



Communication

Single-scan 2D DOSY NMR spectroscopy

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ABSTRACT

Spatial encoding is a particular kind of spin manipulation that enables the acquisition of multidimensional NMR spectra within a single scan. This encoding has been shown to possess a general applicability and to enable the completion of arbitrary n D NMR acquisitions within a single transient. The present study explores its potential towards the acquisition of 2D DOSY spectra, where the indirect dimension is meant to encode molecular displacements rather than a coherent spin evolution. We find that in its simplest form this extension shows similarities with methods that have been recently discussed for the single-scan acquisition of this kind of traces; still, a number of advantageous features are also evidenced by the “ultrafast” modality hereby introduced. The principles underlying the operation of this new single-scan 2D DOSY approach are discussed, its use is illustrated with a variety of sequences and of samples, the limitations of this new experiment are noted, and potential extensions of the methodology are mentioned.

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Introduction

Two-dimensional nuclear magnetic resonance (2D NMR) plays a fundamental role in expanding the resolution and in increasing the information content that can be delivered by this kind of spectroscopy [1]. These experiments will generally encode along their indirect domain an evolution phase $\phi_1 \propto \Omega_1 t_1$, proportional to the frequency set Ω_1 that one is attempting to determine. These coherences can then be identified and correlated against a second set of frequencies Ω_2 , by repeated incrementations of the t_1 time parameter over a set of independent scans [1–3]. A variant to these coherence correlations is offered by the so-called 2D diffusion-ordered spectroscopy (DOSY) experiment, an approach meant to encode along its indirect domain the effects of random Brownian motions [4,5]. DOSY relies on a 2D Jeener–Ernst scheme in the sense of bringing into correlation two different kinds of information along corresponding dimensions; it differs from this classical scheme, however, in that instead of incrementing a t_1 time variable it usually increments the effects of a field gradient. A particularly common approach changes the value of a so-called q -variable, denoting the action that opposed pulsed field gradients will have in encoding the effects of molecular displacement (Fig. 1A). In the resulting pulsed-gradient spin-echo (PGSE) experiment [6,7], the action of a pair of linear $G = \frac{\partial B_0}{\partial z}$ square-shaped field gradients pulsing over a relatively short duration τ and separated by a delay Δ , will impart on an NMR peak a diffusion-derived decay:

$$\ln \frac{A(q)}{A(0)} = -q^2 \left(\Delta - \frac{\tau}{3} \right) \cdot D = -bD; \quad (1)$$

where D is the diffusion constant one is attempting to determine and $q = \gamma \int_0^\tau G(t) dt$. A suitable processing based on a Laplace Transform of the resulting decay as a function of either the b or q^2 variables thereby provides, for each peak, information from which its D -value becomes available. The resulting shift-resolved characterization of molecular mobility has proven particularly valuable as it provides, among other information, a separation of NMR peaks according to the individual chemical components partaking of a complex mixture. It also yields an approximate idea of the hydrodynamic radii characterizing molecules, while freely tumbling in solution. Extensive descriptions on the principles and applications of the resulting 2D diffusion-shift NMR correlation experiment, have been given [4–9].

Although this valuable mobility-related information is unavailable in conventional 1D experiments, DOSY shares with other 2D NMR schemes a basic drawback regarding its minimal duration. In effect, since all such schemes are forced to run a series of measurements as a function of an incremented indirect-domain parameter, they will require the collection of multiple scans regardless of sensitivity considerations. This may present a number of limitations in the applicability of the methodology, particularly when attempting to monitor a chemically dynamic or otherwise unstable system that does not stay constant over the course of the measurement. Recent years have consequently witnessed a number of proposals to speed up 2D NMR experiments in general [10–12]. For the case of DOSY, a particularly large variety of suggestions has been put forward for shortening the diffusion/shift 2D correlations, proceeding all the way to reducing the sampling

