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Fast multi-dimensional Hadamard spectroscopy

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Abstract

Multi-dimensional NMR spectroscopy can be speeded up by large factors by replacing the time-domain evolution dimensions by direct irradiation at signal-bearing sites with a frequency-domain multiplex scheme. There is no loss in sensitivity per unit time. The excitation and transfer operations are encoded according to Hadamard matrices and the detected NMR signals are decoded by reference to the same matrices. Most traditional multi-dimensional NMR pulse sequences can be readily converted into this new Hadamard mode. Three-dimensional TOCSY–HSQC experiments on strychnine at 700 MHz bear out these ideas, indicating that the measurement time can be reduced by as much as three orders of magnitude in favorable cases.

Keywords: Multi-dimensional NMR; Hadamard spectroscopy; TOCSY; HSQC; Strychnine

1. Introduction

Multi-dimensional NMR spectroscopy has many useful applications, particularly for structural studies on biological macromolecules. The NMR frequencies are explored *indirectly* by allowing them to precess freely during two or more successive evolution periods, before passing the information to a direct detection stage. These time-domain NMR signals are processed by Fourier transformation and require extensive and uniform sampling in each evolution dimension. The only serious drawback is the long duration of the data-gathering process, which can run into many hours or even days. The obvious limit on how long an expensive NMR spectrometer can be monopolized by a single investigation imposes some severe practical restrictions—sparse sampling in the indirect time dimensions $(t_1, t_2, \ldots)$, minimal phase cycling, and even deliberate aliasing in the evolution dimensions when this can be tolerated. These are the critical considerations that determine the length of a multi-dimensional experiment, rather than time-averaging for sensitivity purposes.

The culprit is the requirement for *regular* sampling, which is a direct result of data collection in the time domain followed by the fast Fourier transform algorithm. All possible frequencies are monitored, yet most of these carry only noise; only a few generate NMR information. If the *actual* NMR frequencies are already known from a previous one-dimensional measurement, regular sampling is no longer strictly necessary. Direct frequency-domain excitation [1] can be used, concentrating attention on a few signal-bearing regions of the spectrum. If the chemical sites are examined one at a time, the signal-to-noise ratio is poor, but multiplex excitation restores the high sensitivity of the Fourier transform mode. It has already been demonstrated that this can speed up two-dimensional experiments by more than two orders of magnitude without sacrificing sensitivity per unit time [2]. Evolution periods and Fourier transformation are *not* used. Instead an encoding scheme is employed, based either on Hadamard matrices or progressive phase tables. Simultaneous multichannel excitation generates composite NMR signals in the receiver, which are then disentangled by reference to the chosen encoding scheme, rather like the operation of a telephone scrambling device. In multi-dimensional spectroscopy, direct frequency-domain irradiation may

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be employed in two or more frequency dimensions, and the time-saving factors are multiplicative.

2. Operation in the frequency domain

For the initial excitation and for the subsequent links between dimensions, 'polychromatic' radiofrequency pulses are used [3]; they are made up of many simultaneous selective pulses of differing frequencies. In this application the frequencies are chosen to match the chemical shifts measured from standard one-dimensional NMR spectra. This kind of multiplex excitation is readily implemented on modern NMR spectrometers. The pulses are shaped according to a Gaussian envelope [4]. The selectivity is determined by the duration of the pulse train, typically of the order of 10–100 ms. The effective frequency is offset from the carrier by linear phase incrementation along the sequence [5]. Multiplexing entails combining several such pulse trains with the same repetition rate but different rates of phase ramping, and this is achieved by vector summation of the radiofrequency pulses at each step of the sequence [6,7]. A scheme of this kind has been used to generate a comb of more than two thousand simultaneous soft radiofrequency pulses [1]; in the present applications far fewer pulses are required.

In order to separate the resulting NMR free precession signals, an encoding scheme is employed. This may take one of two forms. In the first, the amplitudes of the individual radiofrequencies are coded plus or minus according to the appropriate row of a Hadamard matrix [8] of order N, where N is restricted to $4n$, where n is an integer. The Hadamard technique has already been used to improve the sensitivity of selective irradiation experiments in high-resolution NMR [9–17] and the advantages of the Hadamard transformation have been emphasized in magnetic resonance imaging [18–22].

