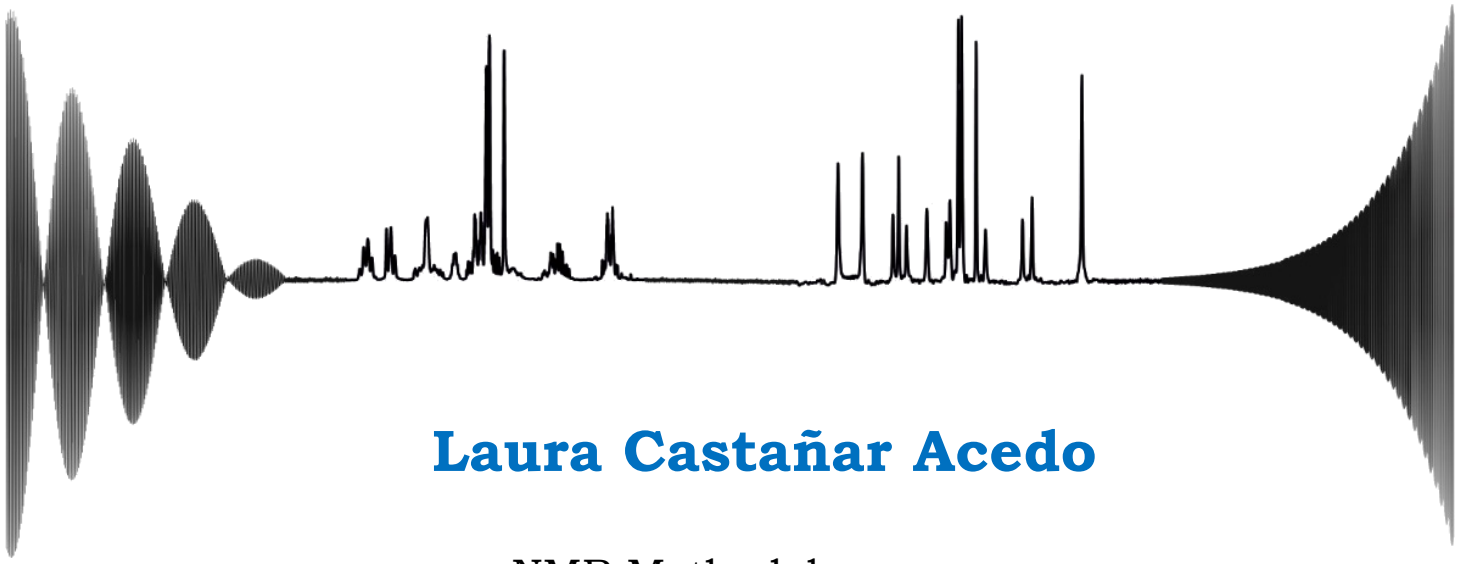
Pure Shift NMR Spectroscopy



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NMR Methodology group

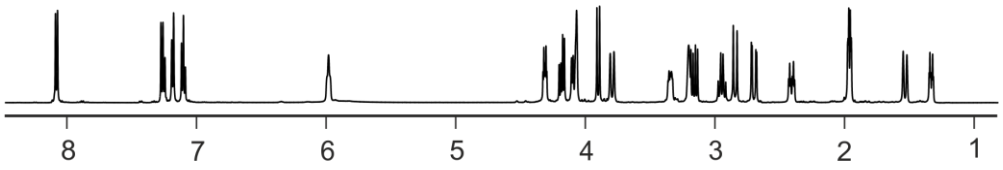
The University of Manchester

June 20th, 2019

Manuel Rico NMR School, Jaca (Spain)

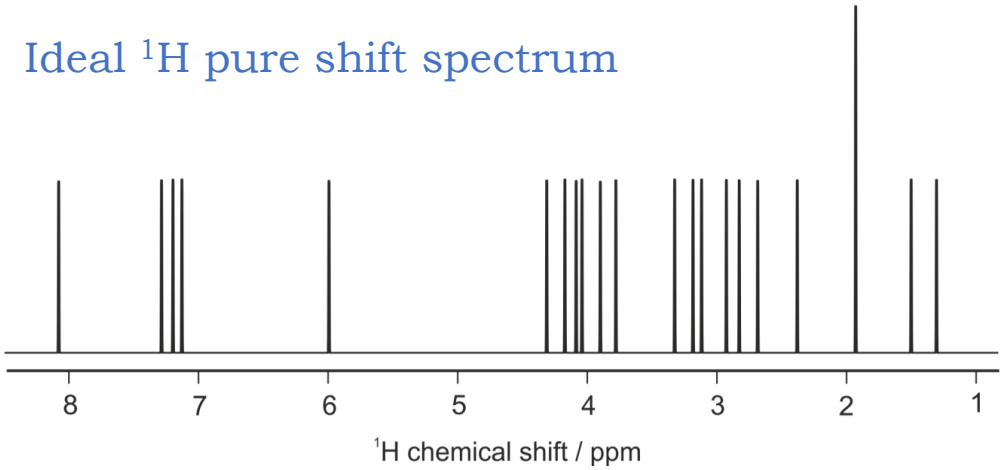
What *is* pure shift NMR?