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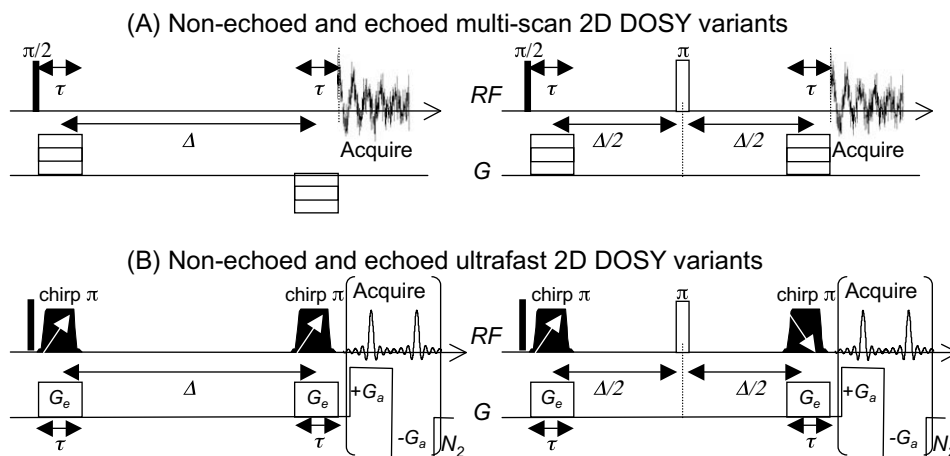


Fig. 1. Comparison between conventional (A) and ultrafast (B) 2D DOSY experiments based on pulsed-gradient spin-echo sequences (solid bars denote non-selective $\pi/2$ pulses throughout this study). Diffusion in (A) is encoded via the incrementation of G -values throughout separate scans; this can be carried out with full refocusing of coherent evolutions by applying a central π pulse and reversing the relative signs of the gradient pulses (right). In (B) this encoding proceeds by imparting spatially-dependent q -values throughout an otherwise homogeneous sample. Without a central refocusing π pulse (left) the directions of the two spatially-encoding pulses need to be identical in order to cancel each other out; if a central refocusing π pulse is employed then the senses of the two π pulses need to be reversed (right). In either case, the $\pm G_a$ oscillating acquisition gradient enables one to read-out this indirect-domain encoding, without compromising the direct-domain spectral resolution.

needs down to a single scan [13–20]. In many of these proposals, however, data are not collected under the optimal resolution conditions that would ideally suit small-molecule solution-state NMR spectroscopy. This may be either due to the methodology's need for carrying out its diffusion measurement under constant magnetic field gradients (thereby limiting the achievable resolution), or due to a need to collect multiple FIDs within times that are short vis-à-vis the longitudinal spin relaxation (thereby assuming that $T_2^* \ll T_1$).

An alternative approach to speed up multidimensional acquisitions consists of spatially encoding the indirect-domain information being sought, and subsequently reading out this information by means of fast, repetitive gradient oscillations. This is the principle underlying so-called “ultrafast” approaches to 2D NMR, which instead of incrementing their indirect-domain delays over an array of scans as in traditional spectroscopy, manage to compress the full 2D protocol by making t_1 a function of position [12,21,22]. Procedures that can impart within a single scan a $t_1 = t_1(z) = C(z - z_0)$ dependence, have thus been shown to lead to fully general 2D spectroscopic executions with no limitations on the type of correlations that can be imparted or on the spectral resolution that can be achieved. This in turn suggests the logic of searching for an analogous approach, capable this time of implementing single-scan 2D DOSY experiments. On considering the measurement described by Eq. (1), it follows that this could proceed by either spatially encoding the q or the Δ parameters; the present Communication discusses the opportunities opened by the former approach.

Theoretical background

As mentioned, DOSY calls for executing a series of high resolution acquisitions as a function of an acquisition time t_2 , subject to a prior displacement encoding by an incremented range of q -values. The approach hereby considered is similar, except that instead of changing q throughout a series of successive scans, we shall impart on it a range of spatially-dependent values: $q = q(z)$. To do so properly it is convenient to re-consider how the typical PGSE experiment encodes random motion, and how it leads to the behavior summarized in Eq. (1). Diffusion is a local phenomenon which will conspire against the gradient refocusing process involved in the PGSE sequence of Fig. 1A at a microscopic level; *i.e.*, in a manner

that is dictated by the local variations of the spin-packets' phases in their transverse Bloch planes. Such effects will therefore depend on the spatial derivatives $\frac{\partial \phi(z,t)}{\partial z}$ taken by the dynamic evolution phases $\phi(z)$ of the spins, throughout the time-course of the experiment. Extending theories discussed in the literature on how to analyze PGSE experiments under arbitrary gradient and radiofrequency (RF) waveforms [18,23], we have recently shown that the cumulative attenuation effects arising due to the presence of diffusion can then be written on the basis of these local evolution phases as [24]

$$\ln \left[\frac{A(z,t)}{A(z,G=0)} \right] = -D \int_0^t \left(\frac{d\phi(z,t')}{dz} \right)^2 dt' = -D \int_0^t K_{\text{local}}^2(z,t') dt'. \quad (2)$$

