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Enabling fast Pseudo-2D NMR Acquisition for Broadband Homonuclear Decoupling – The EXACT NMR approach

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Dedication ((optional))

Abstract: Pseudo-2D NMR provides a means of acquiring broadband homonuclear decoupled spectra useful for structural characterization of complex molecules. However, data points concatenated in the direct dimension in these experiments are acquired over incremented time periods – leading to long acquisition times with no sensitivity benefits due to the absence of signal averaging between scans. Herein, the concept of EXACT NMR ('burst' non-uniform sampling of data points) is explored in pseudo-2D experiments with results revealing little or no loss in spectral quality or signal intensity despite the acceleration of acquisition – up to 400% in some cases.

Introduction

Just over a decade ago, Candès and co-workers^[1] and Donoho^[2] developed a theoretical basis for compressed sensing – a set of methods that allow the acceleration of measurement of signals having compressible representation. In their review of compressed sensing,^[3] Candès and Wakin further expressed the idea that the "information rate of a continuous time signal may be much smaller than suggested by its bandwidth". In effect, under-sampling such signals – that is sampling at a slower rate than that required by the Nyquist-Shannon theory^[4] – can provide enough information to define the frequencies within the signals. This finds application in multi-dimensional NMR spectroscopy where advancement in alternative ('non-Fourier' based) methods of data analysis and processing, provide more rapid access to higher

dimensionality data in what is known as non-uniform sampling (NUS) and a myriad of spectrum reconstruction algorithms have been implemented.^[5,6] Recently, we have demonstrated that "burst" non-uniform sampling and reconstruction approaches can be leveraged in the direct dimension of NMR experiments,^[7] achieving higher resolution in 'pure-shift' experiments that are limited by the excision of the *J*-refocussing periods (during which homonuclear and/or heteronuclear decoupling pulses are applied^[8–14]) or to reduce the high duty cycle and sample heating associated with broadband heteronuclear decoupling during acquisition.^[15] This application of NUS in the direct dimension is termed EXACT (EXtended ACquisition Time) NMR spectroscopy. Pseudo two-dimensional (2D) NMR methods have become especially important recently in generating broadband homonuclear decoupled NMR spectra, exemplified by the Zangger-Sterk (ZS) slice-selective^[16,17] and PSYCHE^[18] pure-shift methodologies. These approaches are distinguished from traditional 2D homonuclear decoupled experiments, such as PSYCHE-TOCSY,^[19] where the decoupling elements are built into the *t*₁ evolution periods – giving rise to a spectrum decoupled in the indirect dimension – and as a result no significant time penalty is observed. In these methods, decoupling in the direct dimension is achieved by covariance NMR spectroscopy^[20–23] – a processing scheme that employs the covariance matrix of a series of 1D spectra to establish nuclear spin connectivity as per 2D experiments.

In pseudo-2D NMR experiments, the final FID is a one-dimensional interferogram generated by concatenation of data points or datachunks acquired over separate incremented time periods. Such approaches require a long experiment time, equivalent to that of a regular 2D NMR acquisition, but offer significant resolution benefits over 'real-time' single scan methods^[8–14] – by avoiding the inherent line broadening accompanying the excision of the *J*-refocussing periods (unless aforementioned 'burst' non-uniform sampling reconstruction is applied). In view of the advantages of pseudo-2D experiments over real-time single-scan pure-shift methods, there are clear benefits to any scheme that reduces their acquisition time without compromising the quality of the spectrum acquired.

Herein, we demonstrate that the EXACT NMR concept can be applied to pseudo-2D acquisition of broadband homonuclear decoupled NMR spectra, offering substantial time savings in ZS-1D^[16,17] and PSYCHE^[18] pseudo-2D experiments without significant loss in spectral quality, resolution or most importantly signal intensity.

The EXACT PSYCHE sequence (Figure 1) and EXACT Zangger-Stark sequences (Figure S2 and Figure S3) are similar to the original sequences published^[16–18] but with non-uniform sampling

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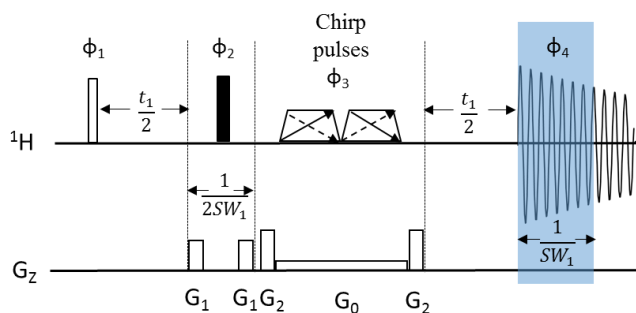


