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A fast method for the measurement of diffusion coefficients: one-dimensional DOSY

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A new experiment for the single-scan measurement of diffusion coefficients is presented. The principle is to introduce a spatial variation in the parameters of a conventional pulse sequence, so that all of the scans required to determine some physical parameter can be recorded simultaneously from different parts of the sample. The spectrum is acquired in the presence of a weak read gradient so that the resulting lineshapes contain the information required. The pulse sequence is described in detail and demonstrated on a sample containing three components; its advantages and limitations are discussed in relation to those of existing techniques. For uncrowded spectra with high signal-to-noise ratio, this experiment provides an order of magnitude reduction in experiment time compared with conventional methods and is likely to be of most benefit where samples are changing rapidly with time or where a long period of polarization, which may be difficult to reproduce accurately, prohibits the use of multiple-scan techniques.

KEYWORDS: NMR; ^{1}H NMR; DOSY; diffusion

INTRODUCTION

In this paper, we describe an experiment which permits the measurement of diffusion coefficients in a single scan. The principle, described in a previous paper, is to introduce a spatial variation in the parameters of a pulse sequence, such that all of the scans required to determine some physical parameter can be recorded simultaneously from different parts of the sample.[1] The spectrum is acquired in the presence of a weak read gradient so that the resulting lineshapes contain the information required. The pulse sequence is a single-scan adaptation of the conventional, many-scan experiment and does not use r.f. pulse trains or require hardware modifications.

Diffusion measurements in NMR utilize magnetic field gradients, during which the field becomes spatially dependent. Usually, the field strength varies linearly with position along the direction of the main magnetic field (z); the strength of the gradient is defined by the rate of change of the field (in T m^{-1}). Figure 1(a) shows how gradients are employed in the stimulated echo (STE) sequence, commonly used for measuring diffusion coefficients.[2] During the gradients G_d, a spin acquires a phase which depends on its position in the sample; as the coherence order is +1 during the first gradient and −1 during the second, these phases have opposite signs and, provided that the spin has not been displaced during the diffusion delay Δ, they will cancel. However, if the spin has moved it acquires a net phase which depends on the displacement; when summed over the whole sample, these phase errors lead to an attenuation of the signal. This attenuation depends on both the gradient strength G_d and the diffusion coefficient D. A numerical value of the diffusion coefficient can be found by repeating the experiment with different gradient strengths and then fitting the resulting decay to a well known expression.[2]

The basic pulse sequence for the one-dimensional diffusion ordered spectroscopy (1D DOSY) experiment is given in Fig. 1(b). It is a conventional STE experiment that has been modified in two ways: first, both of the gradients in the STE sequence have been combined with an adiabatic frequency-swept 180° pulse of duration t_p; second, the FID is acquired in the presence of a weak read gradient G_r. We will describe the effect of each of these modifications in turn.

During the gradient G_d, spins in different parts of the sample have different offsets. As the frequency-swept 180° pulse works by sweeping through a range of offsets, different parts of the sample are affected at different times during the sweep. Further, the position-dependent phase acquired before the pulse is reversed, and any subsequent period of gradient evolution acts to refocus the magnetisation. Thus, spins at one end of the sample experience a 180° pulse immediately and are then dephased by the gradient field for a time t_p. In contrast, spins at the centre of the sample are dephased by the gradient for a time $t_p/2$, then experience a 180° pulse and are then refocused by the gradient for an equal time

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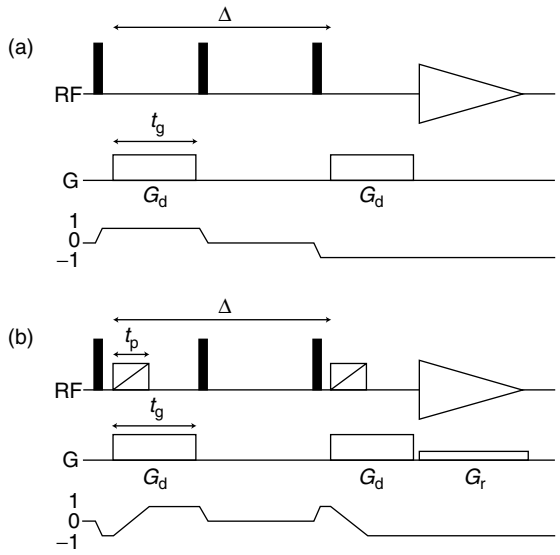