On considering the reliance of PGSE on linear gradients, the time integration of the first spatial derivatives of frequencies $\Omega + \gamma G(t)z$ make the K_{local} wavenumber in this equation solely a factor of $q(\tau) = \gamma \int_0^\tau G(t) dt$; hence the simple form taken by the decay function in Eq. (1). When looking to impose on the $\frac{A(t)}{A(G=0)}$ attenuation an explicit spatial dependence, however, Eq. (2) implies that one needs to impress a spatial dependence on K_{local} . In other words, one needs to impart on the spins a $\phi(z)$ pattern that is no longer linear in z . Keeler et al. have noticed this in their 1D DOSY papers, [18,19] and proposed a number of ways for fulfilling it. In the present case we follow an approach that is analogous to theirs, but adopt the frequency-swept manipulations and the kind of data processing that are usually used in the execution of ultrafast 2D NMR acquisitions, for achieving this goal.

As described in further detail elsewhere, [25–27] ultrafast experiments may rely on the action of chirped RF pulses acting in the presence of linear field gradients, in order to impart a spatially-dependent excitation or refocusing of the spins evolution. Although both of these manipulations can provide a quadratic phase pattern that is suitable for the execution of single-scan DOSY measurements, the former has the drawback that it involves a sequential departure of longitudinal magnetizations as a function of the spins' z position, and may consequently end up being biased by undesirable T_2 -weighting artifacts. We focus therefore on a constant-time scheme where all spins spend the same amount of time precessing in the transverse plane, and examine the diffusion ef-

fects encoded by the application of a pair of frequency-chirped RF pulses leading to the PGSE variants illustrated in Fig. 1B. These sequences are analogous to the ones that would be used in a mixing-less single-scan 2D NMR experiment, except for the fact that (i) chirped pulses are now separated by a relatively long delay Δ meant to encode diffusion effects, and (ii) RF sweeps are applied in such a way that at their conclusion, their own coherent evolution effects will end up being removed. Such full refocusing over the two τ periods demands that the chirped π -pulses involved be swept in identical directions throughout the sample (Fig. 1B, left). Alternatively, if a full refocusing of the shift evolution is also sought during the diffusion-encoding delay Δ , this can be achieved by the insertion of a hard π pulse in the middle of this delay—but the relative sense among the chirped RF pulses needs then to be reversed (Fig. 1B, right). Only a space-dependent diffusion attenuation will thus be left, when monitoring the spins' signals as a function of their position throughout the sample.

To derive the actual functioning of this method one needs to focus on the non-linear $\phi(z)$ phase imposed by the aforementioned gradient/RF combinations, and on how these lead to diffusion effects affecting different positions within the sample length L to different extents. The first-order derivative of the phase function which according to Eq. (2) will define the diffusive attenuation, will be given for the first of the π -sweeps involved in the sequence by [24]

$$\gamma K_{\text{local}}(t, z) = \begin{cases} \gamma G_e \cdot t & 0 \leq t < t_+(z) \\ \gamma G_e \cdot [t - 2t_+(z)] & t_+(z) < t \leq \tau \end{cases} \quad (3)$$

where τ is the duration of the gradient/RF pulse, $t_+(z) = \frac{\Omega + \gamma G_e z - O_i}{R}$ is the time at which the RF addresses spins located at position z , Ω is the spins' chemical shift, $R \approx \frac{\gamma G_e L}{\tau}$ is the rate at which the RF sweeps the overall sample length L , and $O_i \approx \frac{\gamma G_e L}{2}$ is the initial offset of the frequency sweep. Following the creation of the first π -sweep-driven quadratic phase profile, the sequence in Fig. 1B "waits" a relatively long evolution period Δ over which molecular diffusion