Figure 1. The PSYCHE sequence with incorporation of the EXACT acquisition as described in the text of this work. Unfilled and filled boxes are 90° and 180° pulses, respectively, while trapezoids are 20% smoothed chirp pulses (30ms total duration) of low flip angle applied in opposite sweeps (indicated by the arrows within the trapezoids) during a weak gradient, G_0 (1%). The other gradients are G_1 (49%) and G_2 (77%) – each of 1ms duration. The phase cycle is: $\phi_1 = 4(x, -x)$, $\phi_2 = 8(x)$, $\phi_3 = 2(x), 2(y), 2(-x), 2(-y)$, $\phi_4 = 2(x, -x, -x, x)$. The ZS-1D sequence and variant can be found in the SI.

of the t_1 points implemented as follows,

$$t_1 = \{j\Delta T \mid j \in J_p\} \quad 1$$

where,

$$\Delta T = 1/SW_1 \approx 10 - 20ms \quad 2$$

$$J_p \subseteq \{0, 1, 2, \dots, n-1\} \quad 3$$

Here p represents the sampling density (number of elements in the list, J_p), j the selected element in J_p and n the number of datachunks acquired. The number of datachunks (n) acquired is equal to the ratio of the total number of points in the final interferogram or FID (including points of zero intensity, n_{total}) and the number of points collected per chunk, n_{chunk} *i.e.* $n = n_{total}/n_{chunk}$. Note that the first and last chunks (0 and $n-1$) are always acquired. SW_1 is set to at least twice the widest multiplet width in the 1H NMR spectrum to ensure effective decoupling and is related to the desired final spectrum width, SW by equation 4;^[24]

$$1/SW_1 = n_{chunk}/SW \quad 4$$

The general scheme for EXACT pseudo-2D acquisition is illustrated in Figure 2. In the ZS-1D and PSYCHE pseudo-2D acquisition, datachunks acquired over t_1 increments (Figure 2a) are concatenated to give the full FID (Figure 2c). The EXACT pseudo-2D experiment is however acquired in significantly less time by acquiring only a subset of t_1 increments, *i.e.* selected J_p values (Figure 2b). Datachunks not acquired can be considered as points of zero intensity such that the acquired data points exactly match those that would be acquired in the fully sampled FID (compare Figure 2c and Figure 2d). The missing data points in the EXACT FIDs can then be reconstructed with existing algorithms, for example maximum entropy reconstruction^[25,26] or iterative soft thresholding (IST)^[27,28] to provide the complete 1-dimensional FID.