Figure 1. (a) The stimulated echo (STE) pulse sequence, commonly used for measuring diffusion coefficients. (b) The basic 1D DOSY pulse sequence, which permits the measurement of diffusion coefficients in a single scan. The required coherence transfer pathway is shown below each pulse sequence. The filled rectangles on the line marked RF represent 90° pulses and the hollow boxes with diagonal lines represent 180° CHIRP pulses. *z*-Gradients are displayed on the line marked G.

$t_p/2$; these spins are essentially unaffected by the gradient–sweep combination.

More generally, if a spin at position z experiences rotation at time $\alpha(z)t_p$, where $0 \leq \alpha(z) \leq 1$, then the net phase acquired by the spin at the end of the frequency-swept pulse is

$$\gamma G_d z\alpha(z)t_p - \gamma G_d z[1-\alpha(z)]t_p = -[1-2\alpha(z)]\gamma G_d z t_p$$

where G_d is the strength of the gradient and γ is the gyromagnetic ratio. During the frequency-swept pulse, the spin evolves as if under an *effective gradient strength* $G_{eff}(z) = [1-2\alpha(z)]G_d$. In this simple analysis, we have assumed that spins experience a 180° pulse at the moment the sweep is on-resonance. A more detailed treatment, accounting for the non-instantaneous nature of rotation, is described in the Appendix; it is this approach that we use in the data analysis.

In the sequence shown in Fig. 1(b), the gradients G_d continue after the frequency-swept pulse so that all of the sample experiences some dephasing and spins to either side of the centre of the sample experience different degrees of dephasing. What we have, therefore, is a stimulated echo sequence in which the effective gradient strength varies linearly across the sample, from a minimum value at one end to a maximum value at the other. As a result, the signal attenuation due to diffusion will vary across the sample. This provides all the information required to determine diffusion coefficients, provided that it is possible to determine how the resulting signal attenuation changes across the sample. This is achieved by the second modification, which is to acquire the FID in the presence of a read gradient; this results in a spectrum in which all of the peaks become one-dimensional diffusion-weighted images of the sample. Three examples of such lineshapes are shown in Fig. 2(c). Each peak is essentially a graph of signal versus gradient strength and, by careful analysis of the lineshape, a value for the diffusion coefficient associated with each peak can be extracted.

The read gradient is rather weak, so that although there is some line broadening, chemical shift resolution is retained. The minimum strength of the read gradient is determined by the requirement that the gradient-induced broadening should dominate the natural linewidth of a resonance. The method is applicable to multiplets, provided that the broadening in the 1D DOSY spectrum also dominates the splitting (or, in principle, vice versa) and the periods t_g, during which the magnetization is transverse, are short enough that J evolution is insignificant.

The timings, durations and shapes of the gradient pulses were adjusted, and additional compensating gradients added, in order to effect coherence transfer pathway selection without the need for phase cycling and to help reduce the generation and effects of eddy currents. These refinements are described in the Experimental section and a detailed pulse sequence is shown in Fig. 3.