is allowed to impart its randomizing effects, but $K_{\text{local}}(z)$ remains constant at $\gamma G_e[\tau - 2t_+(z)]$. Prior to the data acquisition the sequence incorporates another π -chirp sweep in the presence of a gradient, whose function is to cancel the quadratic dephasing initially imposed on the $\phi(z)$ as this is of no further use past the diffusion-encoding Δ delay. Focusing for simplicity on the version that does not involve the strong π pulse in the middle of Δ , this final RF event will change the $K_{\text{local}}(\tau + \Delta, z)$ wavenumber into

$$\gamma K_{\text{local}}(t + \tau + \Delta, z) = \begin{cases} \gamma G_e[t - 2t_+(z) + \tau] & 0 \leq t \leq t_+(z) \\ \gamma G_e[t - \tau] & t_+(z) \leq t \leq \tau \end{cases} \quad (4)$$

Propagating the K_{local} values in Eqs. (3) and (4) throughout the various stages of the experiment as indicated in Eq. (2), provides then the full attenuation profile resulting for each site in the sample:

$$\ln \left[\frac{A(z)}{A(G_e = 0)} \right] = -4D \frac{(\gamma G_e)^4}{R^2} (\Delta + \tau/2) \cdot \left(z + \frac{\Omega}{\gamma G_e} \right)^2 - \frac{D(\gamma G_e)^2 \tau^3}{6}. \quad (5)$$

Disregarding for simplicity the unimportant z -independent term in this expression and assuming measurements in the usual $\gamma G \gg \Omega$ limit, leads to a site-independent, z -dependent analogue of Eq. (1)

$$\ln \left[\frac{A(z)}{A(G_e = 0)} \right] = -q^2 \left(\frac{2z}{L} \right)^2 \left(\frac{\Delta + \tau}{2} \right) \cdot D. \quad (6)$$

Extracting the diffusion coefficient D requires therefore to monitor, and then fit, the quadratic coefficient of a log plot of the normalized $A(z)$ attenuation profiles arising for each site in the sample, as a function of their z position. In the sequences of Fig. 1B this is made possible by the $\pm G_e$ oscillating acquisition gradient applied throughout the course of the acquisition, yielding a 1D FID that when processed according to the recipes of Echo Planar Spectroscopic Imaging (EPSI) [28], delivers both the $A(z)$ profile information along an imaging dimension as well as an uncompromised

