Other pure shift and related methods

Ralph Adams

A Pure Shift NMR Workshop
The University of Manchester, 12th September 2017

Other pure shift and related methods

A whistle-stop tour of things that haven’t been covered yet, including …

- BIRD, and its use in pure shift NMR
- 2D J spectra, absorption-mode signals in 2D J spectra, and pattern recognition
- Constant-time evolution
- Diagonal-suppressed 2D experiments
- J-scaling
- Measuring couplings to selected signals

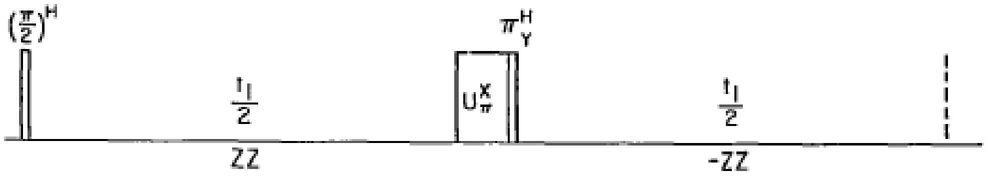
1982 : BIRD

BILINEAR ROTATION DECOUPLING OF HOMONUCLEAR SCALAR INTERACTIONS

J.R. GARBOW, D.P. WEITEKAMP and A. PINES

Department of Chemistry and Lawrence Berkeley Laboratory, University of California,
Berkeley, California 94720, USA

Received 1 September 1982; in final form 5 October 1982



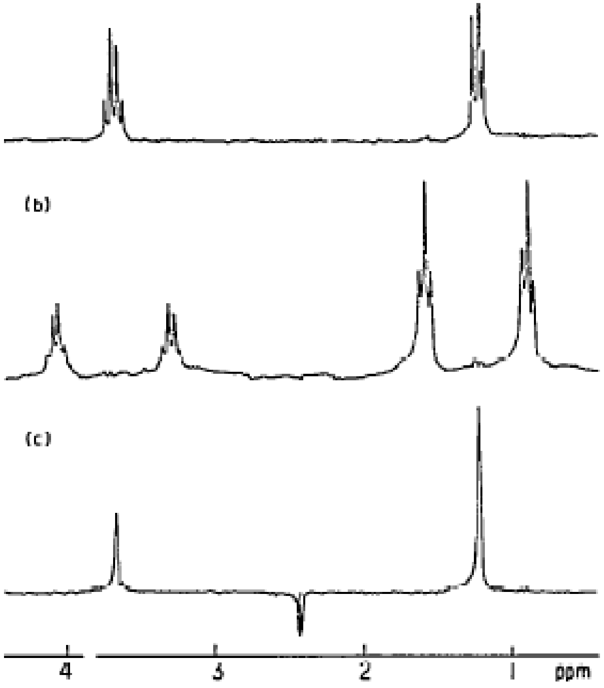
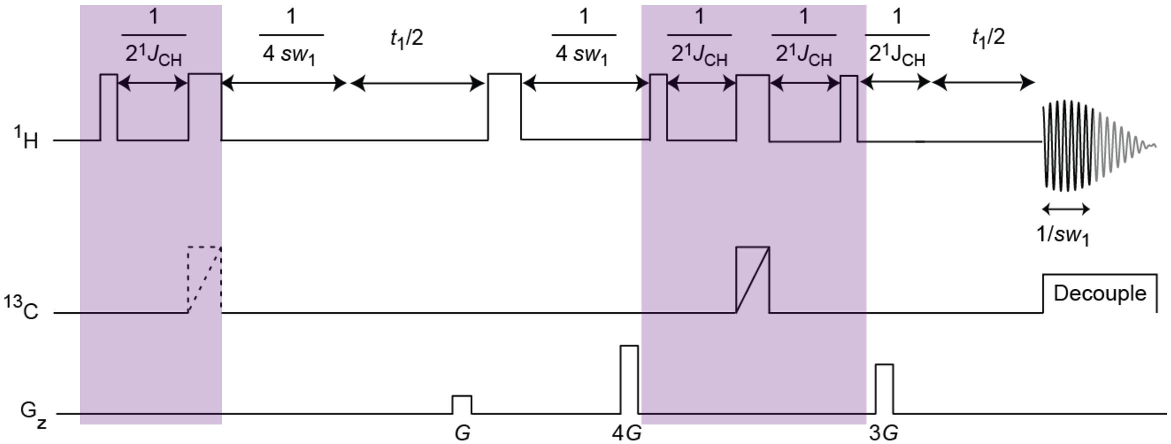


Fig. 1. Proton NMR spectra at 182 MHz of ethanol illustrating removal of *J*-couplings by BIRD. Samples were spun horizontally at 60–80 Hz in a vertical superconducting magnet with a horizontal solenoid r.f. coil.

Chem. Phys. Lett. **93**, 504 (1982)

1D pure shift NMR using BIRD - interferogram

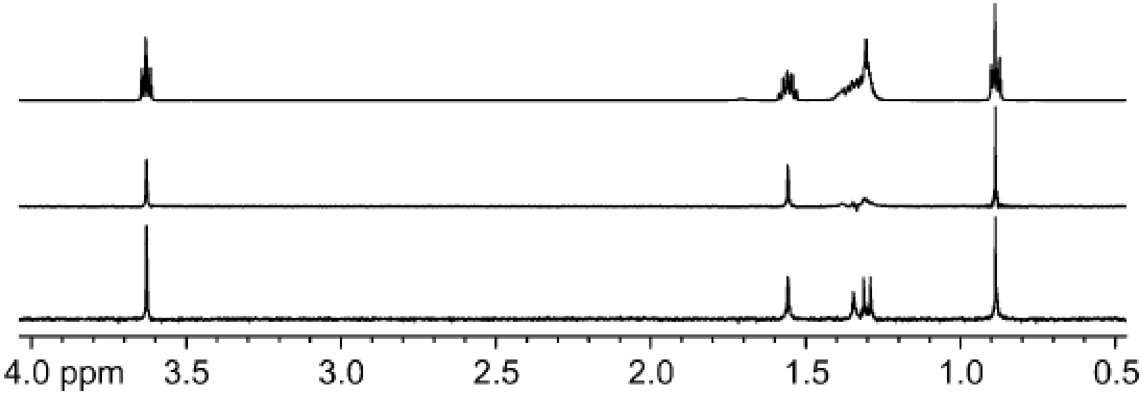


^{1}H-X filter

BIRD$_d$

- The BIRD$_d$ active spin refocusing element inverts only protons directly coupled to ^{13}C (or ^{15}N)
- Isotopic dilution ensures that their coupled partners are not inverted
- Protons are active if attached to ^{13}C (or ^{15}N), passive if not
- A ^{1}H-^{13}C filter is required to suppress contributions from the 98.9 % protons attached to ^{12}C

127 mM
n-hexanol



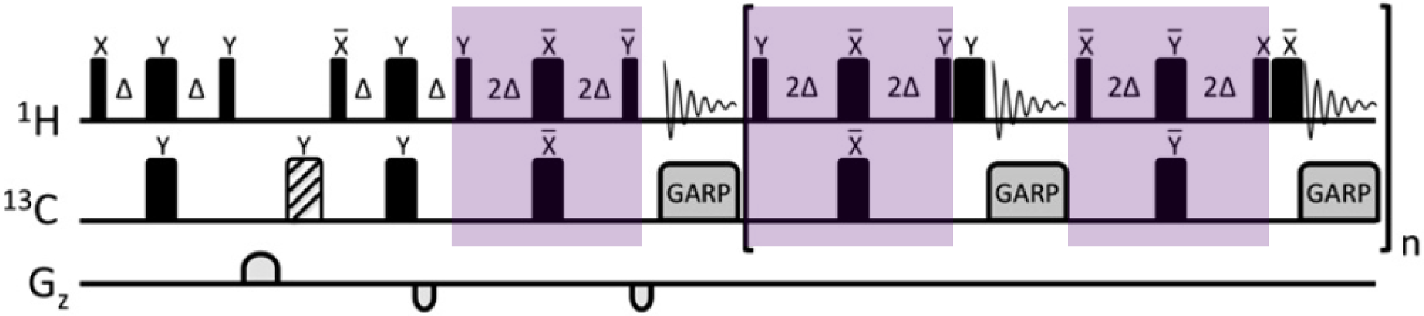
Conventional ^{1}H

ZS

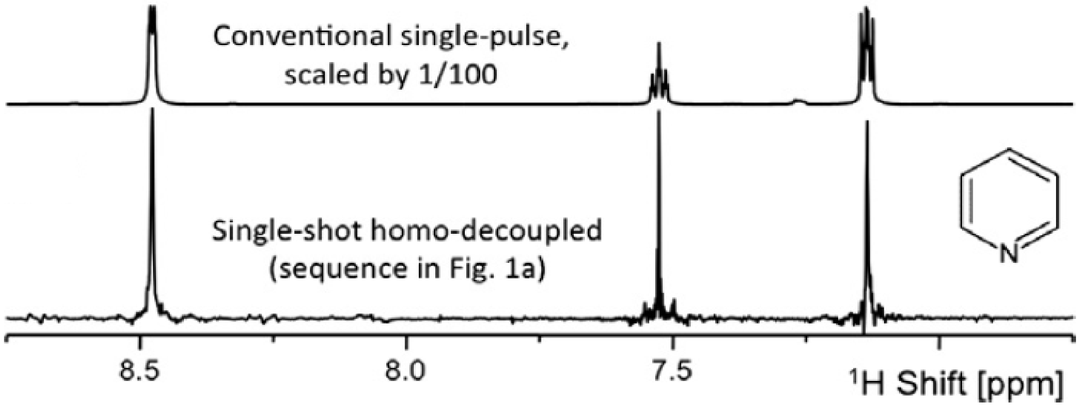
BIRD

Angew. Chem. Int. Ed. **50**, 9716 (2011)

1D pure shift NMR using BIRD – real-time



- BIRD is compatible with both real time and interferogram based acquisition
- In molecules with natural-abundance sensitivity is limited by 1.1 % ^{13}C, 0.37 % in ^{15}N
- For ^{15}N in enriched proteins and peptides there is no sensitivity penalty