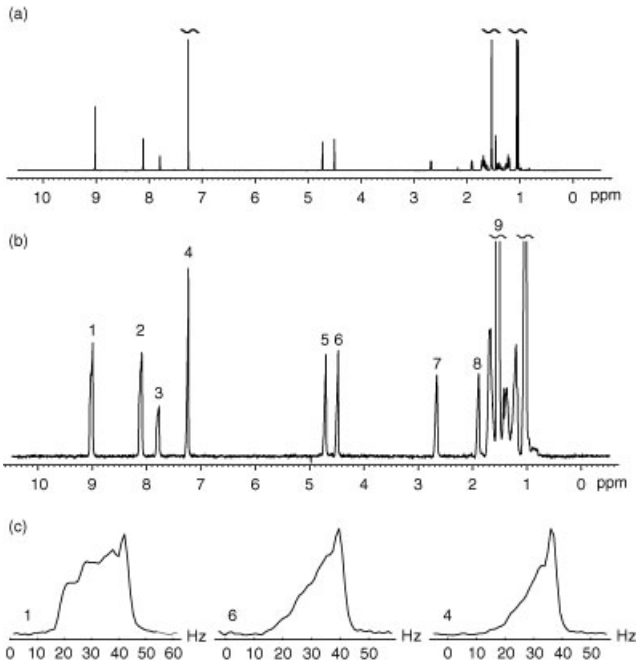

Figure 2. (a) Conventional 1D proton spectrum of a sample containing camphene, a zinc(II) porphyrin and chloroform in $CDCl_3$. (b) 1D DOSY spectrum of the same sample; the diffusion coefficient for each resonance is encoded in its lineshape. (c) Expansions of the 1D DOSY spectrum, showing a zinc(II) porphyrin (1), camphene (6) and chloroform (4) peak. Visual inspection of the peaks gives a qualitative indication of the relative diffusion rates of the three molecules and a quantitative analysis of the lineshapes yields estimates of the diffusion coefficients.

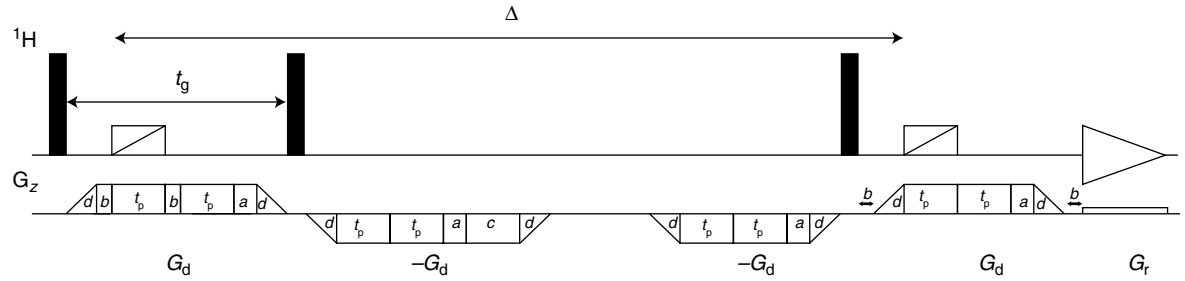

Figure 3. Detailed 1D DOSY pulse sequence. The values of the delays used to record the spectrum in Fig. 2(b) were as follows: $\Delta = 150$ ms, $a = 150$ μs, $b = 225$ μs, $c = 1$ ms, $d = 100$ μs and $t_p = 1$ ms. The gradient strengths used were $G_d = 0.225$ T m^{-1} and $G_r = 6.87 \times 10^{-5}$ T m^{-1}. The CHIRP pulses are adiabatic and the frequency is swept linearly through 100 kHz; the intensity of the field is constant at 9.5 kHz, except during the first and final fifths of the pulse, when the tails of the pulse are smoothed using a sine function.

RESULTS

To test the sequence, a sample was prepared containing camphene, a zinc(II) porphyrin and chloroform in $CDCl_3$. The 1D DOSY spectrum, which was acquired in <1 s, is shown in Fig. 2(b). A qualitative inspection of the peaks immediately distinguishes between the resonances of the three components [see Fig. 2(c)]: the rapidly diffusing chloroform molecules give rise to a peak with a steeply falling edge, while the slow diffusion of the porphyrin is reflected in the flatter profile of its peaks. The unevenness of the lineshapes in Fig. 2(c) is largely due to the inhomogeneity of the gradient strength and of the coupling between the sample and the receiver coil. Both of these factors are accounted for in the lineshape analysis described in the Appendix.