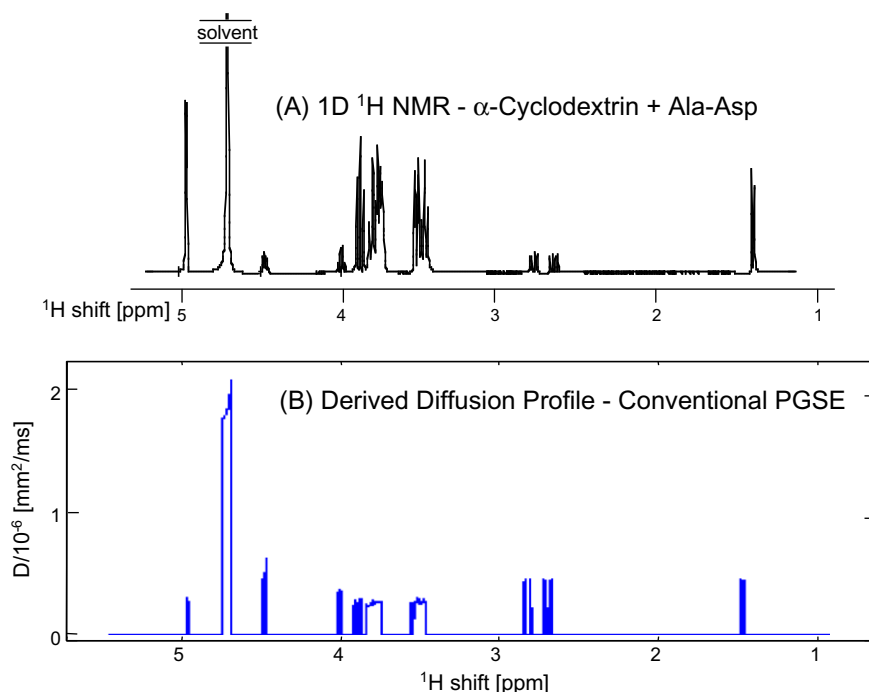


Fig. 2. (A) 1D ^1H NMR spectrum of one of the model systems tested for this study, made up by co-dissolving α -Cyclodextrin and Ala-Asp in D_2O . (B) Diffusion characterization of the various peaks discerned in (A) as measured by a PGSE experiment incorporating 16 different G_e values distributed between 0 and 9.4 G/cm in equal spacing of q^2 -values, four phase-cycled scans per gradient value, and a processing derived from Eq. (1). Notice the relatively faster mobility of the (truncated) solvent, and the relatively slower diffusion of the sugar resonances in the 3.4–3.8 and 4.95 ppm region.

$I(\Omega)$ high-resolution NMR trace along the spectroscopic dimension. Moreover, as discussed elsewhere [24], diffusion effects during this latter part of the experiment are indeed negligible (with an extra decay of under 1% over the full t_2 acquisition) owing to the fast gradient oscillations that are here involved.

Experimental results

The single-scan 2D DOSY principles just described were tested using an INova-based Varian spectrometer operating at 500 MHz,

and equipped with a diffusion probe characterized by relatively small deviations of the gradient's field pattern from linearity throughout its $L = 18$ mm sample length. Given single-scan 2D DOSY's reliance on a faithful $A(z)$ amplitude profile in order to extract its diffusion information, we find this to be an important condition for retrieving quantitatively reliable results upon using this technique. By contrast the relatively strong field gradients that can be delivered by this unit (up to 200 G/cm) were found of secondary importance, as the maximal gradient strengths used never exceeded ≈ 30 G/cm.

