosen to accommodate polydispersity [58]; but for DECRA the assumption of pure exponential decay (Eq. 1) is integral to the algorithm and therefore deviation from this (e.g., polydispersity and the effect of non-uniform gradients) can in general not be treated [59,60], although partial compensation can be achieved by tailoring the gradient levels used during acquisition [25].

4. Experimental

The demonstration sample consisted of 1% sucrose, 0.2% *n*-propanol and, 0.2% isopentanol (w/v) in D_2O with sodium 3-(trimethylsilyl)-propionate-2,2,3,3-d_4 (TSP) as a chemical shift reference. Data were acquired using a 5 mm diameter indirect detection probe on a 400 MHz Varian Inova spectrometer at 25 °C, non-spinning. The Oneshot sequence [61] was used with a diffusion delay (Δ) of 0.3 s, a total diffusion-encoding pulse width (δ) of 3 ms, and nominal gradient strengths ranging from of 3.0 to 27.3 G cm^{-1} in equal steps of gradient squared. For each of 25 gradient amplitudes, 256 transients of 8192 complex data points were acquired. The coefficients $\boldsymbol{c}_1$–$\boldsymbol{c}_4$ in Eq. (2) set by the calibration of the non-uniform field gradients were 0.928, -9.78×10^{-3}, -3.83×10^{-4} and 2.51×10^{-5}, respectively [21].

5. Conclusion

The analysis of mixtures by PFG diffusion NMR is a technique growing in importance. The DOSY Toolbox allows users to have access to a common platform for the processing of DOSY data, irrespective of their brand of spectrometer. The best processing method for DOSY data is very dependent on the individual data set and the information required. It is therefore useful for the analyst to have a range of methods available. In many cases a number of complementary methods may be needed to extract the desired information.

The DOSY Toolbox gives access to some new methods that have not yet become available in commercial software, and the open source licence allows rapid development and implementation of novel processing methods. The programme is released in the hope that it can supply users with the most important current tools for DOSY processing, and that new methods will be quickly implemented as they are developed.

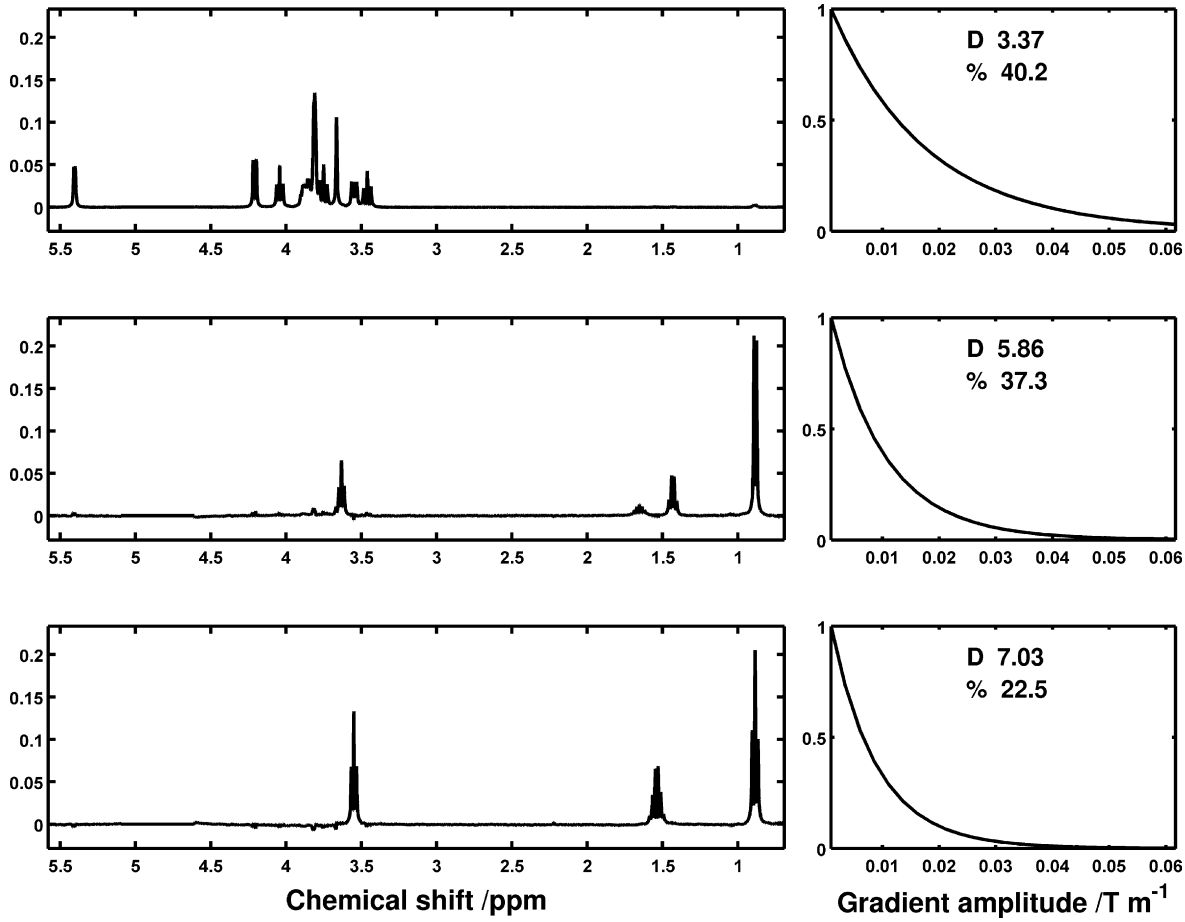

Fig. 4. SCORE components of a three-component fit of the demonstration data. All component component spectra can be easily identified respectively, as sucrose (top), isopentanol (middle), and *n*-propanol (bottom). The diffusion coefficients (D) are in the unit of 10^{-10} m^2 s^{-1}, and the percentage figure quoted is the fitted contribution of each component to the total signal. The region containing the HOD resonance (4.6–5.1 ppm) was excluded from the analysis.

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Appendix A. Requirements/license

The DOSY Toolbox is open source and freely available under the GNU General Public License (version 3) and as such is distributed in the hope that it will be useful but comes with no warranty. All source code is written in the MATLAB® language. The current DOSY Toolbox version is written in MATLAB® version 7.8 (R2009a), but ought to be compatible with version 7.6 and above. The Toolbox can be run directly on any platform that has an appropriate MATLAB® version installed, including the Optimization and Statistics Toolboxes (the dependency on the Statistics Toolbox will most likely be removed in future versions). Compiled versions of the Toolbox that run independent of any MATLAB® installation are available for Windows, Mac, and Linux.

A copy of the DOSY Toolbox (source code and some compiled versions) can be downloaded from the author's homepage (http://personalpages.manchester.ac.uk/staff/mathias.nilsson/), or a copy can be sent by email on request.

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