Values of the diffusion coefficients can be obtained by careful analysis of the lineshapes. Each point in the lineshape corresponds to a position in the sample; this in turn corresponds to a value for the effective gradient responsible for the diffusion attenuation. A simple method for calculating this was described in the Introduction; for the results presented here, the more rigorous treatment given in the Appendix was used. Having calculated the effective gradient associated with each point in the lineshape, a predicted lineshape can be calculated for a trial diffusion coefficient D_{trial} using the well known relationship (assuming that $\Delta \gg t_g$):[3]

$$S(z) \propto \exp[-\gamma^2 A_{eff}^2(z) D_{trial} \Delta]$$

where Δ is the diffusion delay; the effective gradient area $A_{eff}(z)$, which is given by $G_d t_g$ in the STE experiment, is expressed in terms of known parameters in the Appendix.

The predicted lineshape is then fitted to the experimental lineshape by varying D_{trial} and an amplitude scaling factor in a non-linear least-squares fitting procedure. This analysis was performed only on the part of the lineshape corresponding to positions in the sample where rotation by the frequency-swept 180° pulse can be assumed to be complete.

The D values from this analysis are shown in Fig. 4; for comparison, average values obtained from a conventional STE experiment are also shown. It should be noted that the deliberate broadening of the peaks by the read gradient increases overlap in the crowded high-field region of the spectrum, making some of the lineshapes uninterpretable.

DISCUSSION

The results shown in Fig. 4 demonstrate the ability of the 1D DOSY experiment to separate resonances according to their diffusion coefficients, and that the values of D obtained for resonances within the same molecule agree closely.

Compared with the conventional STE results, there is a small systematic difference between the two sets of D values; although the origin of this difference is unclear, we speculate that it is due to lineshape distortions, possibly caused by the presence of eddy currents during acquisition. Certainly, the ability of a spectrometer to produce undistorted lineshapes following a series of gradient pulses will have a strong effect on the quality of the data obtained in this experiment.

Two further factors affect the ability of 1D DOSY to measure diffusion coefficients. First, high sensitivity is important if sufficient data are to be obtained in a single scan, as the signal-to-noise ratio of the spectrum affects the uncertainty in the estimated diffusion coefficients. The magnitude of this effect is estimated in the Appendix. Second, the broadening of the lineshapes in the 1D DOSY spectrum increases the probability of overlap.

A balance therefore has to be struck when choosing the experimental parameters. While reducing the strength of the read gradient will increase the signal-to-noise ratio and reduce crowding in the 1D DOSY spectrum, it is important that the gradient-induced broadening dominates the natural linewidths of the resonances, and also any splittings due to scalar coupling. This is in order to maintain a simple correspondence between frequency and position within the peaks. If this is not the case, it is in principle possible to remove the effects of natural linewidth and splitting by deconvolution; in practice, however, this method proved to be problematic and was not used to process the results presented here. We note that sensitivity and resolution limitations are both reduced at higher magnetic fields.

A number of methods have been proposed for the rapid measurement of diffusion coefficients,[1,4–9] although many of these are more appropriate for measurements in single-line samples and for imaging applications than for high-resolution NMR. One of the sequences that is, in principle,