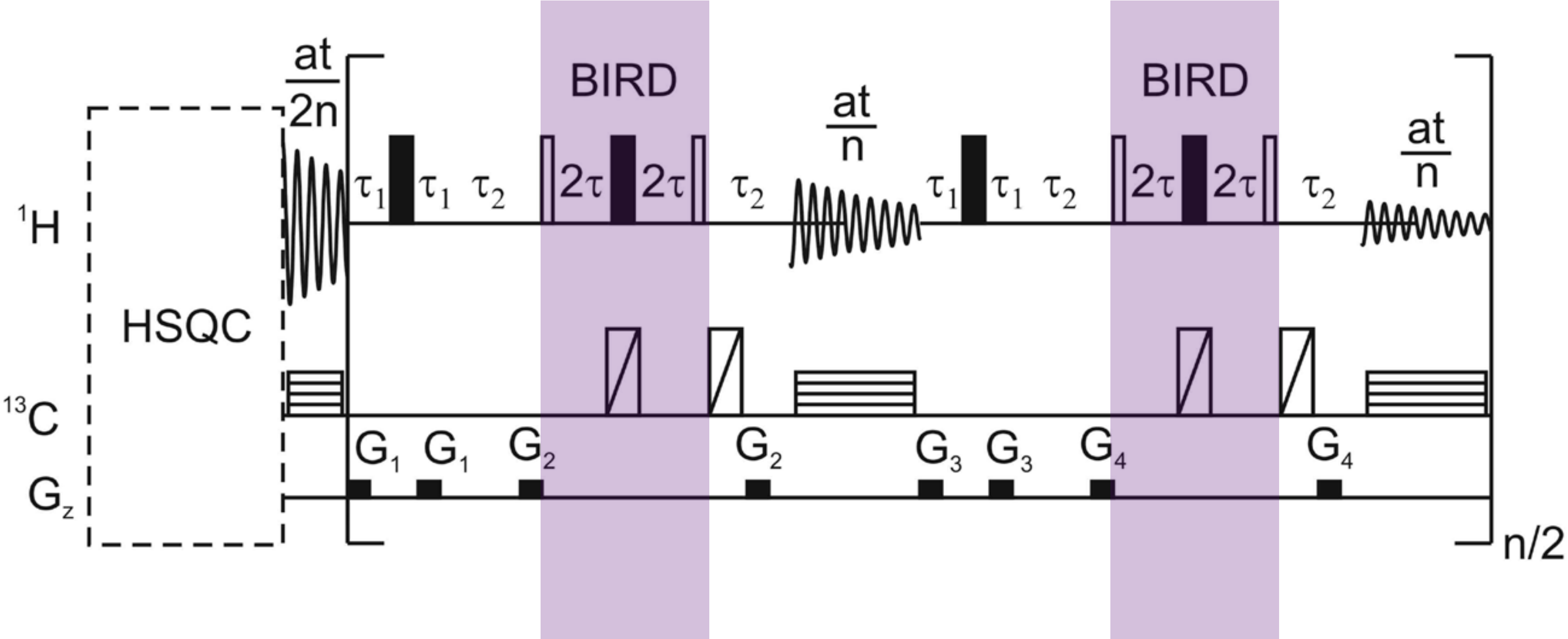
Conventional ^{1}H

BIRD

J. Magn. Reson. **218**, 141 (2012)

2D pure shift NMR using BIRD – real-time HSQC

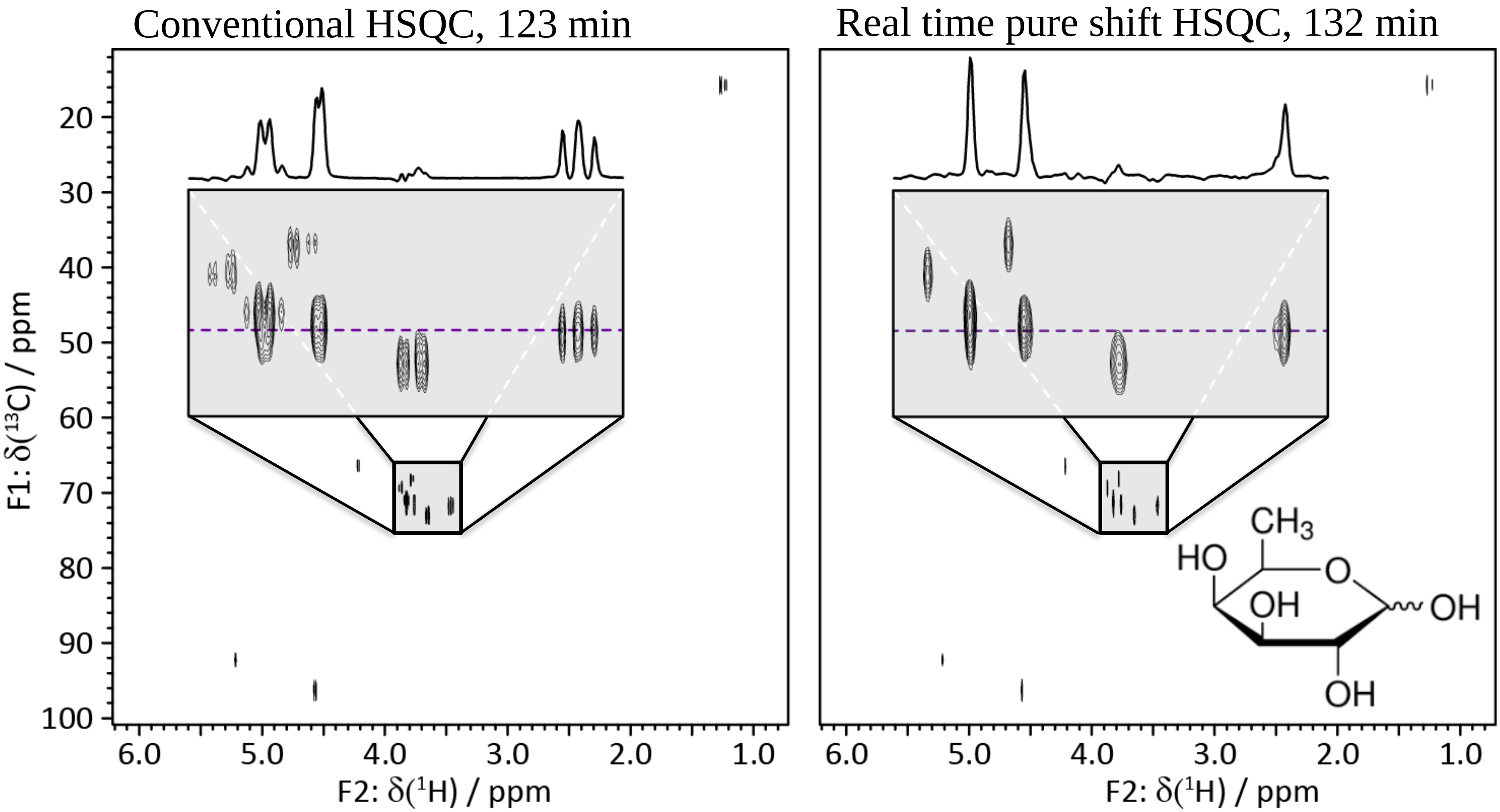
- For experiments such as HSQC which include a ^{1}H-X filter the sensitivity penalty does not have to be paid again when using BIRD-based pure shift
- Real-time pure shift HSQC spectra can have both increased sensitivity and increased resolution when compared to the parent experiment



- For a different but related approach that uses BIRD, CT and linear prediction see: *J. Magn. Reson.* **199**, 192 (2009)
- There are several Bruker library pulse sequences named using 'RESET'

Angew. Chem. Int. Ed. **52**, 11616 (2013)

2D pure shift NMR using BIRD – real-time HSQC



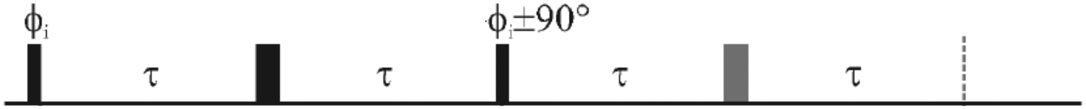
Conventional HSQC, 123 min

Real time pure shift HSQC, 132 min

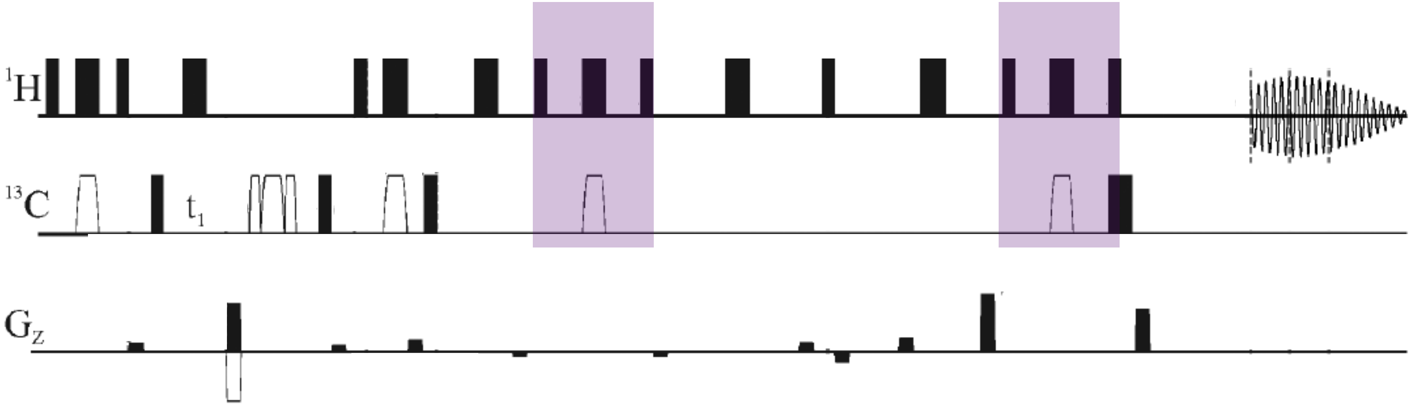
2D pure shift NMR using BIRD – Perfect Echo HSQC

- Protons attached to the same ^{13}C are not decoupled from one another – geminal protons appear as doublets when using a standard BIRD pure shift HSQC

Perfect echo (PE)



HSQC + PE + BIRD

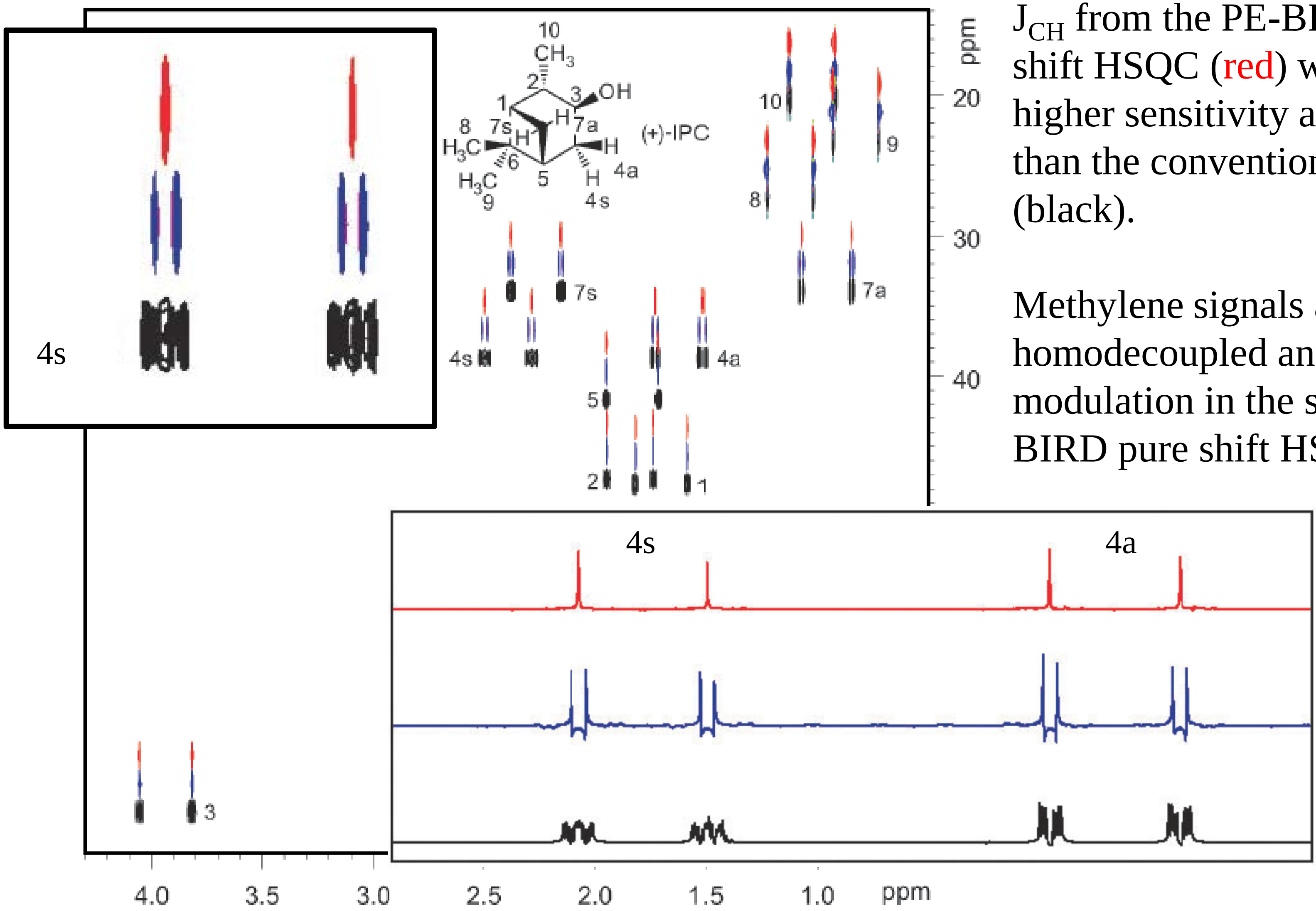


- By inserting a quadrature 90° pulse at the midpoint of a double spin echo to form a ‘perfect echo’, J modulation for an AX system is completely refocused
- The combination of perfect echo and BIRD HSQC can be used to refocus all J_{HH} including those between geminal protons
- Only interferogram acquisition can be used with the perfect echo version of HSQC

Chem. Commun. **50**, 15702 (2014)

2D pure shift NMR using BIRD – Perfect Echo HSQC

^{13}C-coupled HSQC spectra



It is straightforward to measure J_{CH} from the PE-BIRD pure shift HSQC (red) which has higher sensitivity and resolution than the conventional HSQC (black).