In the second method, the radiofrequency pulses are phase-encoded [11] in steps of $2\pi jk/N$ radians, forming an N by N progressive phase matrix where j is an integer $(0, 1, 2, \ldots, N-1)$ that increases across each row, while k is a similar integer $(0, 1, 2, \ldots, N-1)$ that increases down each column. Typical examples of both kinds of matrices are given in an earlier publication [2]. The matrix order N is chosen to equal or exceed M, the number of chemical sites under investigation. Then N scans are performed, with a new code for each successive scan. The radiofrequency pulses that link the first stage of the experiment to the second stage are encoded according to a second matrix of order P nested within the first. This entails a total of NP scans, and unless all are completed the resulting NMR signals cannot be properly decoded. Consequently N and P are kept as small as possible, and always far less than the number of time increments in each evolution dimension of a conventional multi-dimensional experiment. This accounts for a large part of the time saving, but in addition the Hadamard method can safely dispense with phase cycling and quadrature detection, and this also reduces the overall duration of the measurement.

At the end of each scan the spectrometer receiver detects a different composite free induction decay made up of contributions from all the chemical sites, each modulated in its own characteristic manner by the coding sequences. To separate the NMR responses from the individual 'channels' the composite signals are decoded according to the columns of the appropriate encoding matrix. In the case of a Hadamard matrix this involves combining the responses according to the plus or minus signs in a given column; the signals in all other channels vanish. In the case of phase-encoding, the rate of phase incrementation defines a 'virtual frequency' unique to that particular channel, and Fourier transformation with respect to the index k separates the response carried at this virtual frequency. As the actual irradiation frequencies are known, the Hadamard or phase-encoded results are readily converted into spectra with the correct separations between the individual NMR responses.

Consider a conventional three-dimensional spectrum in frequency space (F_1, F_2, F_3). The proposed alternative of direct frequency-domain excitation would select a set of (F_2, F_3) planes at F_1 values that correspond to the known chemical shifts; all other planes are empty of NMR information. In a similar manner, if the direct method is employed for the radiofrequency pulses that link the first and second dimensions, then (F_1, F_3) planes are recorded for specific values of F_2. If both the F_1 and F_2 dimensions are addressed directly, a set of one-dimensional (F_3) traces are obtained, one for every possible combination of F_1 and F_2 frequencies. In this case, the (F_1, F_2) plane may be called the Hadamard plane. In all cases the final dimension employs direct time-domain acquisition and Fourier transformation, and can be uniformly and finely sampled with no significant time penalty.

These principles apply to both homonuclear and heteronuclear spin systems. A very popular NMR procedure [23] applies multi-dimensional spectroscopy to proteins that have been artificially enriched in carbon-13 or nitrogen-15, or both, with a view to simplification of the crowded proton spectra. For the usual case of non-specific enrichment, the proposed direct frequency-domain method would have the advantage that certain carbon or nitrogen sites could be selected by the operator, further simplifying the proton spectra. This would remove any incentive for site-specific isotope enrichment procedures.

3. Three-dimensional Hadamard spectroscopy

The general case of multi-dimensional spectroscopy can be illustrated by reference to three-dimensional

NMR. A schematic diagram is shown in Fig. 1, assuming that both encoding stages employ Hadamard matrices. The first step is to pre-record one-dimensional spectra corresponding to the two 'evolution' dimensions. These are used simply for determining the chemical shift frequencies and can be acquired in quick exploratory experiments. If necessary the operator can designate which frequencies are to be used. This information is used to set up the two multiplex irradiation stages using 'polychromatic' pulses, the first used for excitation and the second for coherence transfer (Fig. 1).

When carbon-13 or nitrogen-15 nuclei are involved, the proton spectra are recorded under conditions of broadband heteronuclear decoupling so that the satellite lines coalesce at the proton chemical shift frequencies. The numbers of peaks selected (M in the first dimension and L in the second) must be less than or equal to the sizes of the successive encoding matrices, N and P, respectively. In practice the 'all plus' column of a Hadamard matrix is usually avoided because it is less effective in reducing instrumental artifacts [2]. If necessary, the spectra can be improved by introducing a phase cycle that helps suppress relaxation-induced residual artifacts. In a four-step cycle, a proton inversion pulse is inserted prior to the direct excitation stage when the transient counter *nt* is 2 or 4, and a carbon-13 (or nitrogen-15) inversion pulse is applied when *nt* is 3 or 4. The receiver phase is inverted when *nt* is 2 or 3. When time is of the essence, this phase-cycling option is not used.

The imposition of the phase-alternation or phase-modulation code takes place before the polychromatic sequences are assembled by vector addition of their component pulses. Practical considerations favor Hadamard encoding because phase-encoding entails the acquisition of both real and imaginary signals and thus requires more scans [2]. The nested encoding operations employ a total of NP successive scans, each with its characteristic modulation. The receiver output consists of composite free induction decays that carry two layers of coding. Two Hadamard matrices of orders P and N feed two decoding stages (Fig. 1) producing NP 'pure' free induction signals, which are then converted by Fourier transformation into a set of traces running in the F_3 dimension. All possible NMR signals lie on these F_3 traces. Standard programs convert this information into a three-dimensional spectrum or into two-dimensional plane sections through that spectrum (Fig. 1).