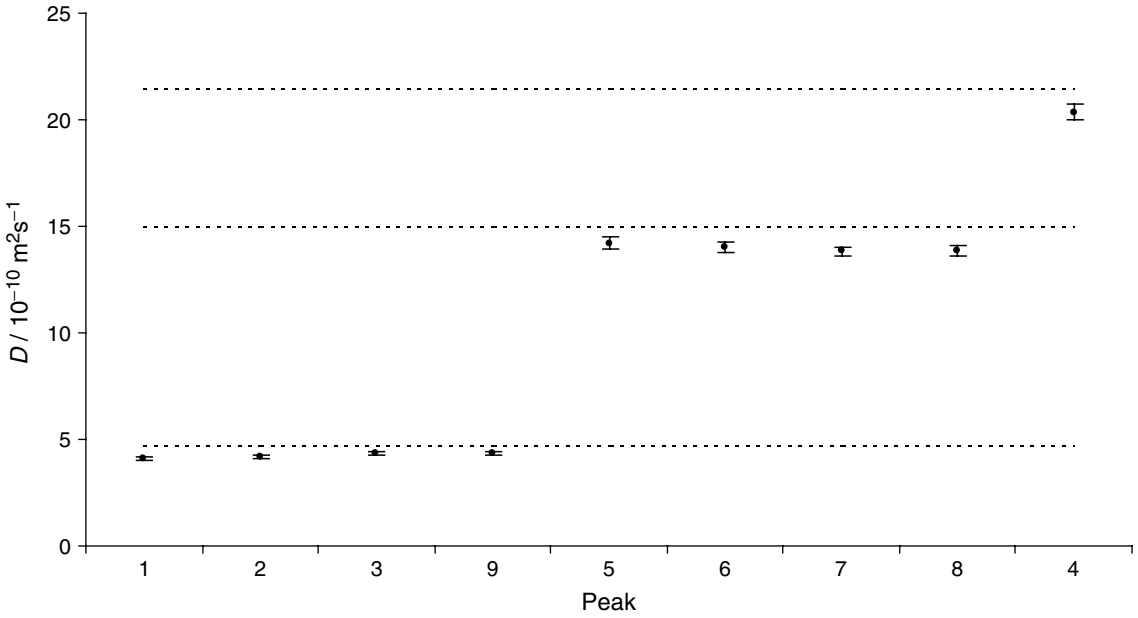

Figure 4. Diffusion coefficients (with error bars) obtained using the 1D DOSY experiment. Each of the measurements was also determined by the STE method and the average value for each of the components is displayed as a dashed line. The peak numbers correspond to those given in Fig. 2(b) and points are grouped according to molecule: zinc(II) porphyrin (1, 2, 3, 9), camphene (5, 6, 7, 8) and chloroform (4). The random error associated with the 1D DOSY measurements was estimated by repetition, whereas that associated with the STE measurements was estimated from the scatter in the data; the latter error is insignificant compared with the former and is not displayed.

applicable to many-line samples is that of Gelderen *et al*.[5] However, the ability of this technique to retain chemical shift resolution is limited by the maximum gradient strength available and the digitisation rate of the spectrometer. Neither of these limitations apply to the sequence proposed here.

More attractive in the spectroscopic context is the 'Difftrain' experiment of Stamps *et al*.[9] In this sequence, magnetization is encoded by a gradient pulse and stored along *z*. An 'aliquot' of this magnetization is then recalled to the transverse plane with a low flip-angle pulse, refocused by a gradient pulse and an FID acquired. This step is repeated until several spectra, each with a different diffusion time, have been recorded. It should be noted that, as with all of these techniques, some chemical shift resolution is sacrificed because of the need to acquire several FIDs before longitudinal relaxation destroys the encoded magnetization. A further limitation is that the observed signal attenuation results from the combined effects of diffusion and relaxation, necessitating a control experiment in addition to a two-step phase cycle.

The 1D DOSY experiment presented here is a single-scan technique and, although some chemical shift resolution is sacrificed, we believe that the sequence has much to commend it in applications where signal strength and spectral crowding are not limiting factors. The simple correspondence with the conventional STE experiment yields three significant advantages: first, since the diffusion time is the same for all spins, time-dependent effects such as relaxation and exchange affect all spins equally and the need for a control experiment is removed; second, the use of a stimulated echo reduces losses from transverse relaxation and makes it possible to study scalar coupled spin systems; third, the sequence does not rely on r.f. pulse trains, which are susceptible to the cumulative effects of pulse miscalibration and to undesirable coherence transfer pathways.

CONCLUSION

We have developed and demonstrated a single-scan method for measuring diffusion coefficients. In cases where sensitivity is high, our technique makes it possible to acquire data in <1 s, as compared with conventional methods, which take minutes. Although some resolution is sacrificed, we believe the approach has much to commend it in cases where a sample is changing with time or where a long period of polarization, which may be difficult to reproduce accurately, prohibits the use of multiple-scan techniques.

EXPERIMENTAL

Materials

The sample was prepared by the addition of camphene (15 mg) and [5,10,15,20-tetrakis(3,5-di-tert-butylphenyl)porphyrinato]zinc(II) (11 mg) to $CDCl_3$ (1 ml). The mixture was shaken and then filtered through a plug of silica in order to remove any undissolved solid. Chloroform was added to the sample to boost the solvent signal.