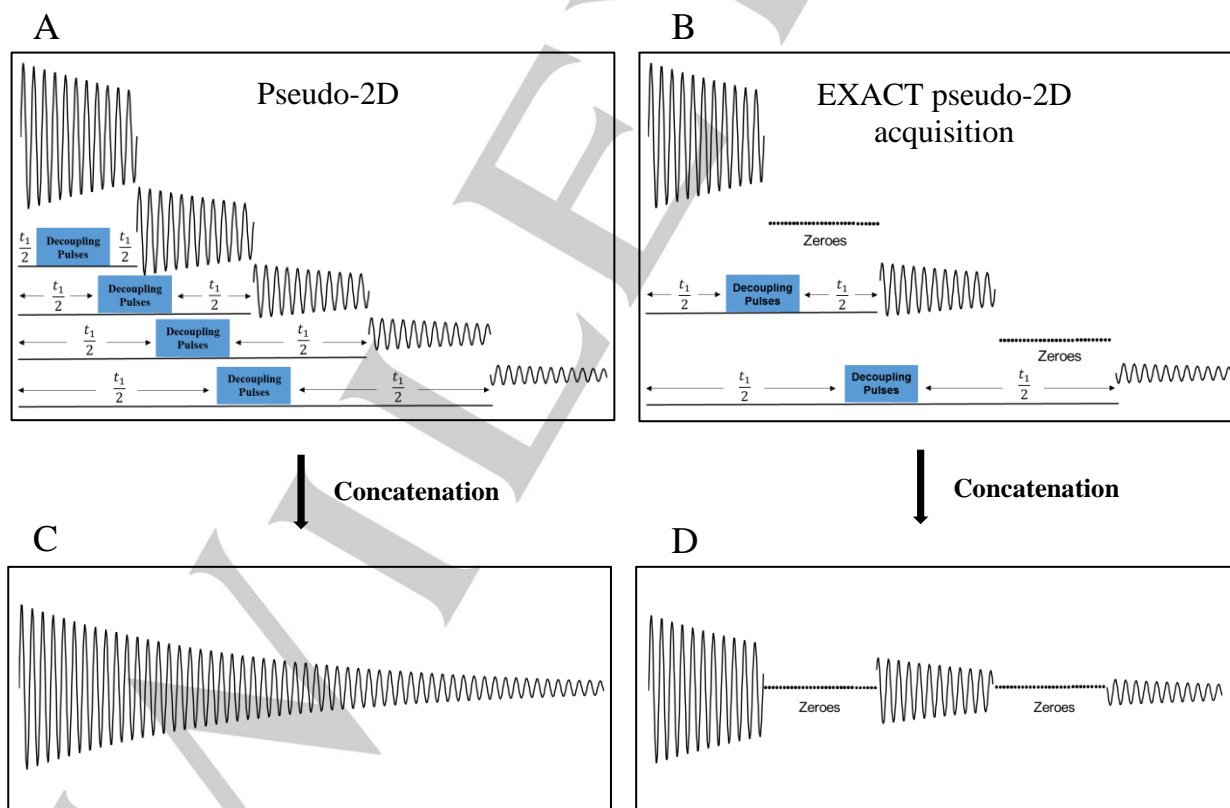


Figure 2. Schematic of (A) Pseudo-2D acquisition and (B) EXACT pseudo-2D acquisition (note that datachunks selected are a function of t_1 and are not in a regular pattern as shown in the figure) with their respective FIDs – (C) and (D) – comprising concatenated data chunks which are acquired over t_1 incremented time period.

Results and Discussion

To illustrate the potential of the EXACT approach to pseudo-2D acquisition, the EXACT PSYCHE sequence (Figure 1) was acquired at 100%, 50%, 37.5% and 25% sampling density from a total of 32 t_1 increments (each datachunk – 20ms long, J_c values are shown in SI, Table S1), on a 15mg sample of cyclosporine-A dissolved in 0.5ml deuterated benzene. Each spectrum was reconstructed, using IST-based algorithms as reported previously,^[7,15] to 3200 points and then zero-filled to 64K (excluding the 100% sampled dataset which was Fourier transformed and then zero-filled to 64K).

The standard (100%) cyclosporine-A PSYCHE spectrum (Figure 3a show zoomed region of Figure S4c), was acquired for approximately 3 minutes. As only a small statistical percentage of active spins are observed in the PSYCHE experiment, there is a substantial loss of sensitivity compared to the ^1H spectrum,^[18] but a high quality of homodecoupling is achieved with linewidths of 1.7 - 2.5Hz. The corresponding EXACT PSYCHE acquisitions with 50%, 37.5% and 25% sampling densities (Figures 3b-d also

show zoomed regions of Figures S4d-f respectively) provide grossly similar homonuclear decoupling quality but in 1.5, 1.1 and 0.78 minutes respectively. Closer inspection of the homodecoupled spectra shows that IST essentially perfectly reconstructs the 50% sampled EXACT PSYCHE dataset (Figure 3a vs Figure 3b) and that there are only minute differences apparent in the 37.5% sampled spectrum (Figure 3c). However, in the reconstructed 25% EXACT dataset (Figure 3d) peak distortions and reconstruction artefacts in the baseline are clearly visible, suggesting limitations with the existing IST algorithms used here.

The key benefit of the EXACT approach to pseudo-2D acquisition is that the experiment is acquired faster, but with no loss of signal intensity. This is demonstrated by the absolute peak intensities shown inset in Figures 3a-d. For example, the peak at 0.65ppm gave absolute intensities of 2675, 2723, 2684 and 2680 respectively for the 100%, 50%, 37.5% and 25% sampled PSYCHE spectra (Figures 3a, 3b, 3c and 3d, respectively) – showing essentially no change in intensity. In fact across all regions of the spectra, peak intensities varied by no more than 5% between the 100, 50 and 37.5% PSYCHE datasets (see