The decoding process can be represented as a two-dimensional Hadamard transformation. Consider the simple case of the heteronuclear single-quantum correlation (HSQC) spectrum of methyl salicylate as an illustrative example. There are four aromatic proton resonances and four (directly bound) carbon-13 resonances. Although this is only a two-dimensional experiment, it is a simple matter to impose two layers of encoding, the first with respect to the proton frequencies (F_1) and the second with respect to the carbon-13 frequencies (F_2). This requires 16 successive scans encoded by means of two nested Hadamard matrices of order 4. Fourier transformation of the 16 different free induction decays creates 16 F_3 traces in the frequency domain, corresponding to a 4 by 4 data array (Fig. 2a). The rows reflect proton encoding in the F_1 dimension, while the

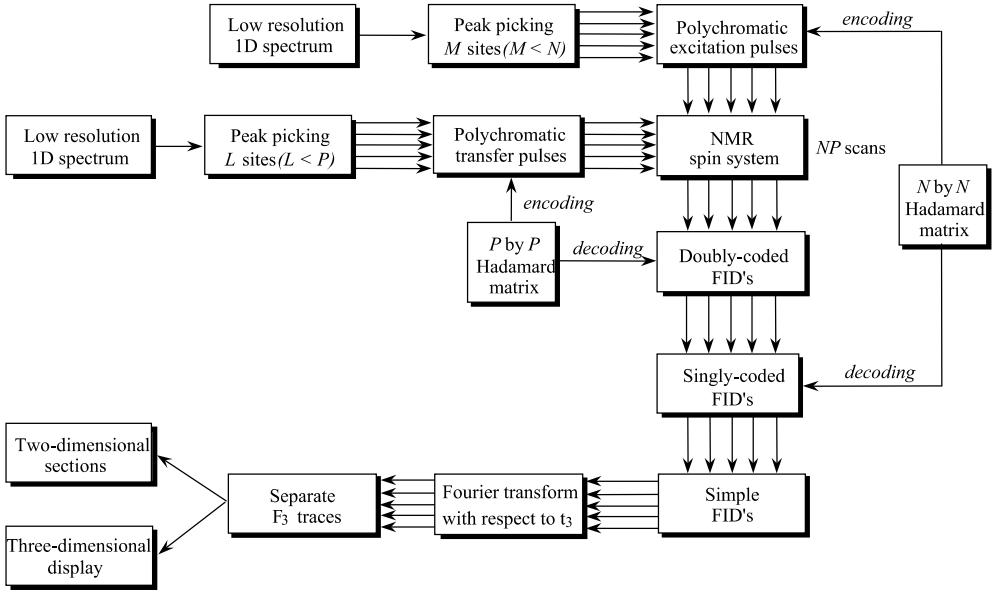

Fig. 1. Schematic diagram of a typical three-dimensional Hadamard experiment showing two layers of encoding of the multiplexed ('polychromatic') radiofrequency pulses. A total of NP scans are performed, generating NP doubly encoded free induction decays, which are then decoded in two stages, giving 'simple' free induction decays that are then Fourier transformed. All the required information is contained in traces running in the F_3 dimension. Standard routines convert this into the three-dimensional spectrum or into selected plane sections.

columns represent carbon-13 encoding in the F_2 dimension. The trace at the top left has all four proton resonances positive; the other traces in this figure have resonances modulated plus or minus in various patterns. The first Hadamard transformation stage generates a new array where a single proton resonance has been selected in each trace (Fig. 2b). The second transformation stage converts this into a form in which proton resonances appear in only four locations—those corresponding to the directly bound carbon-13 sites (Fig. 2c). These spectra are shown purely as an illustration of the two-dimensional Hadamard transform; the same correlation information could have been obtained with only one layer of coding.

The time saving by direct irradiation in the frequency domain may be demonstrated by reference to a two-dimensional HSQC experiment on the crowded region of the strychnine spectrum (1.0–4.5 ppm for protons). The Hadamard encoding was achieved by means of 45 ms Gaussian selective inversion pulses (with 20 Hz bandwidth) applied at the 11 directly bound carbon-13 sites, either inverting the carbon spins (represented by 'plus' in the matrix) or leaving them unaffected ('minus'). Ideally the Hadamard matrix of order 12 would have been used, but in practice the matrix of order 16 was employed because the power-of-two matrices are easy to compute. It is this number ($N = 16$) that determines the overall duration of the Hadamard experiment, whereas 500 t_1 increments were required to complete the conventional measurement with comparable resolution and the same spectral width (10 kHz) in the indirect frequency dimension. The duration of the conventional experiment is then doubled by the requirement for quadrature detection in the indirect dimension, and multiplied by four for