Spectra

All spectra were recorded at 400 MHz using a Bruker Avance 400 spectrometer. The temperature was maintained at 295 K with a gas flow-rate of 535 $dm^3\ h^{-1}$; to minimize convection, the sample was spun about the *z*-axis at 20 Hz, at which speed

the diffusion delay Δ corresponds to an integer number of rotations.[10] The 1D DOSY spectrum was recorded in a single scan; the acquisition time was 350 ms and the spectral width was 4400 Hz, with a resolution of 1.07 Hz per data point after processing. Parameters for the frequency-swept r.f. pulses were determined by simulation, using the 'Bloch simulator' included in the Bruker XWIN-NMR software. These and other parameters are shown in Fig. 3 and its caption.

A number of additional gradient periods were included in the pulse sequence; these are also shown in Fig. 3 and their purposes are as follows: the period *a* ensures that all parts of the sample receive some degree of dephasing; two periods of gradient evolution *b* are included before and after the frequency-swept pulses, so as to reject coherence transfer pathways that result from imperfections in the sweeps; period *c* rejects magnetization that is transverse during the longitudinal delay; *d* is a ramping period for the gradient pulses; finally, the additional gradient period of duration t_p ensures that every position in the sample receives a different diffusion weighting (failure to include this would result in a reduced range of diffusion weightings across the sample). Two gradient pulses of opposite polarity to the others are included during the longitudinal delay for the purposes of gradient compensation; the principles of this method for reducing eddy currents are discussed elsewhere.[11]

The pulse-acquire spectrum was recorded in a single scan; the acquisition time was 3.72 s and the spectral width was 4400 Hz, with a resolution of 0.134 Hz per data point after processing.

The procedure for measuring diffusion coefficients using the STE experiment is described in the literature;[2] half-sine shaped gradient pulses and gradient compensation were used and the resulting data set was analysed by the integration of peaks.

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APPENDIX

Analysis of 1D DOSY spectra

The offset Ω (rad s^{-1}) of any point within a 1D DOSY lineshape corresponds to the position z within the sample, according to

$$\Omega = \Omega_0 - \gamma G_r z$$

where Ω_0 (rad s^{-1}) is the offset of the peak in a simple pulse-acquire spectrum. It is then necessary to calculate the effective gradient $G_{eff}(z)$ experienced at any position during the frequency-swept pulses. A simple method for calculating this is described in the main text. However, this is approximate, as it assumes that the frequency-swept pulse acts on spins at a particular position at the exact time the sweep is on resonance. A more rigorous method is described here.

The phase acquired by a spin at position z during one of the frequency-swept pulses is simply

$$\phi(z) = \int_0^{t_p} \omega_{eff}(t, z)\mathrm{d}t$$

where $\omega_{eff}(t, z)$ is the effective magnetic field strength (in rad s^{-1}) in an accelerating frame that rotates at the (changing) frequency of the r.f. sweep;[A1] $\omega_{eff}(t, z)$ is given by

$$\omega_{eff}(t, z) = \sqrt{[\Omega_0 - \gamma G_d z - \Omega_{rf}(t)]^2 + \omega_{rf}(t)^2}$$

where $\omega_{rf}(t)$ is the strength of the r.f. field.

We now imagine a spatially dependent longitudinal field $B_{eff}(z)$ that would, in the absence of the sweep, result in the same phase label as the r.f. sweep/gradient combination, i.e. $\phi(z) = -\gamma t_p B_{eff}(z)$. The effective gradient strength $G_{eff}(z)$ is simply the derivative of $B_{eff}(z)$ with respect to z:

$$G_{eff}(z) = \frac{\mathrm{d}B_{eff}(z)}{\mathrm{d}z}$$

This allows us to write an expression for the effective gradient in terms of known parameters (the minus sign is discarded, since the sweep inverts the phases of the spins):

$$G_{eff}(z) = \frac{1}{\gamma t_p}\frac{\mathrm{d}\phi(z)}{\mathrm{d}z} = \frac{1}{\gamma t_p}\int_0^{t_p}\frac{\mathrm{d}\omega_{eff}(t, z)}{\mathrm{d}z}\mathrm{d}t$$