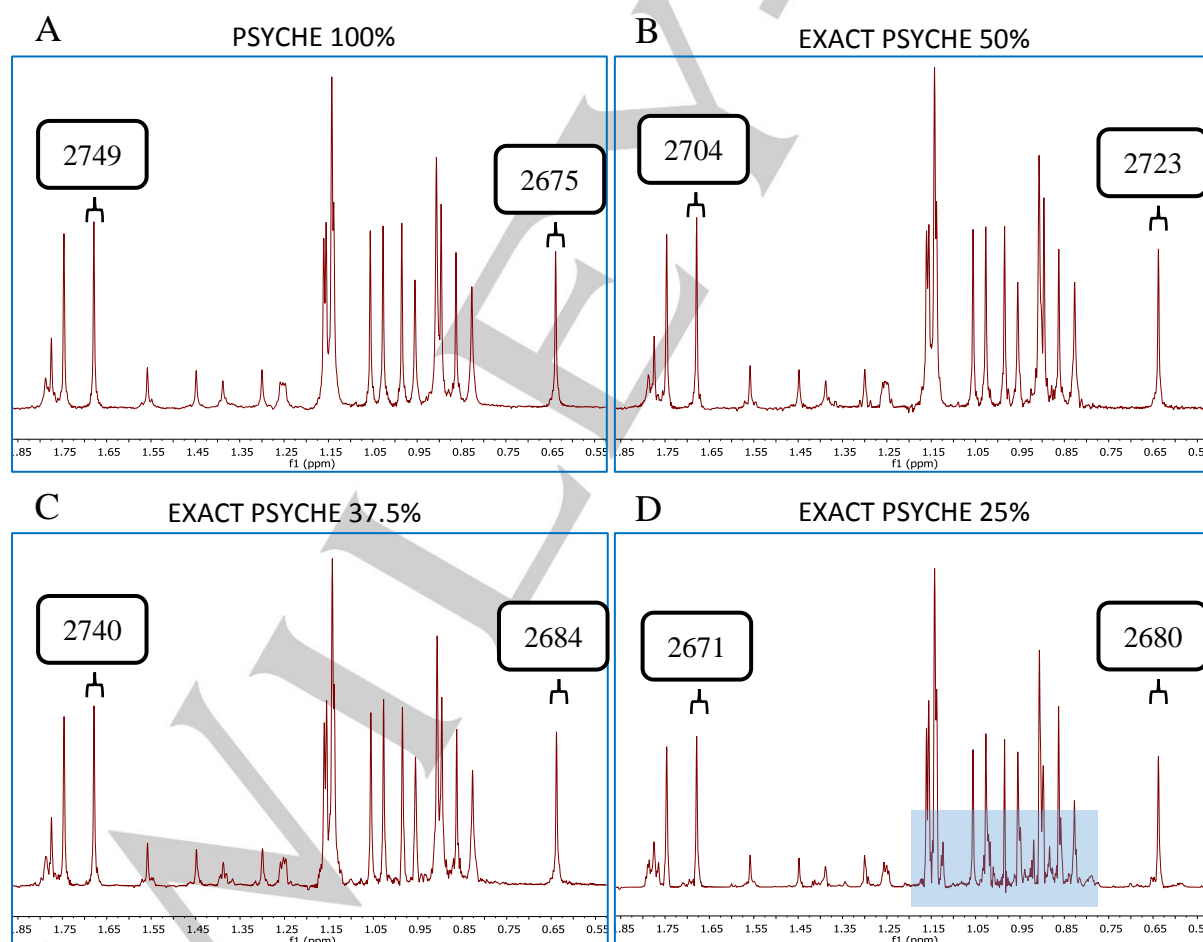


Figure 3. Zoom of a cross-section (0.55 – 0.85ppm) of the PSYCHE and EXACT PSYCHE cyclosporine-A spectrum showing inset the absolute peak integral (*not* signal:noise ratio which cannot be reliably defined for IST-processed spectra) of two equivalent peaks in each spectra of (A) Fully sampled PSYCHE, (B) 50% sampled EXACT PSYCHE, (C) 37.5% EXACT PSYCHE and (D) 25% EXACT PSYCHE dataset. The ^1H NMR of cyclosporine-A is shown in the SI (Figure S4a).

Tables S2 – S4). However, the 25% sampled PSYCHE spectrum (Table S5) showed greater variability which is attributed to the imperfect reconstruction of peakshapes and baseline by the IST algorithm used (see highlighted region with residual side-bands in Figure 3d). This retention of signal intensity appears reasonable as in principle the intensity of a peak is a function of the amplitude of the first data point in the FID. In the EXACT approach, the measured data points are not changed by the reconstruction algorithm – meaning that the peak intensities are fixed in the first measured datachunk of the spectrum. The consequence of this is that a well-reconstructed EXACT PSYCHE spectrum has the same quantitative value as the parent PSYCHE spectrum, but acquired in substantially shorter time. The signal intensity could be enhanced by using relaxation-matched NUS^[29] where the sampling scheme emphasizes the measurement of more datachunks near the beginning of the FID and fewer near the end of the FID – where signal-to-noise ratio is lower.