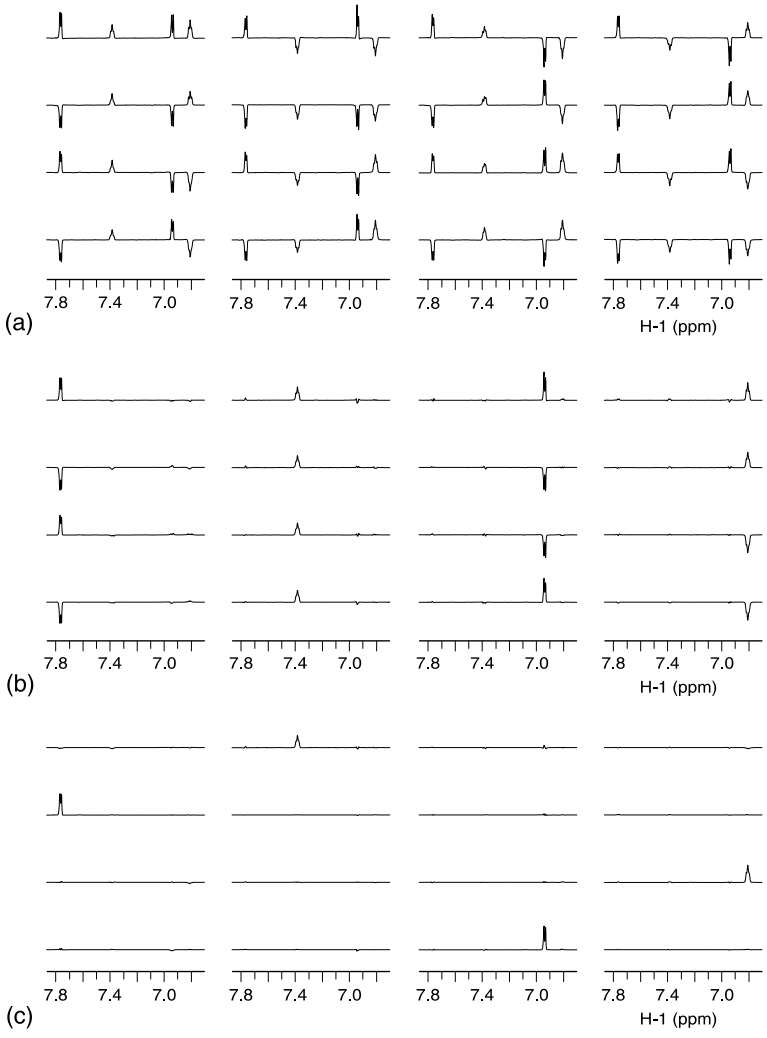

Fig. 2. Visualization of the decoding procedure as a two-dimensional Hadamard transformation. (a) Proton spectra of the four aromatic resonances of methyl salicylate were encoded in two layers, first with respect to the proton frequencies (the rows in this array) and then with respect to the carbon-13 frequencies (the columns) using two Hadamard matrices of order four. (b) After the first Hadamard transformation with respect to the proton-based modulation in the F_1 dimension. Each trace is reduced to a single proton resonance. (c) After the second Hadamard transformation with respect to the carbon-based modulation in the F_2 dimension, leaving only four responses. These serve to correlate proton and carbon-13 chemical shifts.

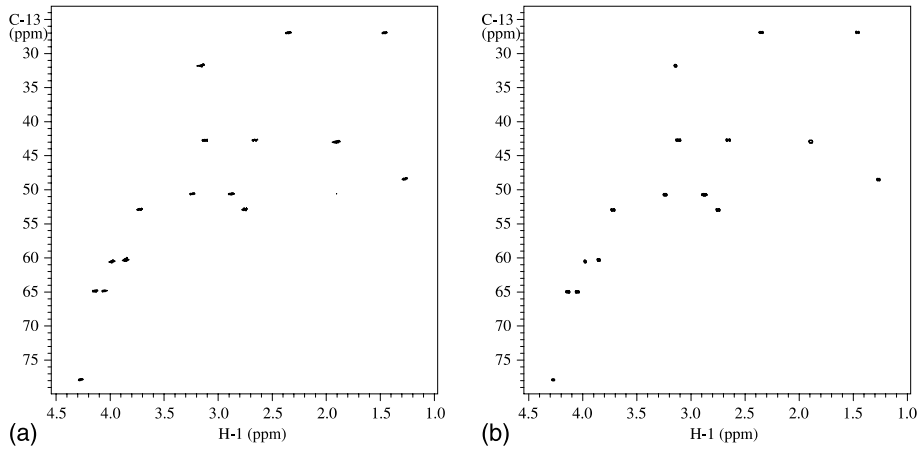

Fig. 3. Comparison of the two-dimensional HSQC spectrum of strychnine obtained by conventional Fourier spectroscopy (a) and Hadamard spectroscopy (b). Methylene groups have two proton responses for each carbon frequency. The Hadamard measurements were completed in only 47 s, whereas the standard experiment required 2 h and 52 min, a factor of almost 220. The conventional experiment incorporated a four-step phase cycle; if this were omitted it would shorten the measurement time by a factor four but at the expense of spectral quality.