Methylene signals are not homodecoupled and show J modulation in the standard BIRD pure shift HSQC (blue)

Chem. Commun. **50**, 15702 (2014)

1976 : 45° Projection of a 2D J Spectrum

Homonuclear broad band decoupling and two-dimensional *J*- resolved NMR spectroscopy*

W. P. Aue, J. Karhan, and R. R. Ernst

Laboratorium für Physikalische Chemie, Eidgenössische Technische Hochschule, 8006 Zürich, Switzerland

(Received 2 March 1976)

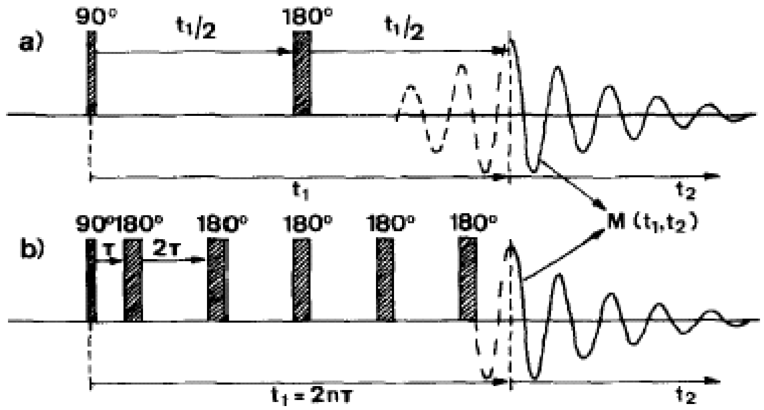
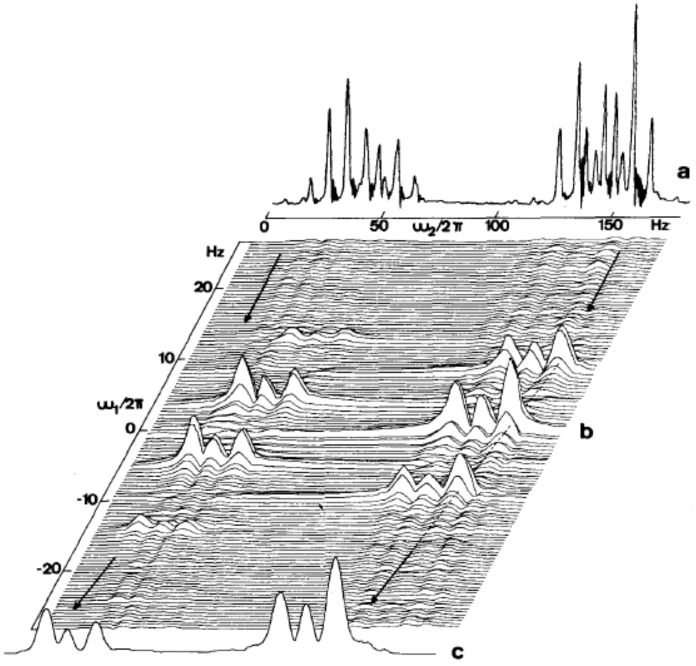
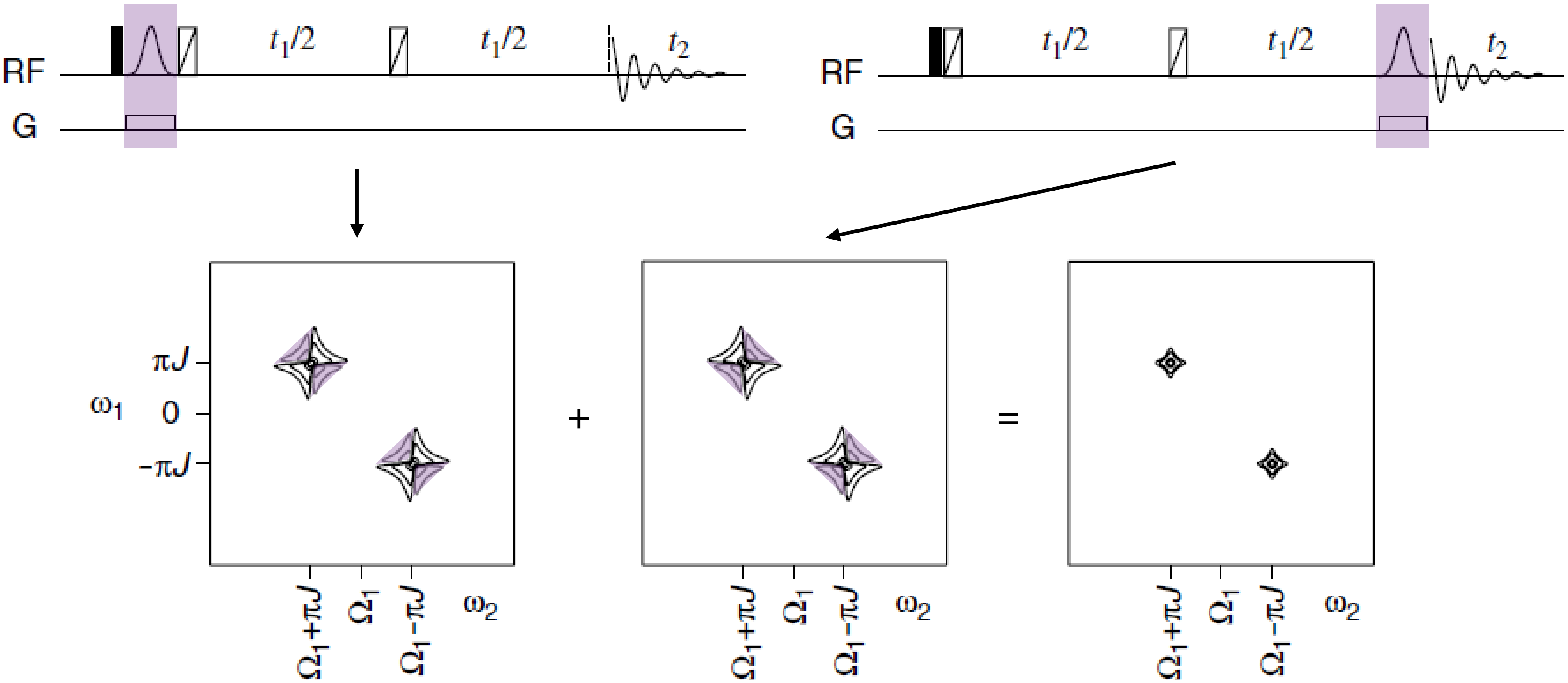


FIG. 1. Two basic schemes for 2D *J*-resolved spectroscopy. (a) Single echo experiment. (b) Spin echo sequence. Except for the effects of diffusion, both experiments produce the same results.



J. Chem. Phys. **64**, 4229 (1976)

2D J Spectroscopy – with absorption-mode signals



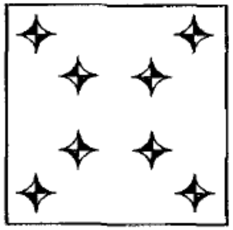
- An active spin refocusing (ASR) element (here ZS) placed at the start of the spin echo in a 2D J experiment yields an edited but conventional J-spectrum
- Placing the ASR element at the end of the echo yields a J spectrum with multiplet tilts in the opposite direction
- Reflecting the second spectrum about $\omega_1 = 0$ then adding the two results produces an absorption mode spectrum
- Sensitivity is limited by the ASR element – BIRD and PSYCHE can also be used

J. Magn. Reson. **189**, 293 (2007)

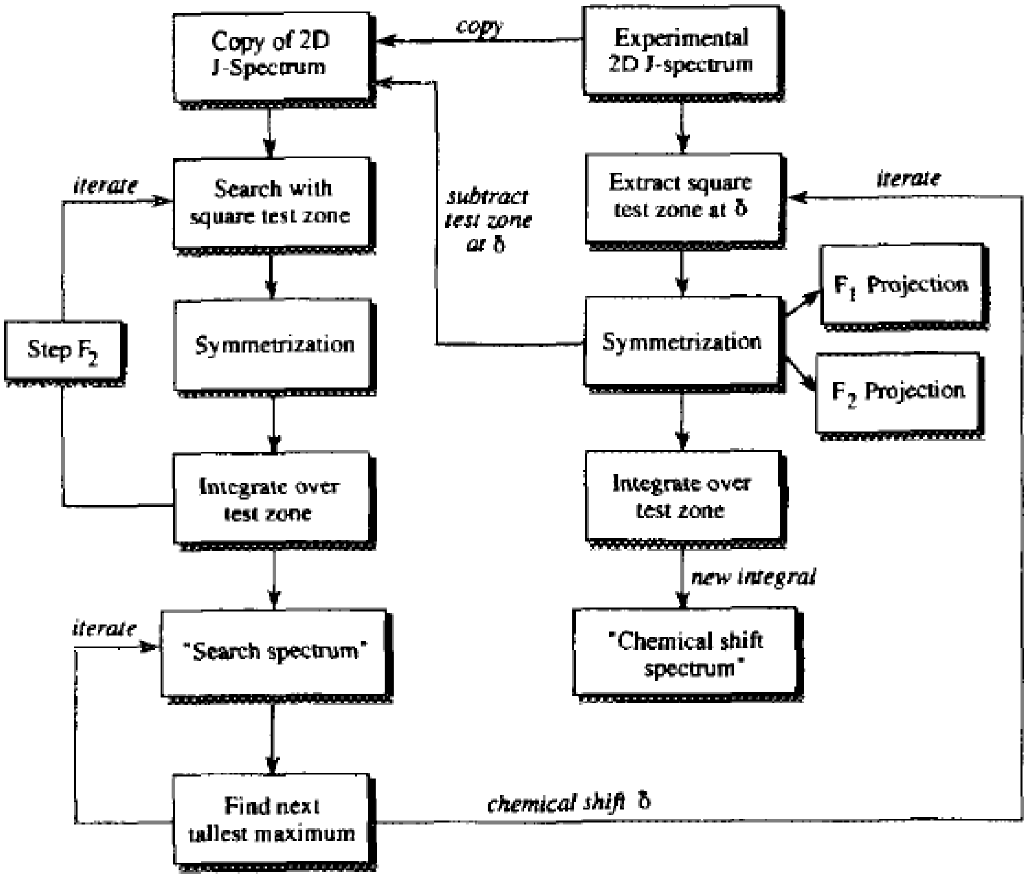
Pattern recognition in 2D J spectra

Conventional
2D J Spectrum

Conventional +
Reflected
2D J Spectrum

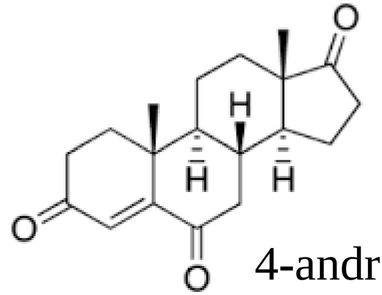


- Pattern recognition can be used to search through a ‘reflected’ J spectrum to give an integral map which resembles a pure shift ^{1}H NMR spectrum
- Processing in this way will not yield true integrals and can lead to overconfident interpretation of data
- Woodley and Freeman’s method is related to iterative soft thresholding, used in reconstruction of non-uniformly sampled multidimensional spectra.

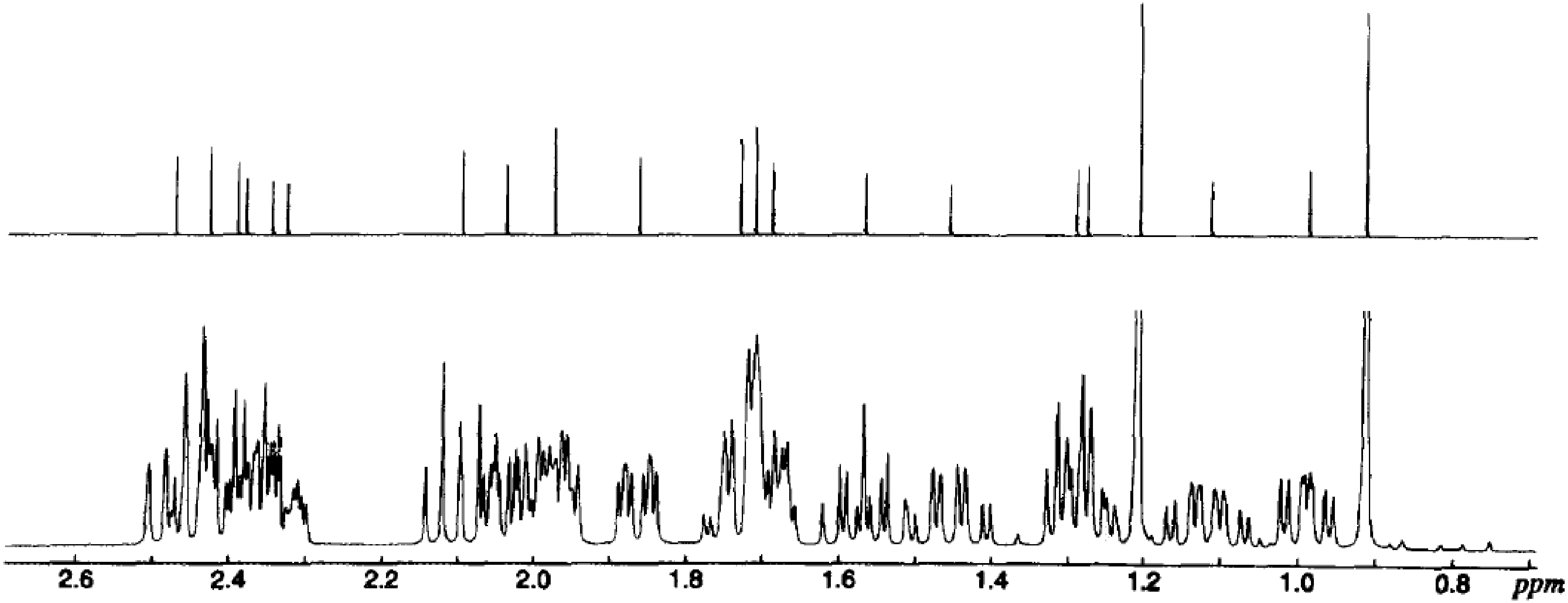


J. Magn. Reson. **124**, 104 (1997)
J. Magn. Reson. A **109**, 103 (1994)

Pattern recognition in 2D J spectra



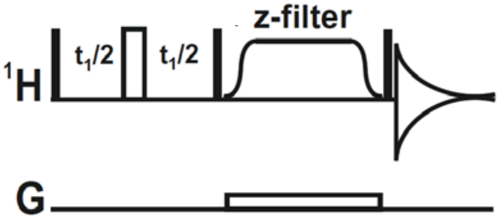
4-androstene-3,17-trione



Signal extraction algorithms are designed to give perfect results but can lead to overconfident interpretation of data