An alternative way to consider the benefit of NUS in pseudo-2D experiments is to compare the resolution which can be obtained in comparable time. This is shown here in a time-equivalent

comparison between the IST reconstructed 37.5% EXACT PSYCHE spectrum (*i.e.* 12 randomly distributed datachunks totalling 1200 data points, followed by IST-reconstruction of the missing data points in the gaps, to a total of 3200 – Figure 4a) and the spectrum from a fully sampled but truncated PSYCHE experiment, that is 12 consecutive datachunks totalling 1200 data points (linear predicted to 3200 data points – Figure 4b). In the EXACT PSYCHE spectrum (Figure 4c), the four peaks in the highlighted region can be clearly identified while the truncated PSYCHE spectrum (Figure 4d) lacks the needed resolution to reveal these peaks, even after linear prediction (LP) of the acquired data points. This reflects the added stability to the recovery of the missing data points provided by interpolation using IST in comparison to extrapolation by LP. An extensive study by Stern *et al.*^[30] on Maximum Entropy method (a similar algorithm to IST) and linear prediction extrapolation has shown that the former approach provides more accurate results than the latter – more so at low signal-to-noise ratios. IST also does not require an assumption of the number of components in the signal as does LP and the large number of components in one-dimensional NMR

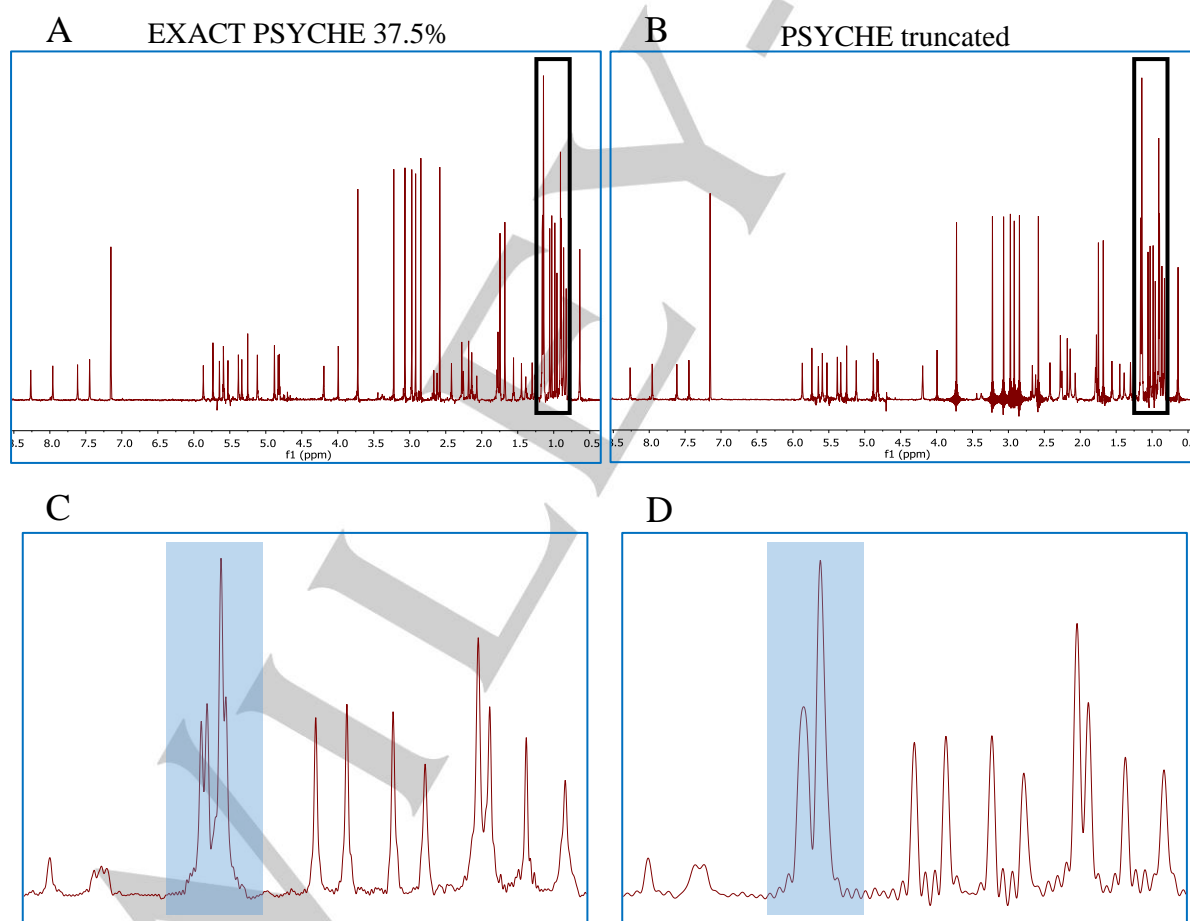


Figure 4. (A) 37.5% EXACT PSYCHE spectrum with 1200 actual data points acquired (but distributed randomly in chunks as described in this work) and reconstructed with IST (300 iterations) to 3200 data points and then zero-filled to 64K. (B) The truncated PSYCHE Fourier transform spectra of 1200 consecutive data points after linear prediction to 3200 data points and zero-filling to 64K. Both spectra of approximately equal experimental time (1.1 minutes), were processed