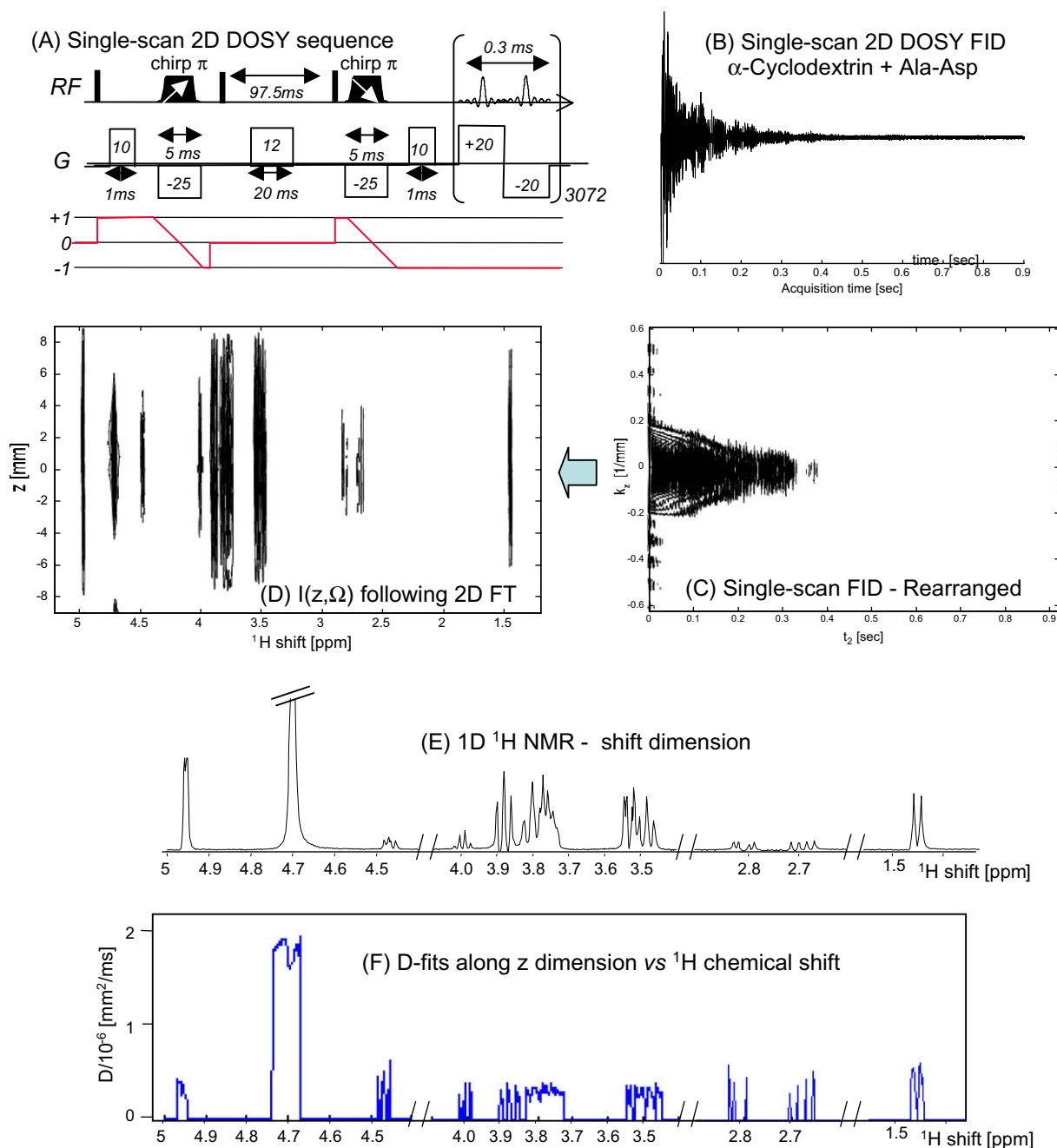


Fig. 3. Experimental corroboration of the single-scan 2D DOSY approach introduced in this work, on the same solution as analyzed in Fig. 2 by conventional means. (A) Sequence employed based on a stimulated-echo version of the approach introduced in Fig. 1B, incorporating the selection of an echo pathway (bottom, red), the indicated experimental parameters (all gradients in G/cm), chirped π -refocusing pulses sweeping over +130 kHz and -130 kHz, as well as a small number of ancillary purging pulses for the sake of achieving a cleaner selection of the desired coherence transfer pathway within a single scan. (B) Single-scan FID afforded by this sequence, leading to a 2D wavenumber/time-domain data set after an EPSI-type reorganization within the (k, t_2) -plane (C). 2D FT of these data (D) leads to a high-resolution spectroscopic dimension (E), correlated against imaging profiles which when fit to Eq. (6) yield the apparent diffusion coefficients for each site. Notice the good overall agreement of these final results (F) against their conventional multi-scan counterparts (Fig. 2). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The new experiment was tested on a number of samples. Fig. 2 focuses on a solution made up by 50 mM of a complex sugar (α -Cyclodextrin, M_W 972.86), co-dissolved with 50 mM of a dipeptide (Alanine-Asparagine, M_W 230.2) in D_2O . The structure-rich 1D 1H NMR spectrum of this solution is illustrated in Fig. 2A; the diffusion coefficients that for the sake of referencing were measured for the different peaks in this compound using a conventional PGSE pulse sequence, are shown in Fig. 2B. Modest but systematic differences of ca. 40% can be found between the D 's of the higher- and lower- M_W compounds, with a significantly larger D for the solvent. Fig. 3A illustrates the sequence and parameters used to repeat this measurement, based on the single-scan 2D DOSY principles given in the preceding Section. Unlike the example that was there discussed, a stimulated-echo

rather than a long free-precession delay Δ was utilized in this experiment to monitor the destructive diffusion effects. This has the well-known advantage of being able to preserve better the information along a T_1 -dependent storage axis, even if at the expense of reducing by 50% the maximum available signal [7,29]. From the point of view of the data analysis, however, no significant differences *vis-à-vis* the treatment of Eqs. (2)–(6) arise. Illustrated in the remaining panels of Fig. 3 are the various stages involved in retrieving the site-resolved diffusion coefficients from this single-scan experiment; these include taking the 1D FID arising from the sequence (Fig. 3B) and rearranging it into a 2D ($k = \int_0^{t_2} G_a(t') dt', t_2$)-plane (Fig. 3C); Fourier transform of the data against these variables as in EPSI (Fig. 3D); extraction from these 2D plots a high-resolution spectroscopic dimension (Fig. 3E); and