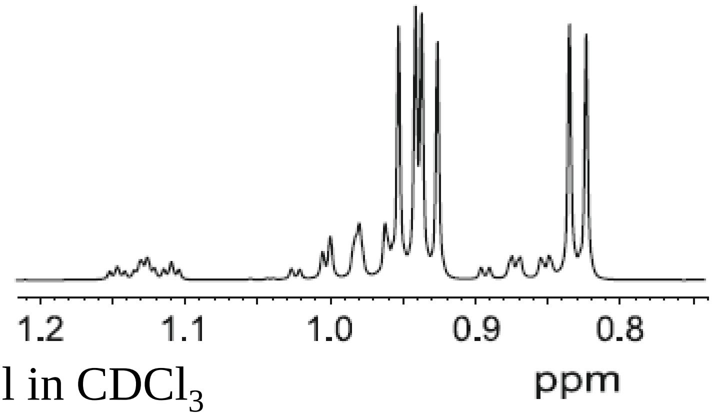
J. Magn. Reson. A **109**, 103 (1994)

Pattern recognition in 2D J spectra



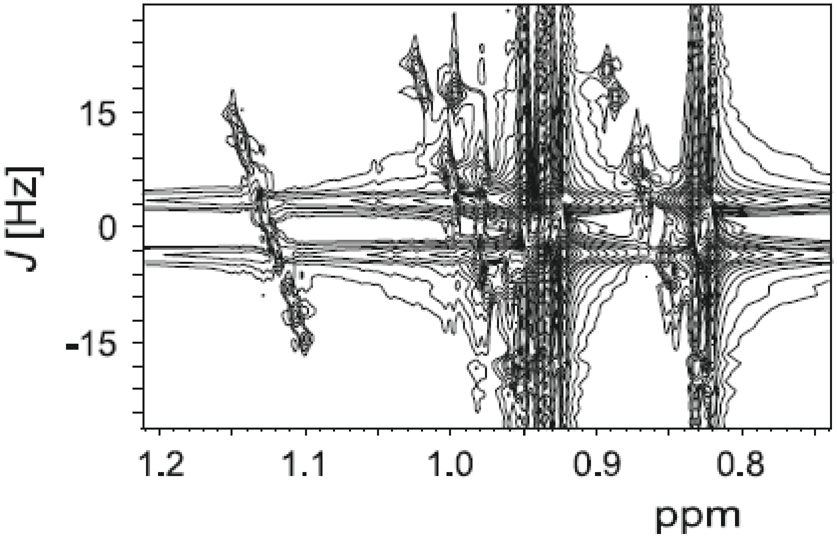
- A z-filter at the end of a 2D J sequence can be used to suppress the dispersive component of signals in a J-spectrum at the cost of frequency discrimination in F_1.
- Application of an appropriate pattern recognition algorithm to the resulting J-spectrum simplifies the 2D multiplets to yield an absorptive J spectrum

Conventional ^{1}H spectrum



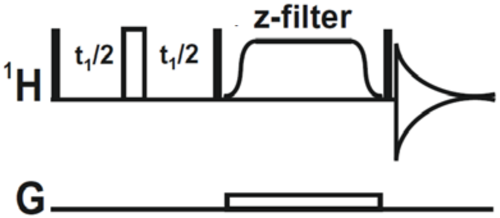
Menthol in $CDCl_3$

Conventional 2D J Spectrum



J. Magn. Reson. **201**, 18 (2009)

Pattern recognition in 2D J spectra



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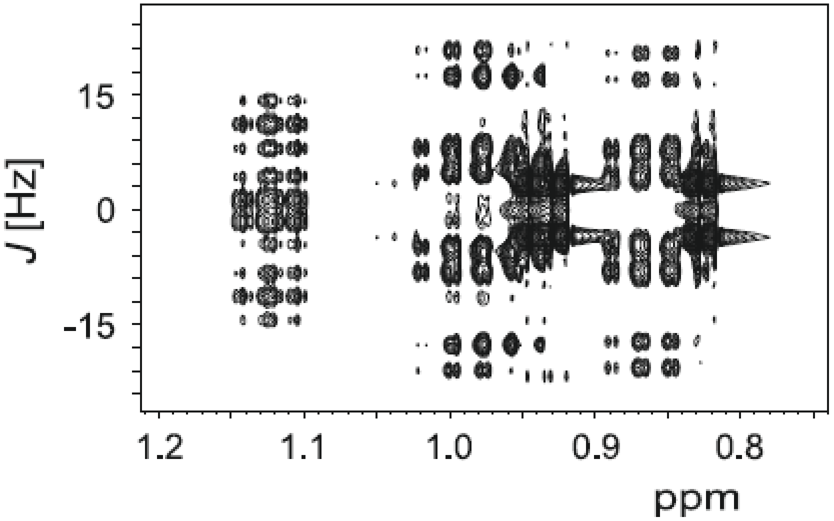
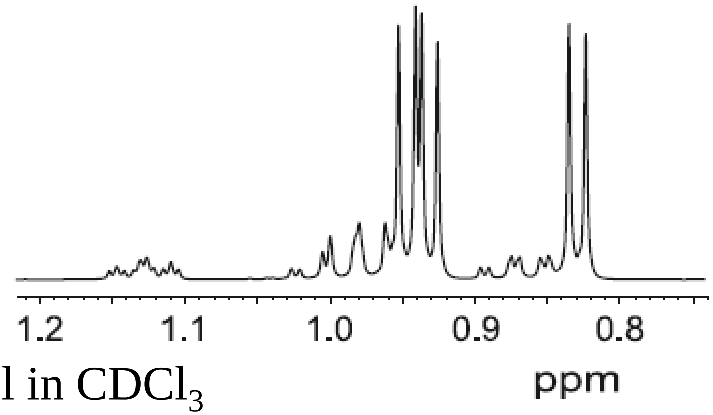
Z-filtered 2D J Spectrum



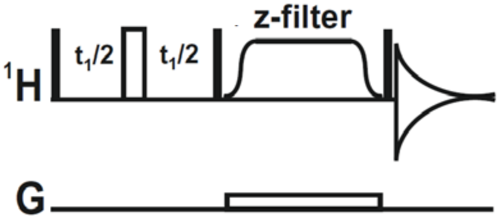
Conventional ^{1}H spectrum



Menthol in $CDCl_3$

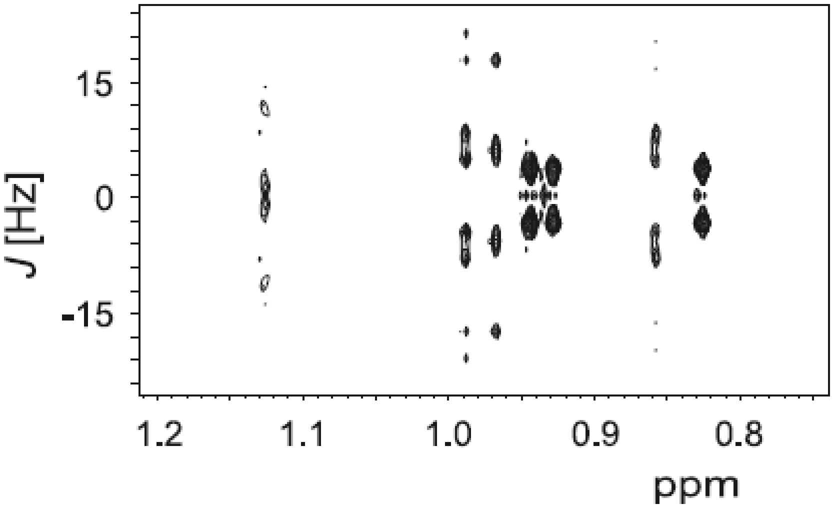
J. Magn. Reson. **201**, 18 (2009)

Pattern recognition in 2D J spectra

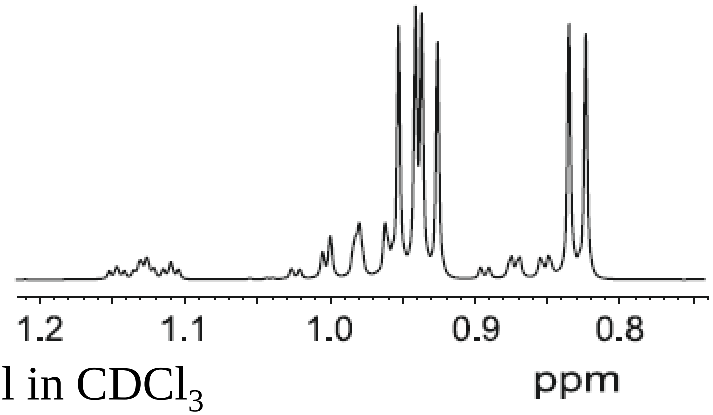


- A z-filter at the end of a 2D J sequence can be used to suppress the dispersive component of signals in a J-spectrum at the cost of frequency discrimination in F_1.
- Application of an appropriate pattern recognition algorithm to the resulting J-spectrum simplifies the 2D multiplets to yield an absorptive J spectrum