with a 0.1 exponential window function and the respective zoom of the highlighted regions shown in (C) and (D). The highlighted portions (blue in C and D) show the difference in the resolution achieved.

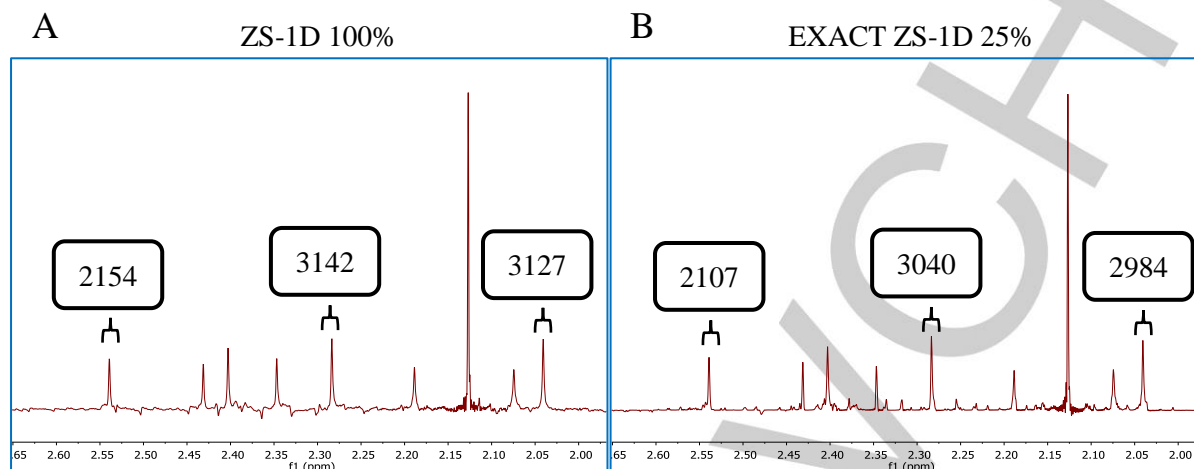


Figure 5. Zoom of a cross-section (1.98 – 2.65ppm) of (a) the 100% sampled ZS-1D Fourier transformed spectrum and (b) the 25% sampled EXACT ZS-1D IST reconstructed spectrum of a 136.29mM CDCl₃ solution of progesterone. Inset are the absolute peak integrals of three equivalent peaks in both spectra. Please note that values shown in boxes are peak integrals – which can be used as a measure of signal intensities – and should not be confused with signal-to-noise ratios.

spectra makes the use of the latter generally ineffective. In addition, LP presumes a pure exponential signal model, which further limits its use, while IST is generally more insensitive to the signal model.

The same outcomes are observed with the EXACT modification of the Zangger-Sterk pseudo-2D experiment (Figure S5). The ZS-1D spectrum of progesterone (Figure S5c) was acquired with 6,400 data points (64 datachunks) in 24 minutes (8 scans). The corresponding IST reconstructed EXACT ZS-1D spectra acquired