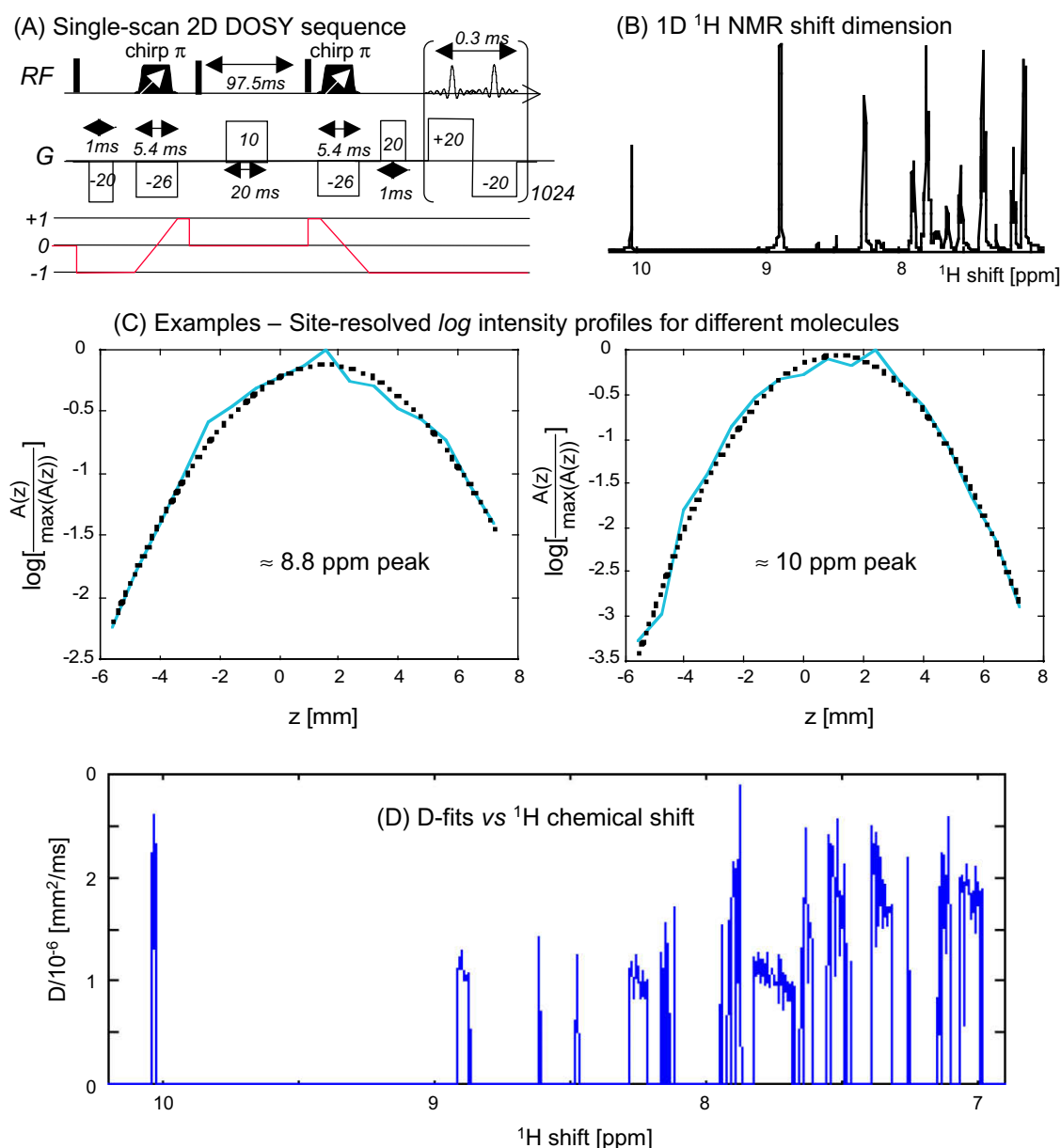


Fig. 4. Results obtained for a TPP, Benzaldehyde and Diphenylether solution (≈ 50 mM each) in $CDCl_3$ at 25 $^{\circ}C$. (A) Pulse sequence and parameters employed in the ultrafast 2D DOSY implementation; notice that unlike the sequence in Fig. 3 this relies on an anti-echo coherence transfer pathway, associated now with equally-sensed π frequency sweeps. (B) High-resolution spectrum afforded by this sequence along the 1H shift dimension. (C) z profiles extracted for clearly resolved Benzaldehyde (≈ 10 ppm) and TPP (≈ 8.8 ppm) peaks (continuous magenta), providing by a quadratic fit to Eq. (5) the corresponding D coefficients of these rapidly- and slowly-diffusing compounds, respectively (dotted lines). (D) Diffusion coefficients extracted in this manner for all peaks in the spectrum, clearly separating the diffusivity of the larger TPP molecule ($D \approx 1.2 \cdot 10^{-6} \text{ mm}^2/\text{ms}$) from the remaining smaller aromatic molecules.