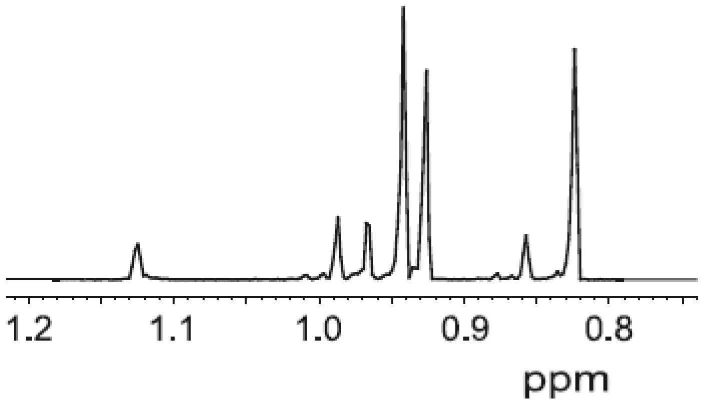
‘Recognition’ processed 2D J Spectrum



Conventional ^{1}H spectrum



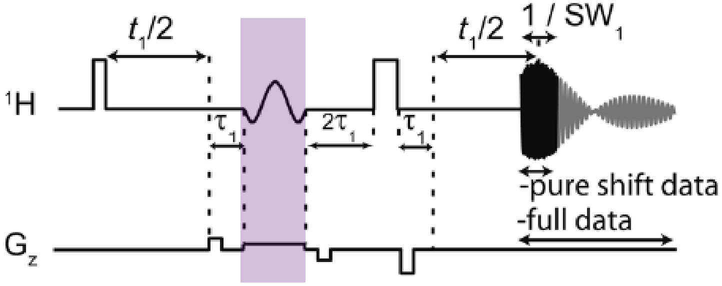
Reconstructed pure shift spectrum



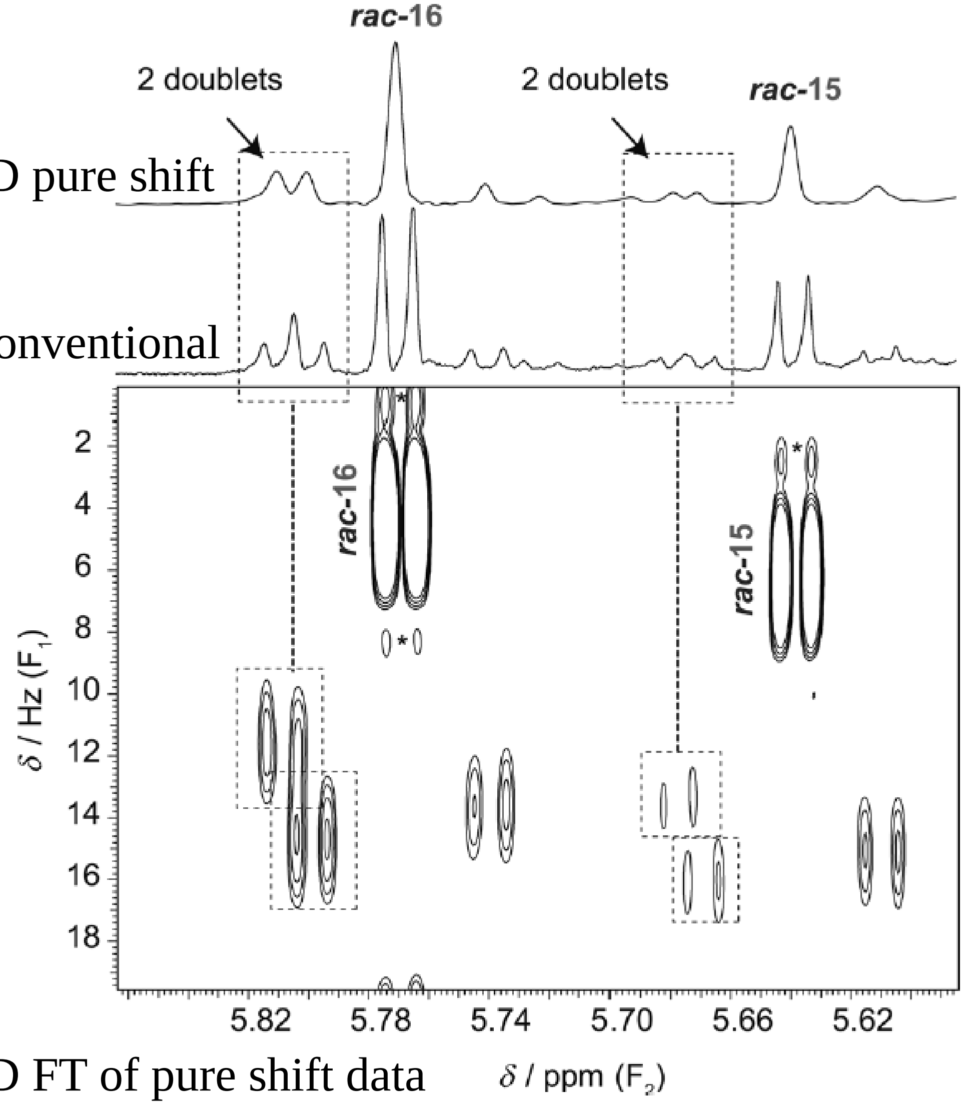
Menthol in $CDCl_3$

J. Magn. Reson. **201**, 18 (2009)

2D Fourier transform of pure shift NMR data



- The standard way to process F_2 interferogram pure shift data is to use data reconstruction to form a pure shift FID
- Alternatively, each collected FID can be extended beyond the duration of a chunk, and a 2D FT applied
- The result is a multiplet map
- Signals are homodecoupled in F_1, but also aliased
- Multiplicity – and J – can be established from the 2D spectrum



1D pure shift

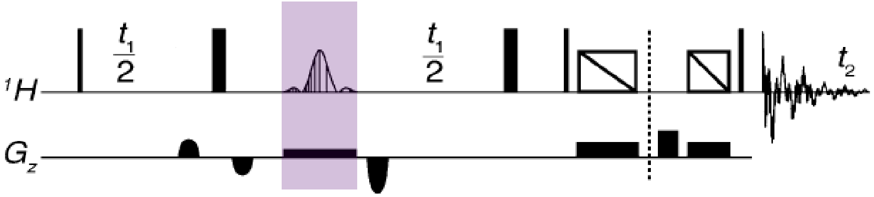
Conventional

2D FT of pure shift data

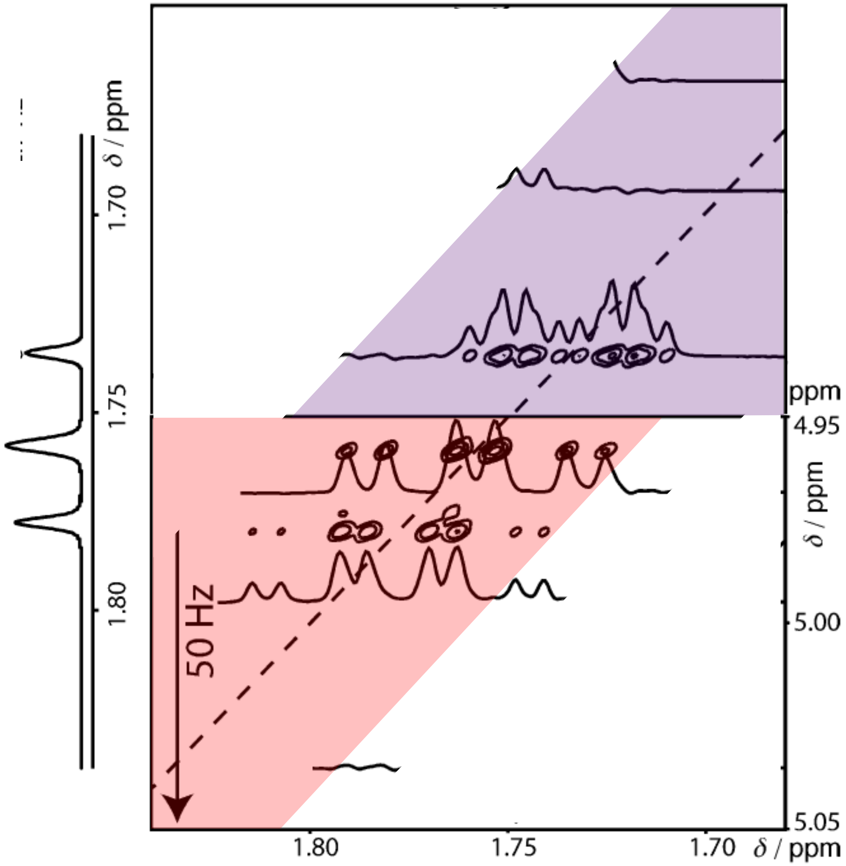
Chem. – Eur. J. **19**, 4586 (2013)

2D Fourier transform of phase-sensitive pure shift NMR data - DIAG

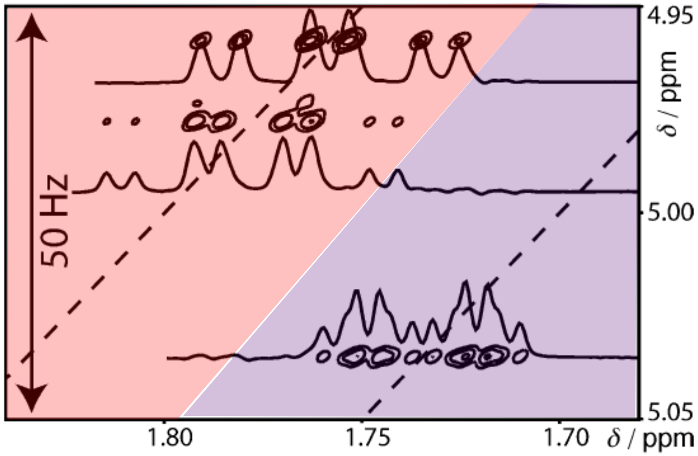
- 2D FT of a standard interferogram pure shift experiments does not yield signals that are distorted in *F_1*.
- *F_1* absorption mode signals can be achieved by collecting the diagonal of a NOESY (t_{mix} = 0 s) with a J-refocusing element at the midpoint of *t_1*
- To maximise resolution in *F_1*, the spectrum can be aliased and then the diagonal reconstructed



'DIAG' reconstructed *F_1* pure shift NOESY

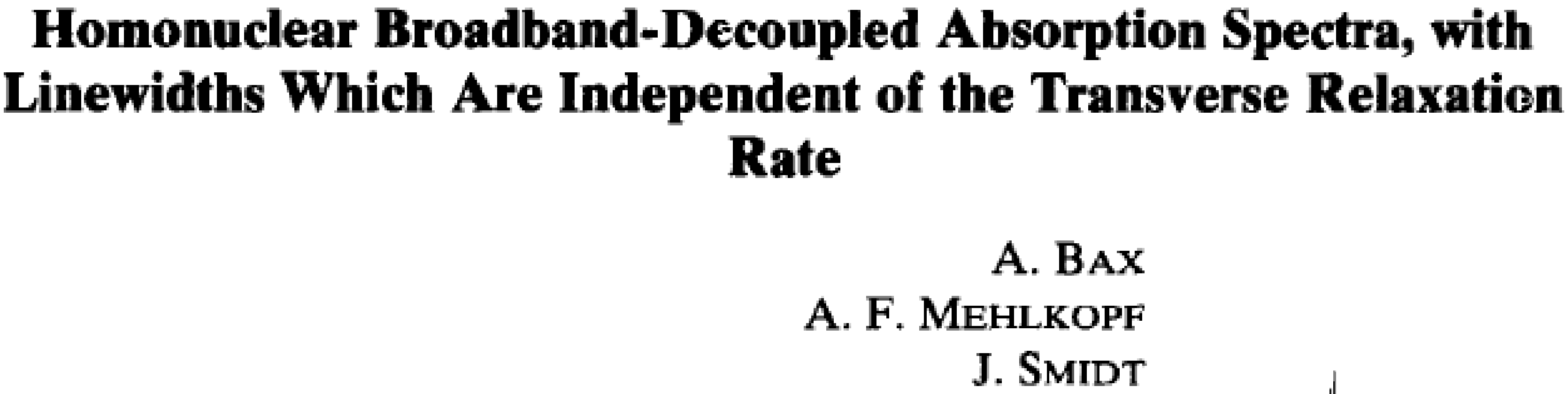


Aliased *F_1* pure shift NOESY



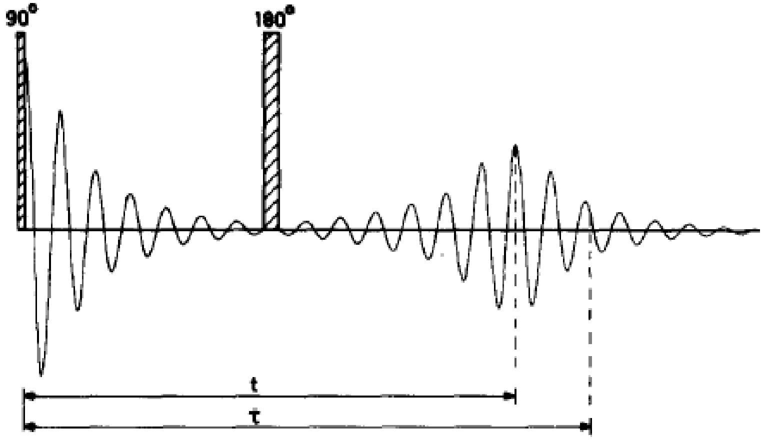
Sequences on http://nmr.chemistry.manchester.ac.uk c/o Brucka/Jeannerat *Angew. Chem. Int. Ed.* **54**, 6016 (2015)

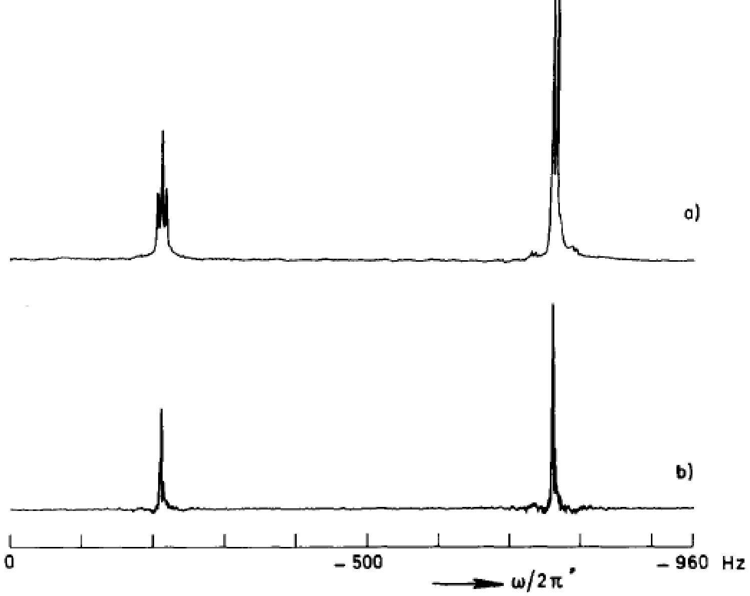
1979 : Constant-Time Evolution



Homonuclear Broadband-Decoupled Absorption Spectra, with Linewidths Which Are Independent of the Transverse Relaxation Rate