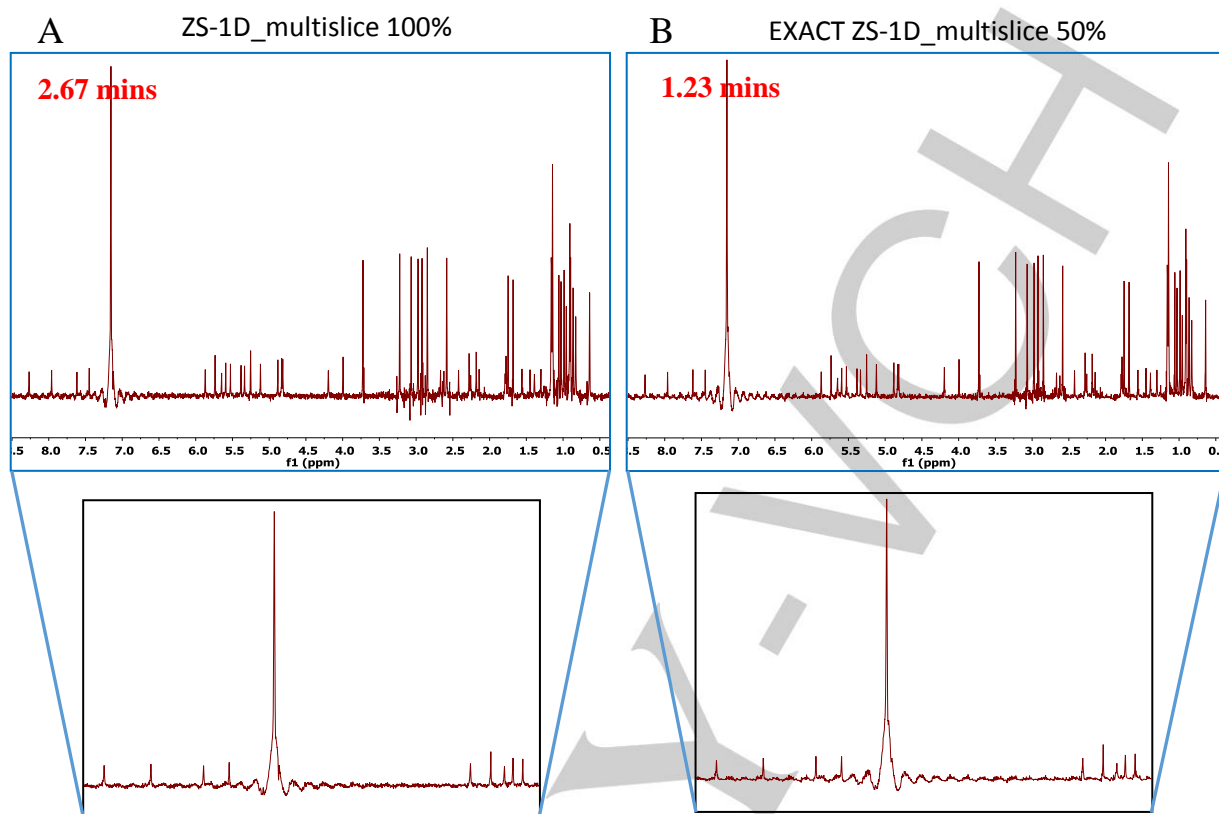


Figure 6. (a) The spectrum of the sensitivity enhanced ZS-1D (ZS-1D_multislice) experiment – 100% sampled (2.67 minutes acquisition time) and (b) the IST reconstructed 37.5% sampled EXACT ZS-1D_multislice variant (1.23 minutes acquisition time) acquired on a 15mg cyclosporine-A sample dissolved in 0.5ml benzene- D_6 . Insets are zoom of 5.5 – 8.3ppm region, highlighting the perfect reconstruction of weak peaks in the presence of a strong solvent signal.

at 50, 37.5 and 25% sampling densities (that is 32, 24 and 16 datachunks) in 12, 8 and 6 minutes respectively are shown in Figures S5d, S5e and S5f. Again, the signal intensities of the EXACT ZS-1D slice-selective experiments were equivalent to the parent 100% ZS-1D experiment, even for the 25% EXACT ZS-1D dataset, where signal intensity losses were < 7% in most cases. This is exemplified by the 1.98 – 2.65ppm region of progesterone shown in Figure 5. The singlet resonances at 2.54, 2.28 and 2.04ppm gave similar peak integrals in both the fully sampled ZS-1D (2154, 3142 and 3127) and the 25% sampled EXACT ZS-1D (2107, 3040 and 2984) spectra with differences attributed to imperfect baseline in the former and/or the presence of reconstruction artefacts in the latter. This is clearly seen in Figure S6 where both spectra were superimposed and all peaks showed excellent fitting in linewidths and peak heights – even for weak peaks – with the only difference between both spectra being the baseline concatenation and reconstruction artefacts of the ZS-1D and EXACT ZS-1D datasets respectively.

The sensitivity enhanced ZS-1D^[16] (ZS-1D_multislice) sequence of Figure S3 speeds-up the acquisition of the parent ZS-1D pure-shift experiment by reducing the recycle delay between increments to ~ 100ms in addition to the acquisition of only the required number of data points per t_1 increment – that is the number of points in each datachunk (t_2 acquisition time is ~ 1.64s in the latter whereas it is ~ 0.12s in the former). In this sequence,

fresh magnetization, from previous ‘unperturbed’ slices, is accessed by moving the offsets of the selective 90° and 180° pulses between increments (see list of offsets in the caption of Figure S3). The selective pulses’ offsets are iterated such that the excitation bands at successive offsets do not overlap – providing ample time for used magnetization to relax. The sensitivity enhanced ZS-1D sequence ensures that unused magnetization (that is magnetization outside the selected regions) returns to the +z – axis at the end of the sequence by the use of a pair of 180° Broadband Inversion Pulses (BIP). The ZS-1D_multislice experiment can now be acquired around four times faster than the original sequence.^[17]