the phase cycling needed for good spectral quality. The Hadamard experiment was completed in 47 s, whereas the conventional equivalent using two-dimensional Fourier transformation required 2 h and 52 min, almost 220 times longer (Fig. 3). Naturally the more protracted conventional measurement yields a higher signal-to-noise ratio, but in both cases this ratio is more than adequate, even with carbon-13 in natural abundance. This speed advantage depends very much on the number of sites chosen for irradiation; it is smaller for more complicated spectra. Disregarding phase cycling and quadrature detection for the Fourier method, the Hadamard technique would reach the same sensitivity in the hypothetical limit of one NMR response for every single data point in the F_1 dimension. In practice this is never the case. For three-dimensional spectroscopy far greater time savings are anticipated because both evolution dimensions are replaced by direct irradiation.

4. Results

Strychnine was chosen as an example to illustrate three-dimensional spectroscopy applied to a small molecule. Spectra were recorded at 700 MHz for protons on a Varian INOVA 700 spectrometer, concentrating on the crowded region between 1.0 and 4.5 ppm where there are 17 proton resonances. A peak-picking program examined the conventional spectrum with 45 Hz line broadening and found 15 resolved responses (two sets of coincidences). Broadband decoupling of the carbon-13 spins collected the satellites in the proton spectrum at the chemical shift frequencies. Polychromatic pulses with a duration of 45 ms were used to excite these 15 proton sites. The Hadamard matrix of order 16 was employed for encoding, leaving one unused irradiation channel corresponding to the column with all plus signs.

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The remaining 15 proton frequencies define the F_1 axis of the final three-dimensional spectrum.

The popular TOCSY–HSQC experiment was chosen as an illustrative example. It involved homonuclear Hartmann–Hahn coherence transfer [24,25] between the proton sites during a fixed isotropic mixing interval using the WURST-2 adiabatic sequence [26]. The encoded TOCSY stage was followed by round-trip transfer of nuclear magnetization from protons to carbon and back to protons involving two INEPT sequences [27], designed to label the TOCSY proton spectra according to the carbon-13 frequencies. (A decoupled carbon-13 spectrum supplied the required information about the carbon-13 chemical shifts.) Note that no evolution of carbon-13 frequencies was involved in this experiment. Instead, the labeling of the NMR signals with the carbon-13 frequencies was achieved by means of 180° polychromatic pulses, coded 'on' or 'off' according to the plus and minus signs in the appropriate row of the Hadamard matrix. During this multiplex irradiation period, evolution of the J_{CH} coupling was suppressed by broadband decoupling of the protons. The decoupling technique must be chosen with some care so that protons complete an integral number of 360° rotations. In practice, adiabatic decoupling with WURST-40 pulses [26] was employed, spanning a complete 20-step phase cycle [28]. The polychromatic proton excitation and these polychromatic carbon pulses were the only new features introduced into the conventional TOCSY–HSQC sequence. Other classic three-dimensional protocols can be modified in a similar manner simply by replacing the evolution periods by direct irradiation in the frequency domain (Fig. 4).

Fig. 5 shows the resulting three-dimensional TOCSY–HSQC spectrum of strychnine derived from traces running in the F_3 dimension. Much as in traditional three-dimensional spectroscopy, the responses have widths in the F_1 and F_2 dimensions defined by a single data point. Nevertheless, the contour plotting routine is up to the task and bestows an apparent linewidth in these dimensions. Cross-peak fine structure is of little consequence in these correlation experiments. Sections through this three-dimensional array at selected F_2 frequencies show (F_1, F_3) planes corresponding to six of the carbon-13 sites (Fig. 6). These subspectra highlight the TOCSY 'ladders' of proton–proton correlations. Note that (b), (d), and (f) represent cases of non-equivalent methylene protons and consequently include two parallel ladders. Because this is a TOCSY–HSQC experiment rather than HSQC–TOCSY, the correlation ladders run in the F_1 dimension.