A. BAX
A. F. MEHLKOPF
J. SMIDT

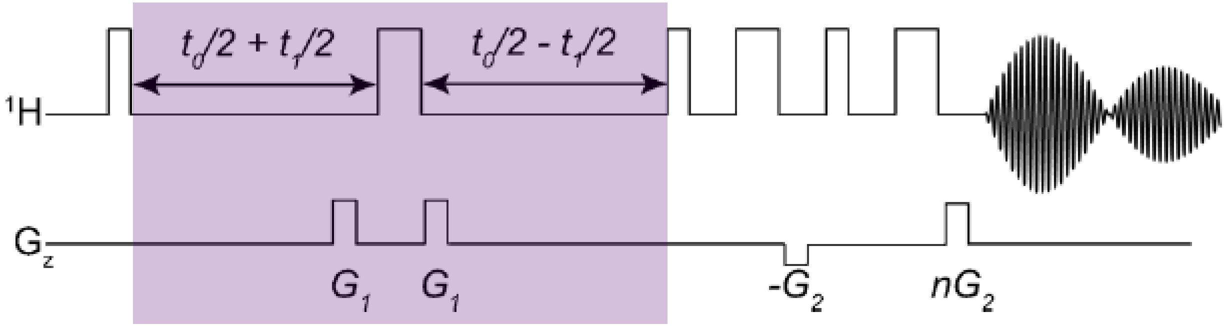




J. Magn. Reson. **35**, 167 (1979)

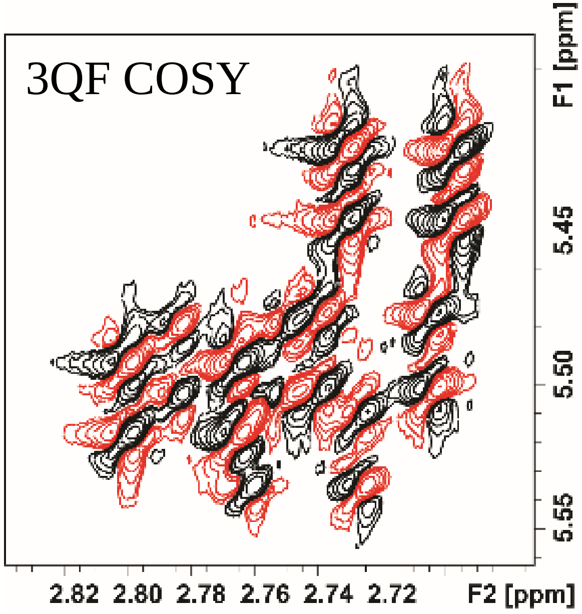
Constant-Time Evolution

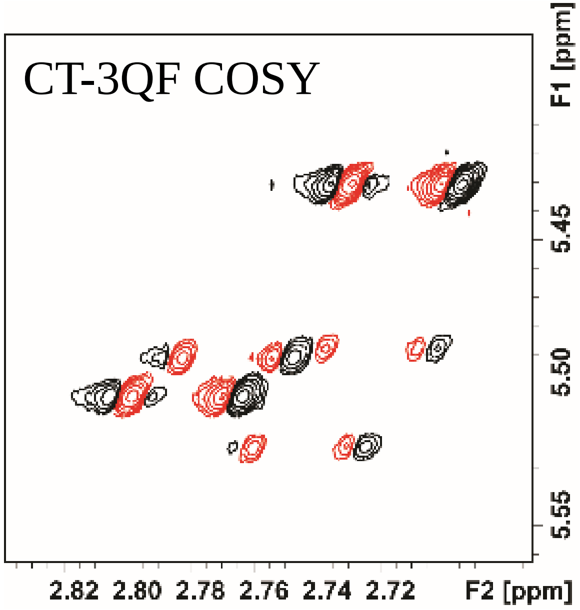
CT-nQF COSY

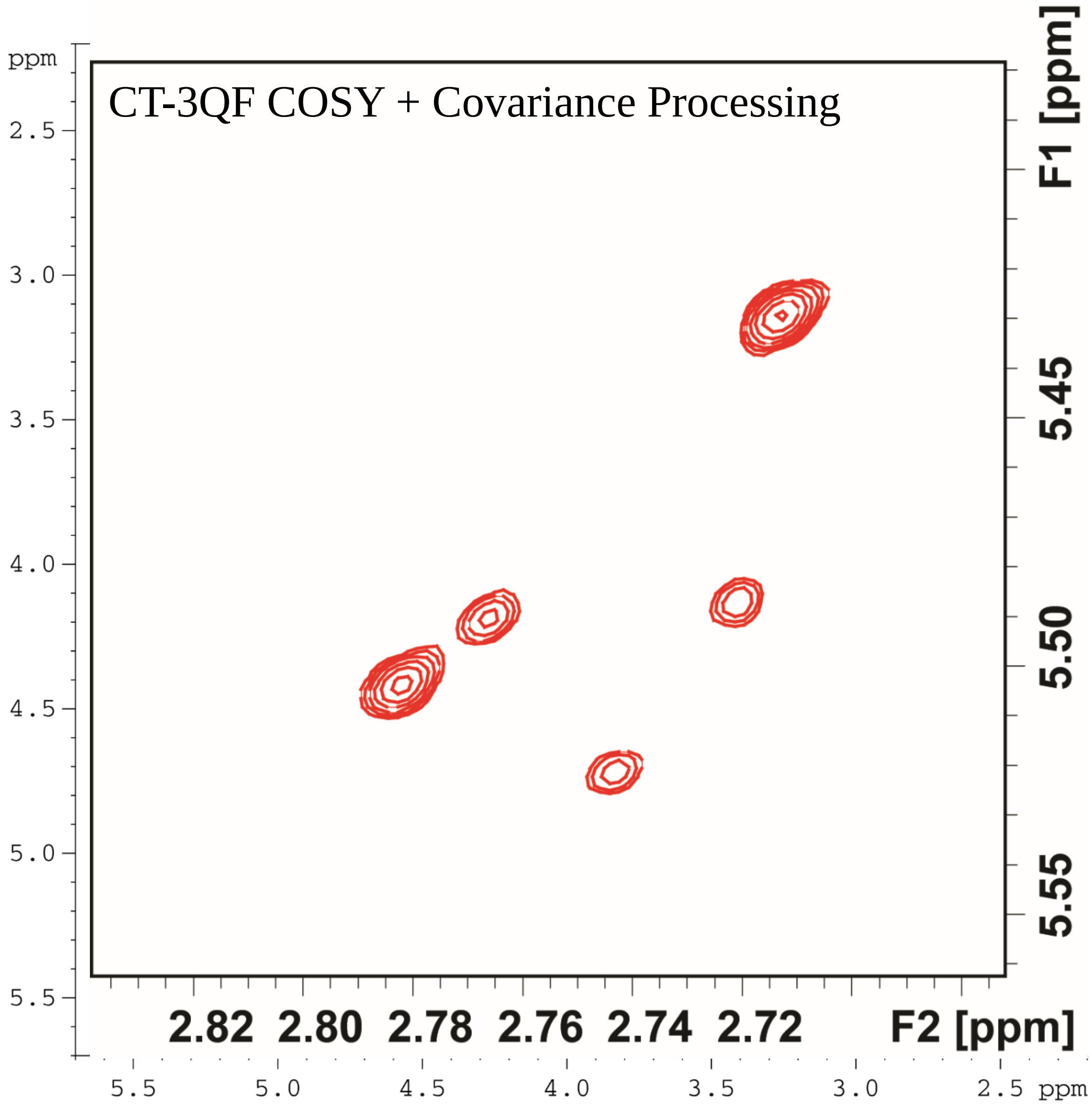


- In a 2D series of experiments the spin system is allowed to evolve under J for a constant time, t_c, during which the chemical shift acts only for a variable portion t_1, before an FID is measured
- Evolution time for the chemical shift is t_1, which varies
- Evolution time for couplings is fixed at t_c
- Double FT yields a spectrum which is ‘pure shift’ in F_1
- Constant-time methods are intrinsically two-dimensional so can be performed instead of standard 2D experiments at no extra time cost
- The amount of J-evolution that occurs is fixed rather than reduced to zero

Constant-Time Evolution + Covariance Processing

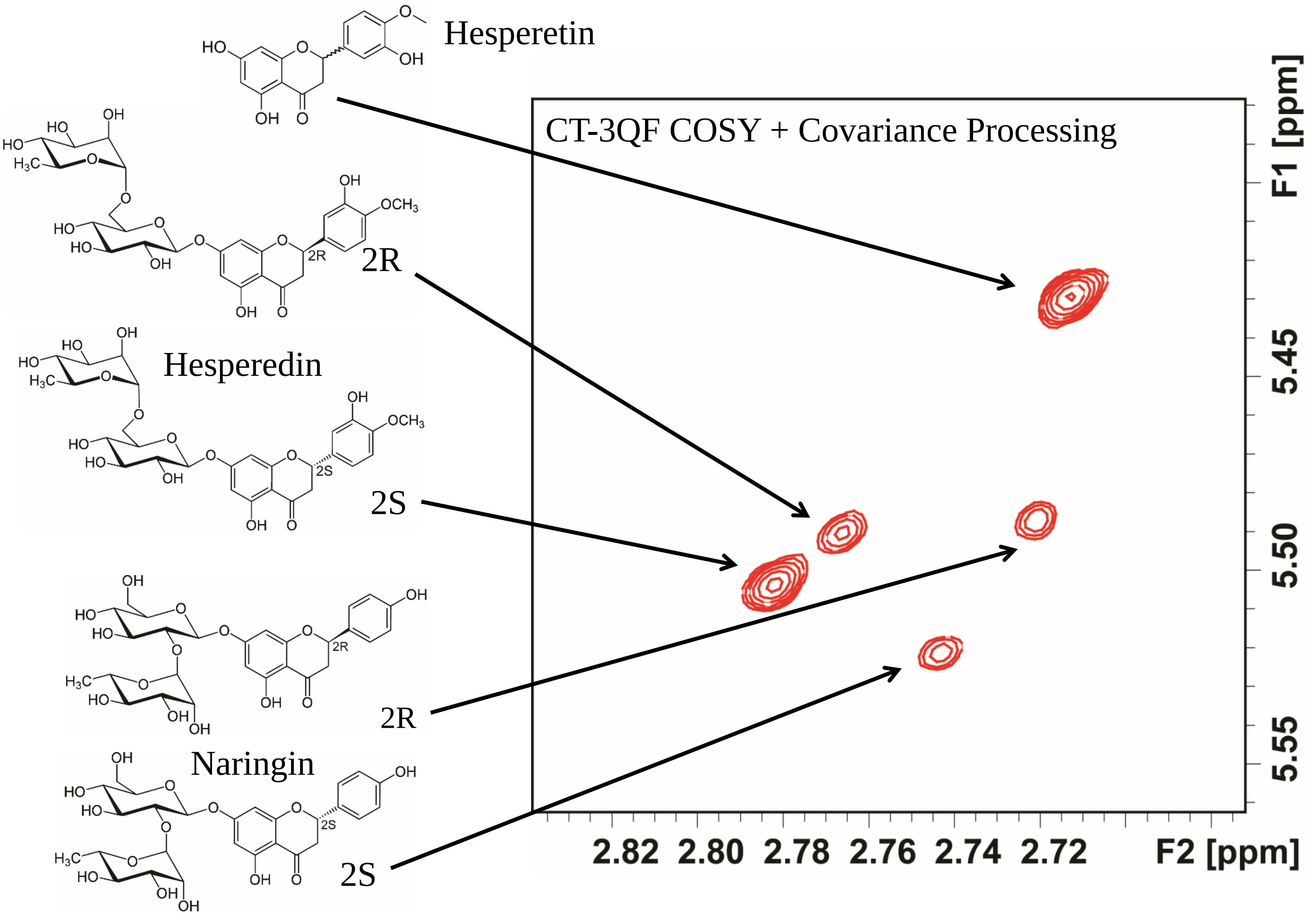

3QF COSY


CT-3QF COSY


CT-3QF COSY + Covariance Processing

Angew. Chem. Int. Ed. **51**, 6460 (2012)

Constant-Time Evolution + Covariance Processing



Angew. Chem. Int. Ed. **51**, 6460 (2012)

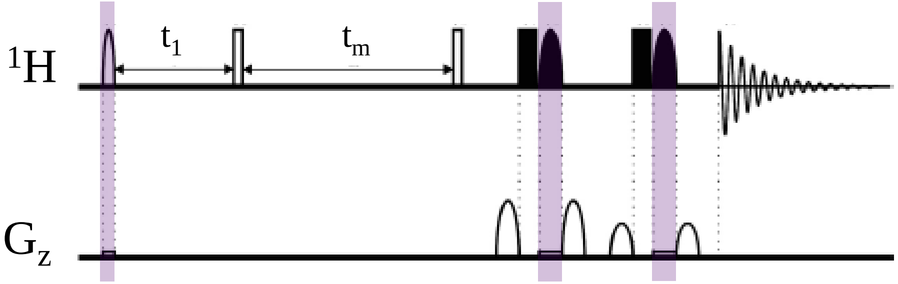
Other pure shift and related methods

Ralph Adams

A Pure Shift NMR Workshop
The University of Manchester, 12th September 2017

ZS diagonal-suppressed homonuclear 2D

ZS (ES) Diagonal-suppressed NOESY

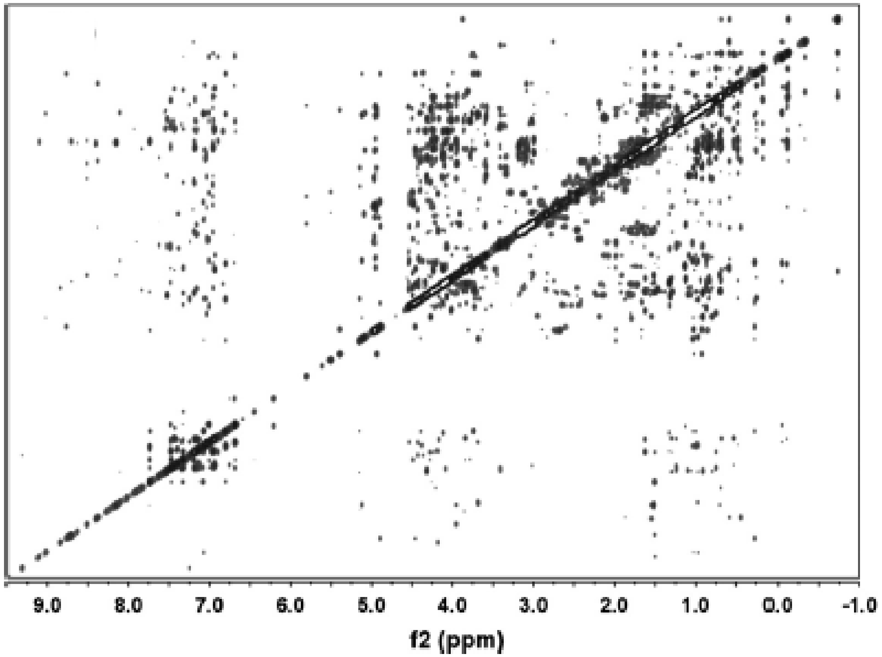


- Diagonal signals in a homonuclear 2D NMR experiment can be suppressed by replacing the initial excitation pulse with a ZS spatial and frequency selective excitation and adding a J-refocusing element to the end of the sequence.
- Signals on the diagonal, experience both the selective and hard 180° pulses at the end of the sequence and are suppressed
- Crosspeaks, which arise from evolution at different frequencies during in t_1 and t_2, experience only the hard 180° pulse, and survive