The EXACT approach to pseudo-2D acquisition, as described herein, is applied to the sensitivity enhanced ZS-1D sequence. Figure 6 shows comparative spectra acquired with the ZS-1D_multislice sequence (Figure S3) at 100% sampling density (Figure 6a, 2 minutes and 40 seconds) and at 50% sampling density (Figure 6b, 1 minute and 14 seconds) after FT and IST processing respectively (see SI for the 37.5% spectra). Key highlight of this methodology is shown inset as weak peaks were correctly reconstructed, even in the presence of the strong solvent signal. Peak integrals of the 100 and 50% ZS-1D_multislice datasets (Table S10 – S11) reveal only small differences in signal intensity (<7%) between the spectra.

Conclusions

In conclusion, EXACT pseudo-2D acquisition provides a means of acquiring homo-decoupled spectra of complex molecules much more rapidly, with little or no loss in signal intensity, resolution or peakshape. The correct homo-decoupled spectra of the test molecules, cyclosporine-A and progesterone, were perfectly recovered in all cases from the 50% sampled EXACT pseudo-2D datasets while a good homo-decoupled spectrum could be obtained for progesterone with sampling as low as 25% – representing four-times acceleration in speed of acquisition – using existing IST reconstruction algorithms. This highlights the key role played by the complexity of the homo-decoupled spectrum with respect to the number of data points needed for recovery of the correct spectrum. The experiment time thus gained can be leveraged to improve the notoriously low sensitivity of these pseudo-2D methods. Partial randomization of the sizes (lengths) and sampling distribution of data points within each datachunk, and gaps as well as improved reconstruction algorithms for burst-sampled datasets will further aid the recovery of the correct spectrum from lower sampled datasets.

Experimental Section

Test samples used in this work include; a 128.16mM strychnine sample (30mg/0.7ml CDCl₃), a 274.25mM menthol sample (30mg/0.7ml CDCl₃), a 136.29mM progesterone sample (30mg/0.7ml CDCl₃) and/or a 24.95mM cyclosporine-A sample (15mg/0.5ml C₆D₆). Experiments were acquired on a Bruker Avance III 500 MHz spectrometer equipped with a 5mm Bruker two-channel DCH cryoprobe and all experiments were acquired at 25°C. The spectral widths were set to 5000Hz (SW) and 50Hz (SW1) respectively for the direct and indirect (pseudo) dimensions for all experiments. Acquisition parameters for the EXACT PSYCHE and ZS sequences are listed in the captions of the individual sequences and experiments were acquired with 2 scans and 8 scans per t₁ increment respectively with a relaxation delay of 0.5s for PSYCHE and ZS-1D experiments and 0.1s for sensitivity enhanced ZS-1D variant. Missing data points corresponding to the un-acquired t₁ increments in these experiments were reconstructed with IST algorithm^[27,28] implemented in the *mddnmr* 2.4 package (see www.mddnmr.spektro.com) and can be downloaded here; <http://nmr.cent.uw.edu.pl/index.php/download/category/5-pure-shift>. This version was adapted to processing 1D datasets by a Python wrapper written by Alexandra Shchukina and Krzysztof Kazimierczuk (co-authors of this manuscript), where virtual echo^[31] option was included. The concatenation and IST reconstruction of the 1D FIDs from the acquired pseudo-2D datasets is now supported in Mestrenova processing software, courtesy Vadim Zorin and Carlos Cobas (also co-authors of manuscript).

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Keywords: EXACT • Pure Shift • Non-uniform Sampling • Pseudo-2D acquisition • Homonuclear decoupling

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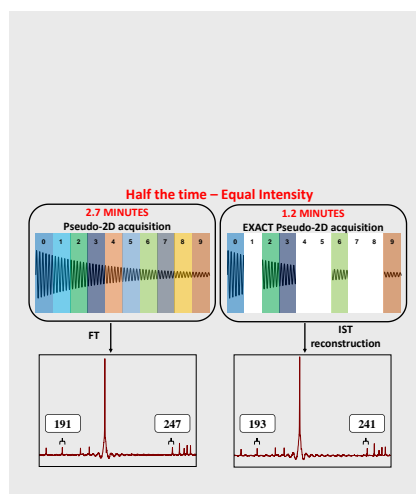
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