This integral has to be evaluated numerically; having done so, the result yields the effective gradient at any point in the sample tube. It is then trivial to show that the resulting signal at any point in the lineshape (assuming that $\Delta \gg t_g$) is given by

$$S(z) = S_0 \exp[-\gamma^2 A_{eff}(z)^2 D_{trial}\Delta]$$

where the effective gradient area $A_{eff}(z)$ is simply $G_{eff}(z)t_p$, D_{trial} is the trial diffusion coefficient and S_0 is a scaling factor.[3]

However, in the pulse sequence the gradient is extended by a time $a + t_p$ beyond the r.f. sweep, so an extra term must be added to $A_{eff}(z)$:

$$A_{eff}(z) = G_{eff}(z)t_p + G_d[t_p + a]$$

The predicted lineshape is then fitted to the data by varying the parameters S_0 and D_{trial}.

Correction for the inhomogeneity of receiver sensitivity and gradient strength

According to the theory outlined, the 1D DOSY peaks should have a flat profile in the absence of diffusion. In practice, however, this is not the case, owing to the spatial variation of various properties, such as the coupling of the receiver coil to the sample and the strength of the read gradient. In order to account for these factors in the analysis, two calibrations must be performed on the spectrometer.

First, a one-dimensional image of the sample is acquired by applying a 90° pulse and recording the FID in the presence of a read gradient. The image, which would ideally be of uniform intensity, is distorted by the spatial variation of sensitivity and gradient strength and thus provides a map which can be used to scale the predicted intensities $S(z)$ of points in the 1D DOSY lineshapes.

Second, the spatial variation of the gradient strength also affects the diffusion weightings experienced in different parts of the sample. This variation can be mapped by recording a conventional STE experiment in which a read gradient is applied during acquisition. By studying the signal decay at different points in the resulting image, the gradient strength (as a fraction of the nominal value) is calculated as a function of position. This information is used to scale the $A_{\mathrm{eff}}(z)$ values used in the analysis.

Effect of noise on the accuracy of diffusion measurements by 1D DOSY

Noise in the 1D DOSY spectrum gives rise to a random error in the measured diffusion coefficient. The size of this effect was estimated by generating an ideal 1D DOSY lineshape for Peak 1, based on the diffusion coefficient obtained from the STE measurement, then adding noise to each data point and fitting the resulting 'noisy' lineshape to obtain a new diffusion coefficient. This procedure was performed 10 times and a standard deviation and mean were calculated for the resulting set of diffusion coefficients. This was repeated with different values of the signal-to-noise ratio and the percentage error (defined as the standard deviation as a percentage of the assumed diffusion coefficient) is plotted against signal-to-noise ratio (defined as the maximum signal intensity divided by the standard deviation of the noise distribution) in Fig. A1. The parameters used in the generation of the ideal lineshapes were the same as those used in the 1D DOSY experiments presented here.

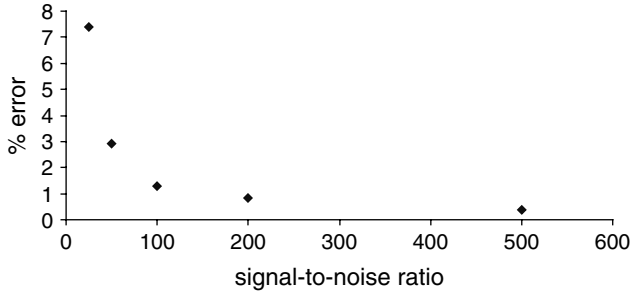

Figure A1. Estimated random error in the diffusion measurement as a function of the signal-to-noise ratio in the 1D DOSY spectrum, for a typical set of experimental parameters.