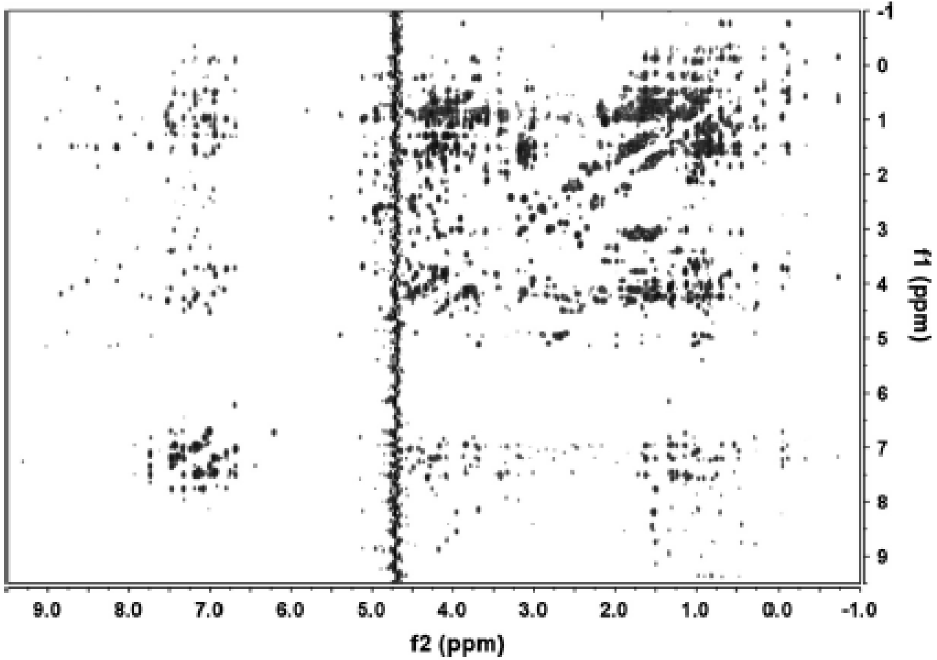
J. Magn. Reson. **232**, 1 (2013)
J. Magn. Reson. **256**, 52 (2015)

ZS diagonal-suppressed homonuclear 2D

Conventional NOESY



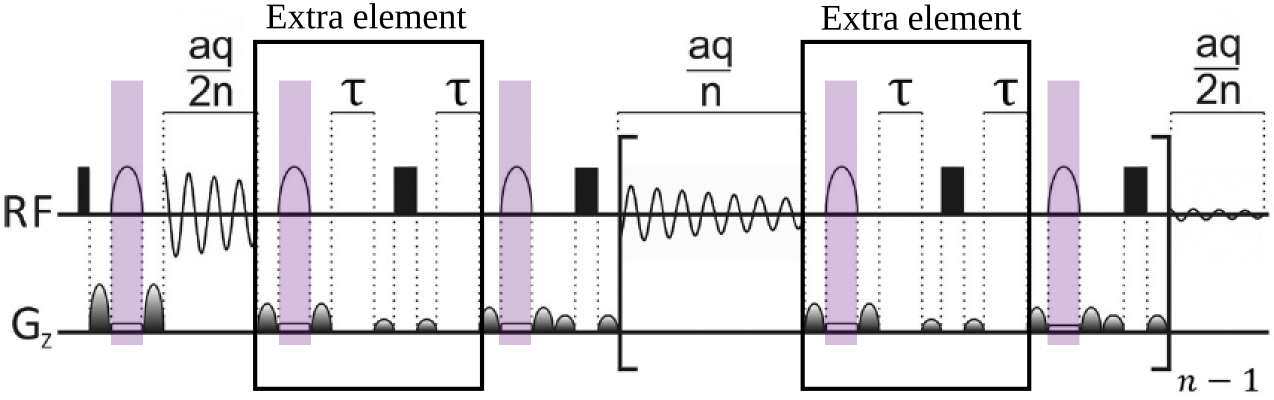
Diagonal suppressed NOESY

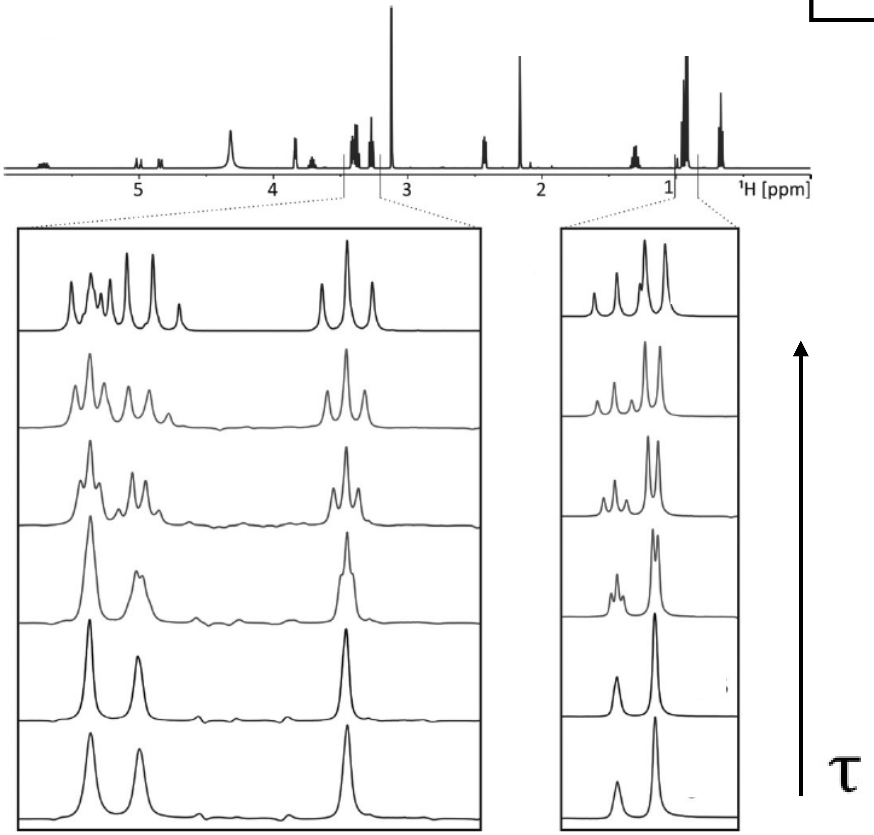


3 mM solution of lysozyme in D_2O

J. Magn. Reson. **232**, 1 (2013)
J. Magn. Reson. **256**, 52 (2015)

Real-time J scaling



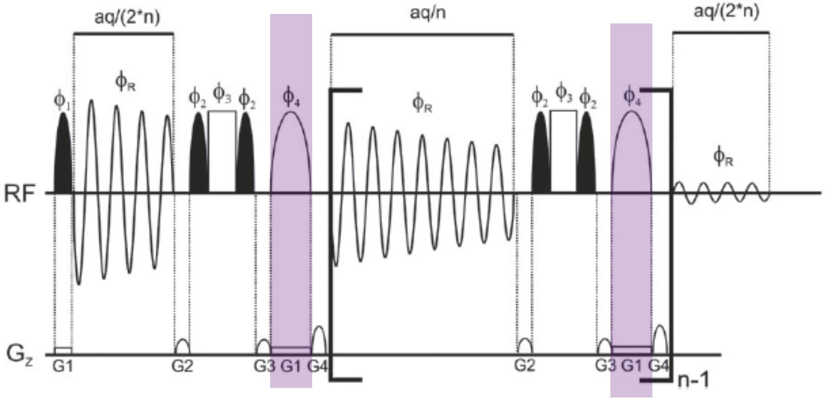


Mixture of alcohols (n-propanol, isopropanol, ethanol, n-methylaminoethanol and allyl alcohol) in $CDCl_3$ with J-scaled spectra

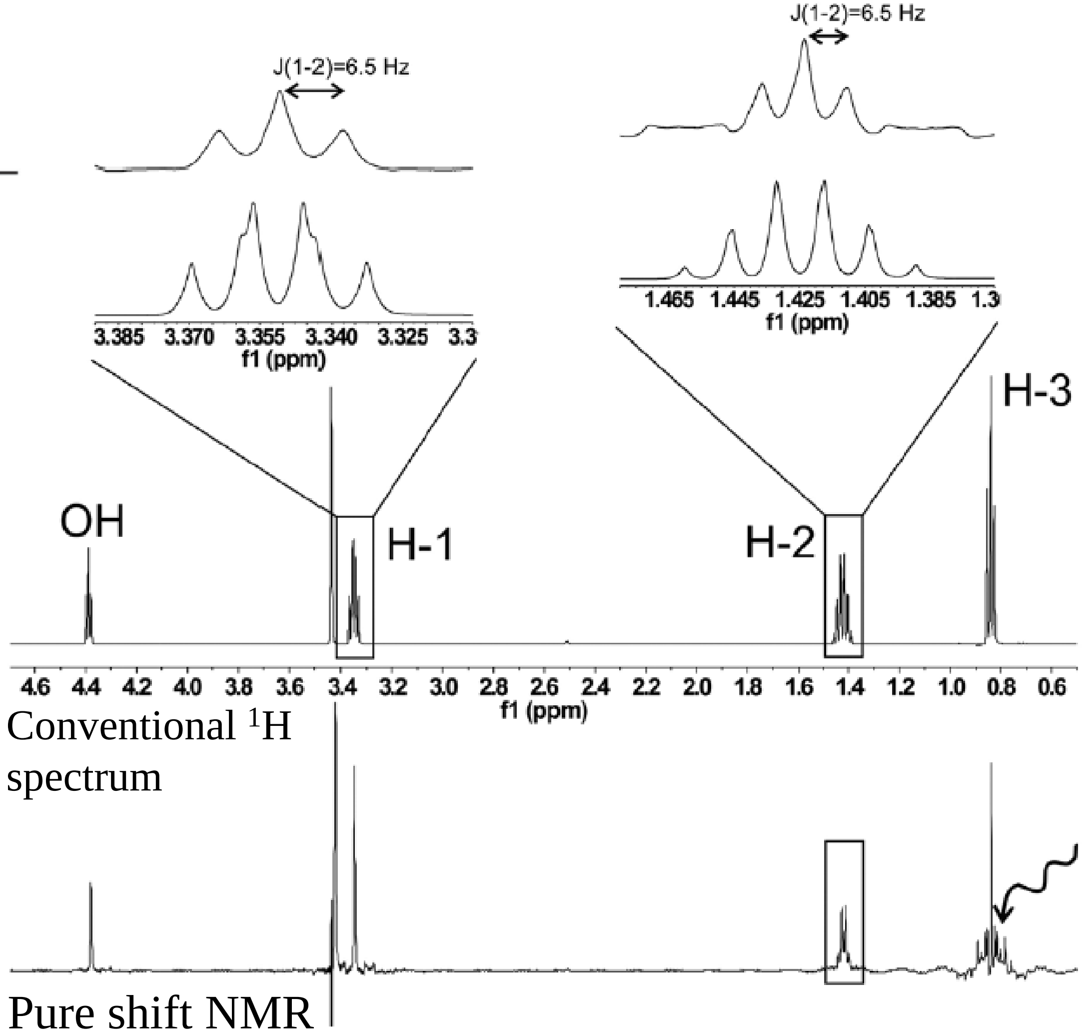
- Addition of J refocusing elements, with modified timing, to real-time pure shift experiment reintroduces J
- J values are scaled depending on τ
- The approach is related to changing the projection angle through multiplet in a 2D J experiment

ChemPhysChem **16**, 3313 (2015)