Provided that the intrinsic sensitivity is already high enough, the duration of such a three-dimensional Hadamard experiment is largely determined by the product of the number of peaks in the F_1 and F_2

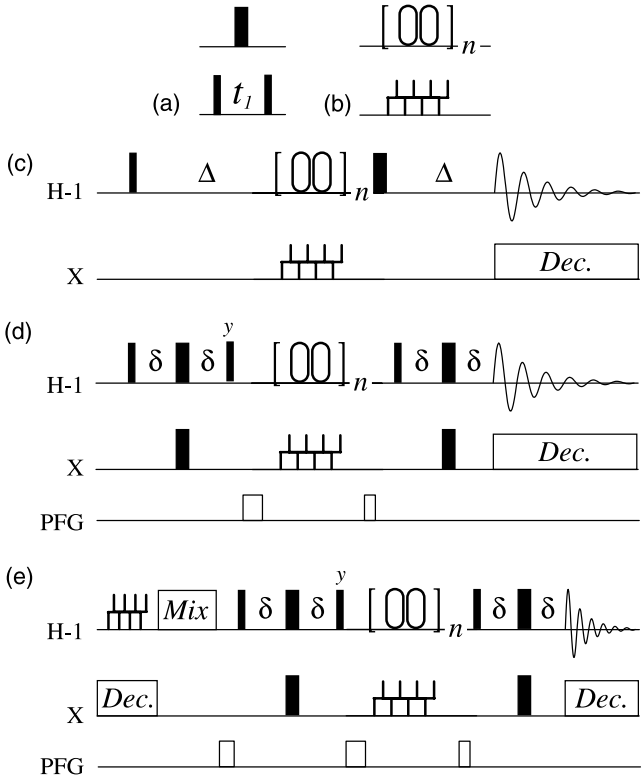

Fig. 4. Pulse sequences illustrating the conversion of traditional multi-dimensional experiments into direct-irradiation Hadamard spectroscopy. The conventional evolution periods (a) are replaced by a polychromatic irradiation sequence (b) with simultaneous broadband decoupling using an even number of adiabatic sweeps, represented by $[00]_n$. (c) Heteronuclear multiple-quantum correlation (HMQC) with $\Delta = 1/(2J_{XH})$. (d) Heteronuclear single-quantum correlation (HSQC) with $\delta = 1/(4J_{XH})$. (e) Three-dimensional TOCSY–HSQC with two layers of encoding.

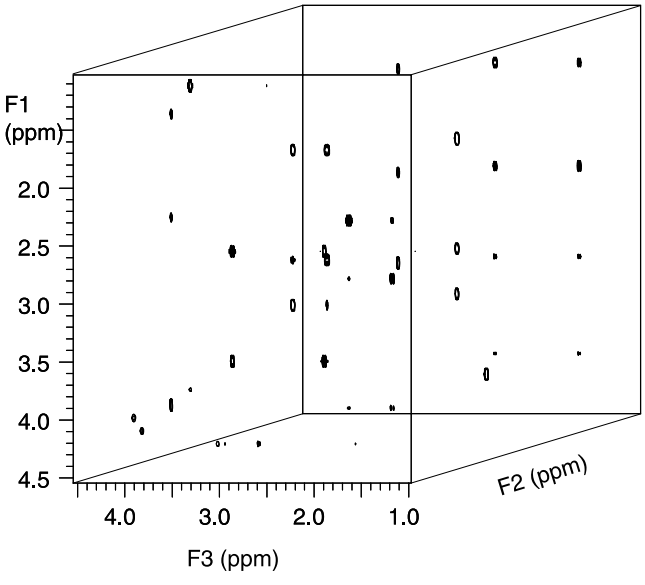

Fig. 5. The three-dimensional TOCSY–HSQC spectrum of the crowded region of strychnine obtained by Hadamard spectroscopy. The proton dimensions are F_1 and F_3 and the carbon-13 dimension is F_2. The measurement time was only 10 min 43 s, three orders of magnitude shorter than a conventional experiment with comparable resolution.