Figure A1 shows that as the signal-to-noise ratio falls below 50, the accuracy in the measured diffusion coefficient deteriorates severely. However, since the peaks are broadened in the 1D DOSY experiment, the required signal-to-noise ratio in the 1D proton spectrum is significantly higher than this. To estimate this, we make the following assumptions: (i) that a peak in the 1D proton spectrum has the absorption-mode Lorentzian lineshape, with linewidth at half-height $\Delta\nu$; (ii) that the corresponding 1D DOSY peak, in the absence of diffusion, is rectangular, with linewidth $\Delta\nu_{\mathrm{DOSY}}$; (iii) the decay of the 1D DOSY FID due to transverse relaxation is negligible compared with the effect of dephasing by the gradient; and (iv) acquisition in both experiments ends when the amplitude of the signal has decayed to a fraction β of the initial signal intensity.

We begin by considering the peak height S in the 1D proton spectrum. The shape of an absorptive lineshape, centred at f_0 (Hz), is given by the following equation:

$$s(f) = \frac{k\Delta\nu}{\pi[\Delta\nu^2 + 4[f - f_0]^2]}$$

where k is a constant and f represents offset (Hz). S and the area under the peak are given by

$$S = \frac{k}{\pi\Delta\nu}$$

and

$$\text{area} = \int_{-\infty}^{\infty} S(f)\mathrm{d}f = \frac{k}{2}$$

respectively.

Since the gradient-induced broadening has no effect on the peak area, the peak height in the 1D DOSY spectrum S_{DOSY} is given by

$$S_{\mathrm{DOSY}} = \frac{k}{4\Delta\nu_{\mathrm{DOSY}}}$$

(An additional factor of 0.5 accounts for the inevitable signal loss in a stimulated echo.)

The relative noise levels in the two spectra can also be calculated, given the fact that the r.m.s. noise amplitude N is proportional to the square root of the acquisition time t_{aq}, for a constant spectral width.[A2] In the FID of the 1D proton spectrum, the signal amplitude decays exponentially, and reaches a fraction β of its initial value when

$$\exp[-\pi\Delta\nu t_{\mathrm{aq}}] = \beta$$

Therefore,

$$t_{\mathrm{aq}} = \frac{-\ln\beta}{\pi\Delta\nu}$$

In order to estimate the acquisition time required in the 1D DOSY experiment, we ignore the effect of diffusion on the lineshape. In this case, it can be shown that the time domain signal decays as a sinc function. Ignoring the oscillatory part, the envelope of the signal reaches a fraction β of the initial signal amplitude when

$$\frac{1}{\pi t_{\mathrm{aq,DOSY}}\Delta\nu_{\mathrm{DOSY}}} = \beta$$

Therefore,

$$t_{\mathrm{aq,DOSY}} = \frac{1}{\pi\beta\Delta\nu_{\mathrm{DOSY}}}$$

It is now possible to express the relative noise levels in the two spectra:

$$\frac{N^{\mathrm{1DDOSY}}}{N^{\mathrm{1D}}} = \sqrt{\frac{t_{\mathrm{aq,DOSY}}}{t_{\mathrm{aq}}}} = \sqrt{\frac{-\Delta\nu}{\Delta\nu_{\mathrm{DOSY}}\beta\ln\beta}}$$

The reduction in signal-to-noise ratio in the 1D DOSY spectrum is therefore given by

$$\frac{(S/N)}{(S_{\mathrm{DOSY}}/N_{\mathrm{DOSY}})} = \frac{4\Delta\nu_{\mathrm{DOSY}}}{\pi\Delta\nu}\sqrt{\frac{-\Delta\nu}{\Delta\nu_{\mathrm{DOSY}}\beta\ln\beta}}$$

$$= \frac{4}{\pi}\sqrt{\frac{-\Delta\nu_{\mathrm{DOSY}}}{\Delta\nu\beta\ln\beta}}$$

For typical values of $\beta = 0.05$, $\Delta\nu_{\mathrm{DOSY}} = 30$ Hz and $\Delta\nu = 1$ Hz, this factor is approximately 18, suggesting that a signal-to-noise ratio of at least 900 would be required in the 1D proton spectrum to obtain reasonable estimates of D in a single scan. We note that this figure is strongly dependent on the experimental parameters chosen and on the natural linewidth of the resonance in the 1D proton spectrum.

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