Selective reintroduction of J into pure shift spectra



- Adding additional frequency-selective refocusing to the J-refocusing element in a pure shift experiment reintroduces coupling to the selected resonances
- Coupling between other spins remains suppressed
- This method is the opposite of conventional homodecoupling



Conventional ^{1}H spectrum

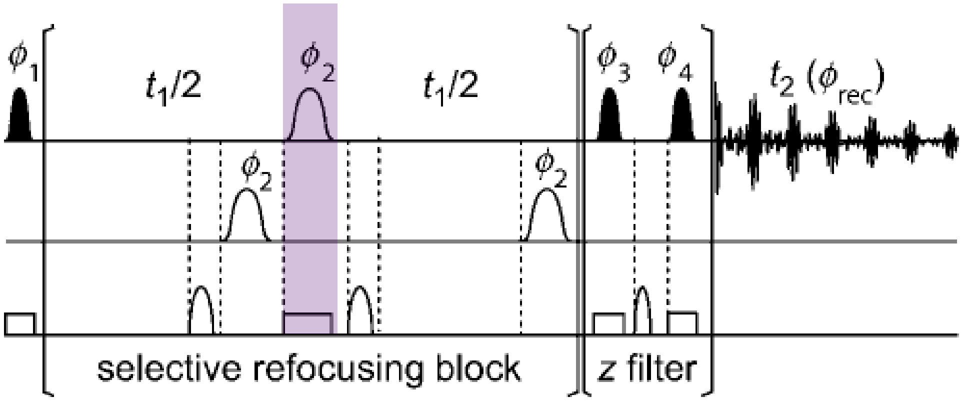
Pure shift NMR
spectrum with coupling to H-3 reintroduced

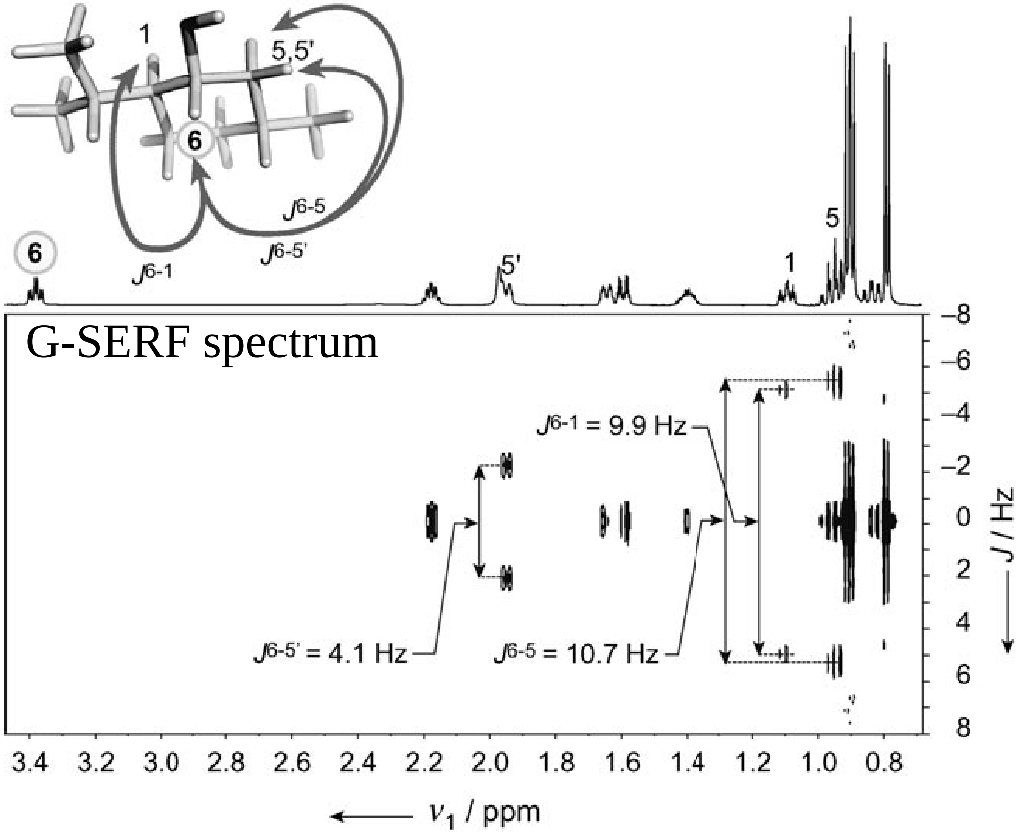
n-propanol

Chem. Commun. **50**, 12254 (2014)
Chem. Commun. **50**, 15597 (2014)

Selective introduction of J into 2D J spectra

- The G-SERF experiment also provides details about coupled spins but is based on a 2D J experiment
- Unlike a 2D J experiment, only J couplings to a selected resonance are seen
- Signals from selected resonances are suppressed



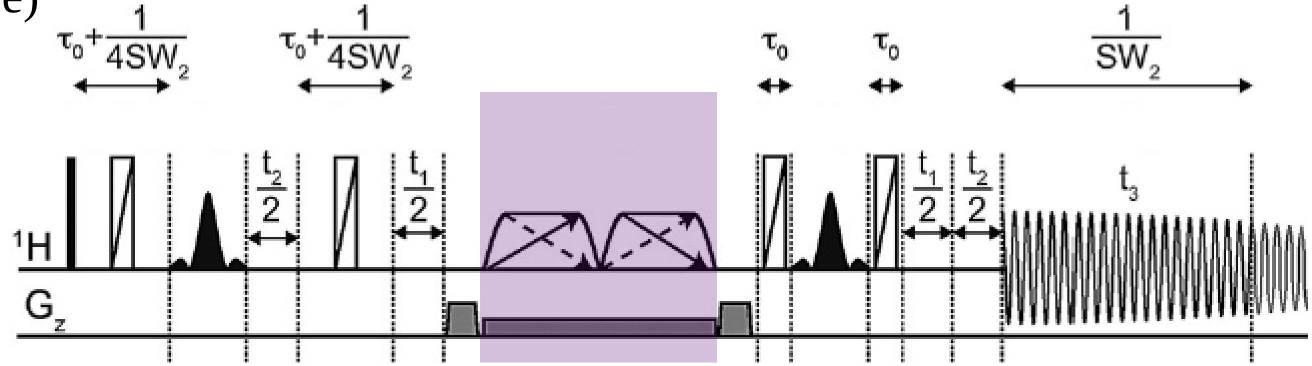


G-SERF spectrum

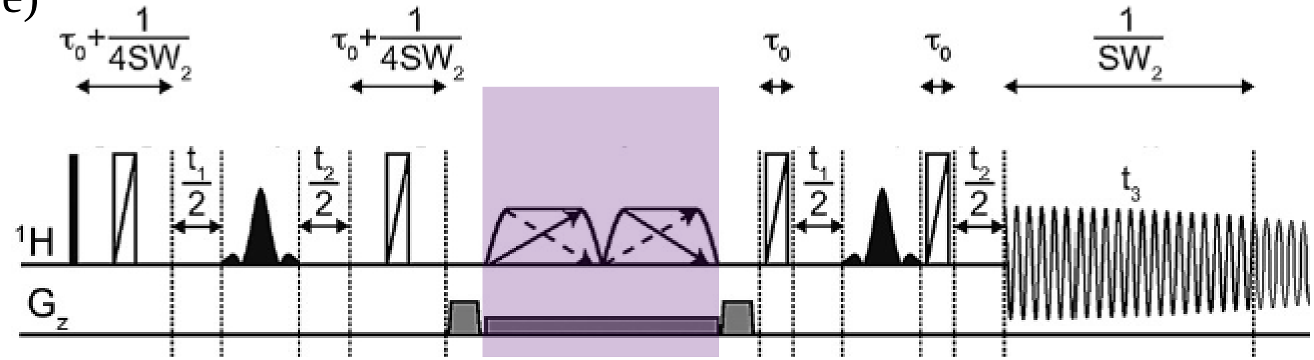
Angew. Chem. **122**, 3559 (2010)

Selective introduction of J into 2D J spectra

PSYCHEDELIC pulse sequence
(N-type)

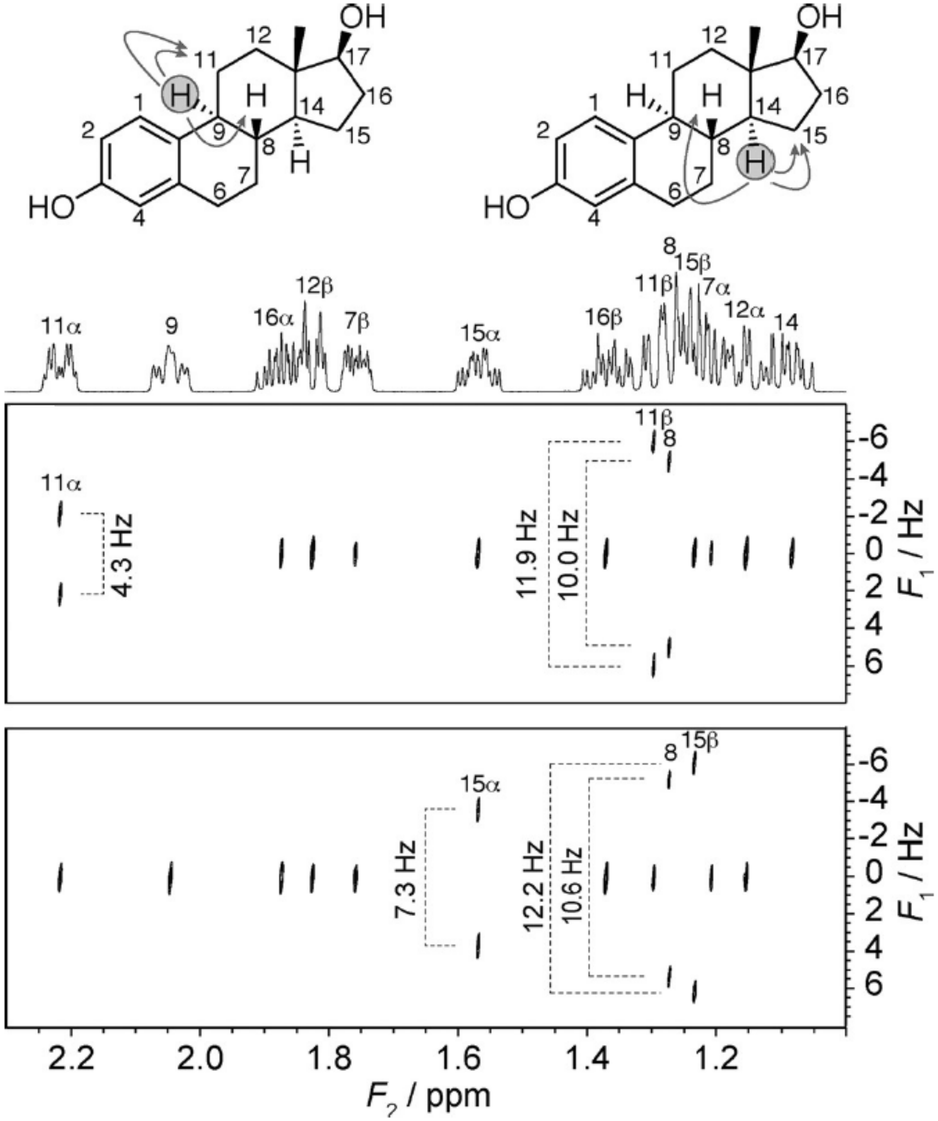


(R-type)



Angew. Chem. Int. Ed. **55**, 1090 (2016)

Selective introduction of J into 2D J spectra



- PSYCHEDELIC produces a 2D J spectrum containing the same coupling information in F_1 as G-SERF
- Additionally, multiplet structure is suppressed in F_2 so PSYCHEDELIC generally has higher resolution than its G-SERF equivalent

Similar spectra can be collected using pure shift variants of G-SERF, see *Chem. Commun.* **51**, 7939 (2015) and *Magn. Reson. Chem*. **44**, 1096 (2006)

Angew. Chem. Int. Ed. **55**, 1090 (2016)

Other pure shift and related methods

A whistle-stop tour of things that haven't been covered yet, including …

- BIRD, and its use in pure shift NMR
- 2D J spectra, absorption-mode signals in 2D J spectra, and pattern recognition
- Constant-time evolution
- Diagonal-suppressed 2D experiments
- J-scaling
- Measuring couplings to selected signals

A Pure Shift NMR Workshop

11.00	Gareth Morris	**Welcome, introduction and history**
11.30	Peter Kiraly	**Interferogram and real-time acquisition methods**
12.00	Laura Castañar	**Zangger-Sterk and band-selective methods**
12.30	Mohammadali Foroozandeh	**PSYCHE**
13.00		*Lunch and poster session*
14.00	Ralph Adams	**Other pure shift and related methods**
14.30	Mathias Nilsson	**Practical implementations**
15.00	Adolfo Botana	**JEOL pure shift implementation**
15.10	Vadim Zorin	**MestreNova pure shift implementation**
15.20	Ēriks Kupče	**Bruker shaped pulse implementation**
15.30		*Question and answer session*

The University of Manchester, 12th September 2017