fitting for each of the resulting spectral peaks the z -dependent \log profiles according to Eq. (5), so as to quantify the corresponding D -coefficients (Fig. 3F). Although slightly more scattered than their PSGE counterparts, the values extracted from this last procedure agree very well with the diffusion coefficients measured by traditional DOSY (Fig. 2B). Notice as well the clear J -multiplet structures that can be resolved for each chemically-inequivalent site within the resulting $I(z, \Omega)$ 2D trace.

Fig. 4 illustrates another example of the single-scan DOSY experiment, this time to a solution containing bulky tetra-phenylporphyrin (TPP) molecules co-dissolved with aliquots of the smaller Benzaldehyde and Diphenylether molecules; all of these in CDCl_3 at ca. 20 mM levels. As in the previous example measurements were here carried using a stimulated-echo sequence, this time choosing the anti-echo coherence pathway (Fig. 4A). Shown in Fig. 4B–D are summaries of the data including the high-resolution spectrum afforded by the single-scan procedure, the quadratic profiles that can be observed for selected sites as a function of the z dimension, and the clearly different D coefficients that can be then observed for the high- and low- M_w compounds. Notice that also in this case the resolution available along the shift dimension is high, and unimpaired by the diffusion measurement.

Discussion and conclusions

This study discussed a novel approach to the characterization of molecular diffusion by site-resolved NMR. Although the execution of this experiment—along with much of its data processing and interpretation—are intimately related to spectroscopic ultrafast 2D NMR, the technique also shows parallels to the 1D DOSY experiment described by Thrippleton et al. [19]. Like the latter it involves pairs of frequency-swept pulses; unlike the latter, it does not execute the data acquisition in the presence of a constant gradient, and hence is free from constraints which may otherwise compromise spectral resolution or complicate the deconvolution of the diffusion information—particularly when dealing with J -coupled systems. The usefulness of these features for monitoring diffusion and flow phenomena in more complex systems will be further assessed in upcoming studies.

One of the features highlighted before in connection to these ultrafast 2D DOSY experiments, is their need for a reliable linearity in the field gradients in order to quantify their data. Departures from such linearity will still allow one to obtain diffusion-dependent $A(z)$ profiles from which quantitative values of D could be extracted; such analyses, however, would suffer from a complication as their fits would no longer involve the simple quadratic forms given in Eqs. (5) and (6). Similar effects could in fact be expected from any other systematic departure from the ideal behavior assumed to derive these equations; experimental observations indicate that, in addition to being sensitive to gradient non-linearities, these fits can be affected by B_0 inhomogeneities (which will distort the straight patterns otherwise arising in the $I(z, \Omega)$ space), as well as by local convection effects. Another potential source of spatial distortions, arising from B_1 inhomogeneities, appears to play a secondary role thanks to the adiabatic-like nature of the π RF chirps employed in the ultrafast 2D DOSY sequences. In any case it should be noticed that, if *a priori* mapped and suitably known, the effects imparted by any systematic $B_0(z)$, $B_1(z)$ or $G(z)$ non-ideality can be accurately accounted for at a data analysis stage, and quantitative site-resolved D -values be extracted.

As often happens with this kind of developments, various additions and improvements could be considered on top of the basic pulse sequence that was here described. A more general operation of ultrafast 2D DOSY could be achieved, for instance, by inserting coherence transfer blocks to hetero- or to multiple-quantum

coherences in-between the various modules to enhance spectral resolution of sensitivity to diffusion. The addition of supplementary field gradients could also enable the characterization of shift-resolved diffusion tensors along multiple spatial dimensions. We also trust to report on some of these options and their consequences in the near future.

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