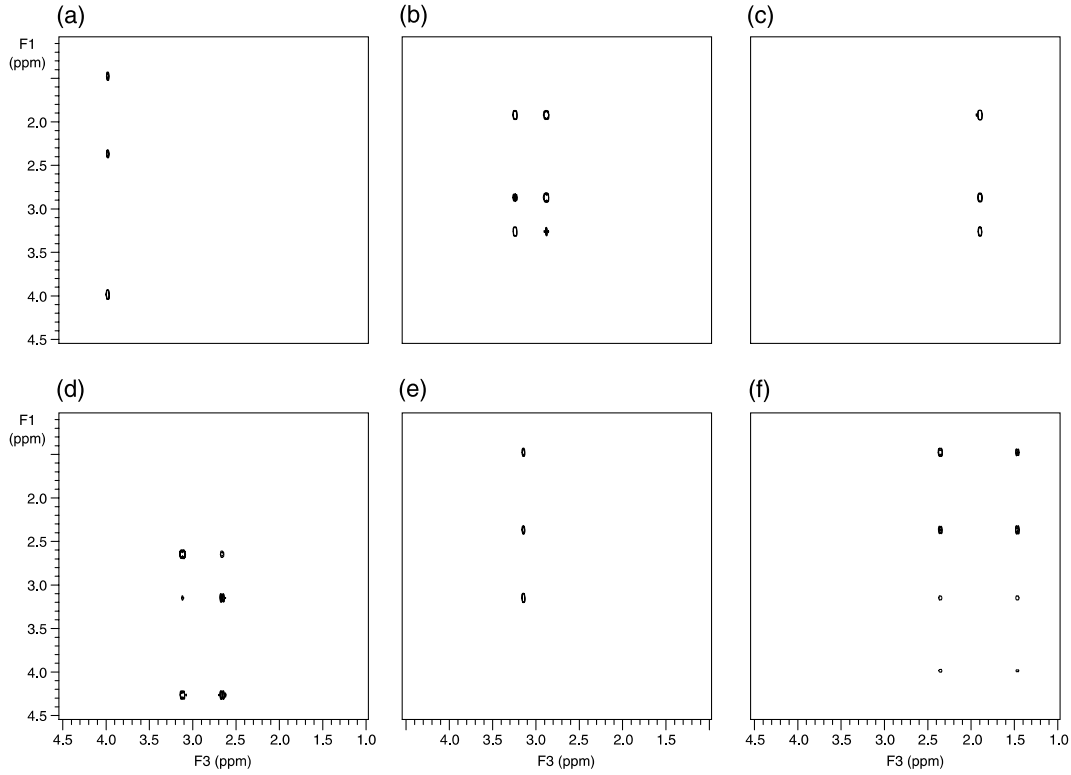

Fig. 6. Six (F_1, F_3) sections through the three-dimensional TOCSY–HSQC spectrum of strychnine, extracted at selected values of the carbon-13 chemical shifts at (a) 60.5 ppm, (b) 50.6 ppm, (c) 43.0 ppm, (d) 42.7 ppm, (e) 31.7 ppm, and (f) 26.9 ppm. Sites (b), (d), and (f) are non-equivalent methylene groups. The 'ladders' of proton–proton correlations arising from the homonuclear Hartmann–Hahn transfer are clearly visible.

dimensions, slightly increased because of the constraint on the size of Hadamard matrices. In the present example the overall duration of the measurement was 10 min 43 s. (The time required to obtain the two initial one-dimensional spectra was negligible in comparison.) The duration of a comparable measurement by the conventional Fourier transform methodology is determined by the product of the number of time increments in the two indirect dimensions, parameters that are set by the respective spectral widths and the desired resolution. With phase cycling reduced to a minimum (two steps), and quadrature detection in both evolution dimensions, it is calculated that the conventional mode with comparable resolution (125 and 500 increments in the evolution dimensions) requires 174 h and 5 min (over 7 days). This is a time-saving factor for the Hadamard mode of 975. To be fair, it is the accepted custom in conventional multi-dimensional spectroscopy to take several short-cuts to reduce the instrument time to more manageable levels. Typically resolution would be sacrificed by significantly reducing the number of increments in the evolution dimensions, and the spectral widths in these dimensions would be restricted by deliberate aliasing where this does not lead to confusion. Hadamard spectroscopy has no need to accept such compromises.

5. Discussion

The time-saving factor of the Hadamard technique is reduced roughly in proportion to the number of sites chosen for irradiation, so it is always important to keep this figure as small as possible. However the Hadamard experiment is always faster than the conventional Fourier transform measurement. The two would only be competitive in the hypothetical limit where the number of distinguishable chemical sites equals the number of evolution-time increments employed by the Fourier mode. This unrealistic regime would have such coarse definition in the F_1 dimension that individual resonances, even if regularly spaced across the spectrum, would not be resolved.

The main curb on more widespread applications of multi-dimensional spectroscopy has been the time factor—expensive modern NMR spectrometers should not be tied down to a single experimental project for days at a time unless there is no alternative. Preplanned Hadamard experiments reduce these experimental times to a much more manageable duration and thereby open up multi-dimensional techniques to a wider range of investigations, both for small molecules and also for isotopically enriched biomolecules. Having to examine the appropriate one-dimensional spectra beforehand is a

very small price to pay for the impressive increase in speed.

Speed is not the only advantage of Hadamard spectroscopy. The multiplex irradiation principle makes it possible to limit the investigation to just a few selected chemical sites and thus record a subspectrum that is appreciably simpler than the full multi-dimensional spectrum. This could have useful applications in biochemical screening studies, for example in certain branches of metabonomics [29] where the aim is to detect changes in protein structure caused by a xenobiotic agent. Investigations along these lines are being planned.

References

[1] E. Kupče, R. Freeman, Frequency-domain Hadamard spectroscopy, J. Magn. Reson. 162 (2003).
[2] E. Kupče, R. Freeman, Two-dimensional Hadamard spectroscopy, J. Magn. Reson. 162 (2003).
[3] E. Kupče, R. Freeman, Polychromatic selective pulses, J. Magn. Reson. A 102 (1993) 122–126.
[4] C.J. Bauer, R. Freeman, T. Frenkiel, J. Keeler, A.J. Shaka, Gaussian pulses, J. Magn. Reson. 58 (1984) 422.
[5] H. Geen, X.L. Wu, P. Xu, J. Friedrich, R. Freeman, Selective excitation at two arbitrary frequencies. The double DANTE sequence, J. Magn. Reson. 81 (1989) 646–652.
[6] E. Kupče, R. Freeman, Techniques for multi-site excitation, J. Magn. Reson. A 105 (1993) 234–238.
[7] E. Kupče, R. Freeman, Wideband excitation with polychromatic pulses, J. Magn. Reson. A 108 (1994) 268–273.
[8] J. Hadamard, Bull. Sci. Math. 17 (1893) 240–248.
[9] C. Müller, H.R. Bircher, P. Bigler, Magn. Reson. Chem. 30 (1992) 1247.
[10] C. Müller, P. Bigler, Increased efficiency for the selective detection and measurement of carbon–carbon couplings, J. Magn. Reson. A 102 (1993) 42.
[11] E. Kupče, R. Freeman, Multisite correlation spectroscopy with soft pulses. A new phase-encoding scheme, J. Magn. Reson. A 105 (1993) 310–315.
[12] V. Blechta, R. Freeman, Multi-site Hadamard NMR spectroscopy, Chem. Phys. Lett. 215 (1993) 341.
[13] V. Blechta, F. del Rio-Portilla, R. Freeman, Long-range carbon–proton couplings in strychnine, Magn. Reson. Chem. 32 (1994) 134–137.
[14] T. Nishida, G. Widmalm, P. Sandor, Hadamard long-range proton–carbon coupling constant measurements with band-selective proton decoupling, Magn. Reson. Chem. 33 (1995) 596–599.
[15] T. Nishida, G. Widmalm, P. Sandor, Hadamard long-range proton–carbon coupling constant measurements with pulsed field gradients, Magn. Reson. Chem. 34 (1996) 377–382.
[16] J. Schraml, H. van Halbeck, A. De Bruyn, R. Contreras, M. Maras, P. Herdewijn, Hadamard 1D ^{1}H TOCSY and its application to oligosaccharides, Magn. Reson. Chem. 35 (1997) 883–888.
[17] K. Krishnamurthy, Hadamard excitation sculpting, J. Magn. Reson. 153 (2001) 144–150.
[18] L. Bolinger, J.S. Leigh, Hadamard spectroscopic imaging (HSI) for multivolume localization, J. Magn. Reson. 80 (1988) 162–167.
[19] G. Goelman, J.S. Leigh, Multiband adiabatic inversion pulses for use with the 8-th order Hadamard spectroscopic imaging technique, Isr. J. Chem. 32 (1992) 271–280.
[20] G. Goelman, G. Walter, J.S. Leigh, Hadamard spectroscopic imaging technique as applied to the study of human calf muscles, Magn. Reson. Med. 25 (1992) 349–354.
[21] R.A. de Graaf, K. Nicolay, Multislice imaging with adiabatic pulses using transverse Hadamard encoding, J. Magn. Reson. B 113 (1996) 97–101.
[22] R.A. de Graaf, In vivo NMR spectroscopy. Principles and techniques, Wiley, Chichester, UK, 1998.
[23] A. Bax, S. Grzesiek, Acc. Chem. Res. 26 (1993) 131–138.
[24] L. Braunschweiler, R.R. Ernst, J. Magn. Reson. 53 (1983) 521.
[25] A. Bax, D.G. Davis, J. Magn. Reson. 65 (1985) 355.
[26] E. Kupče, R. Freeman, An adaptable NMR broadband decoupling scheme, Chem. Phys. Lett. 250 (1996) 523–527.
[27] G.A. Morris, R. Freeman, Enhancement of nuclear magnetic resonance signals by polarization transfer, J. Am. Chem. Soc. 101 (1979) 760.
[28] R. Tycko, A. Pines, R. Gluckenheimer, J. Chem. Phys. 83 (1985) 2775.
[29] J.K. Nicholson, J. Connelly, J.C. Lindon, E. Holmes, Metabonomics: a platform for studying drug toxicity and gene function, Nature Rev.: Drug Discovery 1 (2002) 153–161.