Conventional ^{1}H spectrum



- ✓ Chemical shifts (δ_H)
- ✓ Homonuclear couplings (J_{HH})
- ✓ Heteronuclear couplings (J_{HX})

Ideal ^{1}H pure shift spectrum

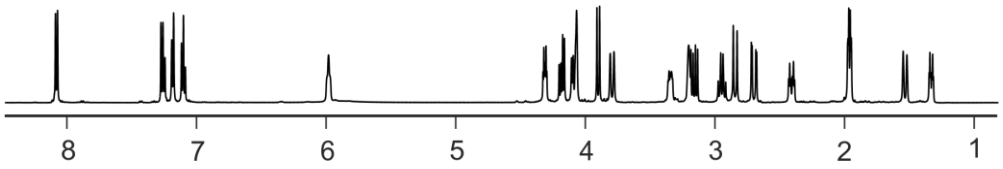


- ✓ Chemical shifts (δ_H)
- ✗ Homonuclear couplings (J_{HH})
- ✗ Heteronuclear couplings (J_{HX})

A pure shift spectrum is one in which peak positions are determined solely by chemical shifts

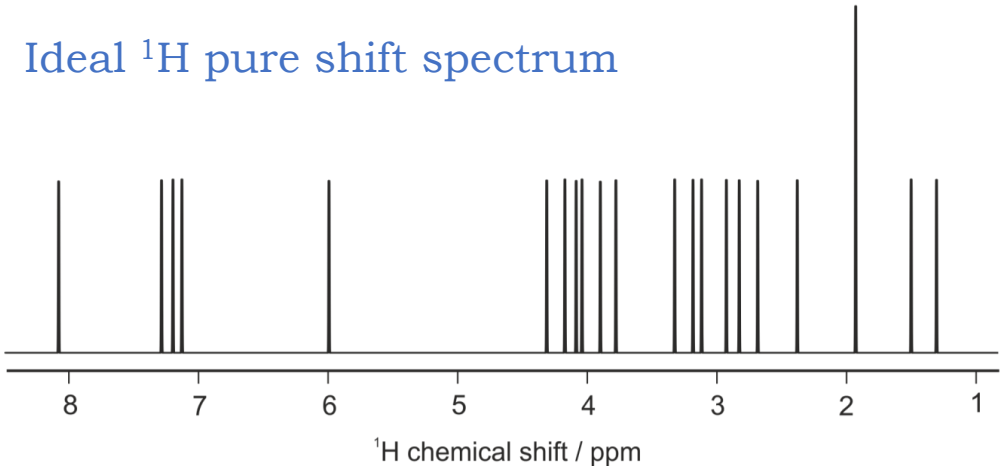
Why is pure shift NMR useful?

Conventional ^{1}H spectrum



- Signal overlap
- Poor spectal resolution
- Challenging spectral analysis

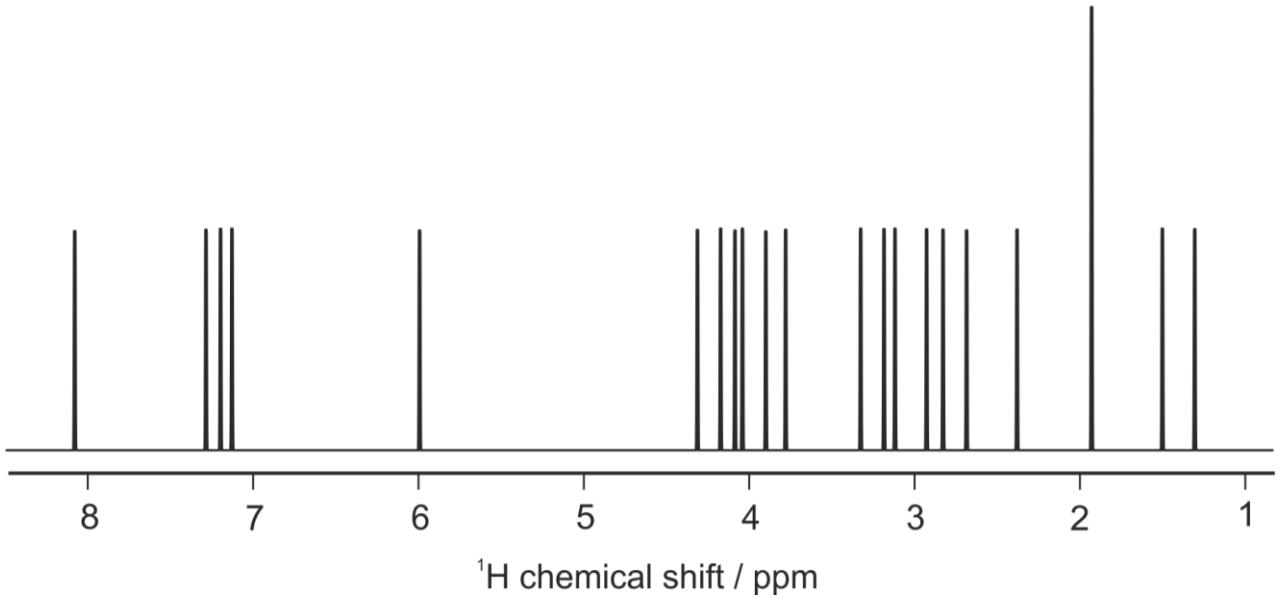
Ideal ^{1}H pure shift spectrum



- Reduced spectral complexity
- Enhanced signal resolution
- Easier spectral analysis

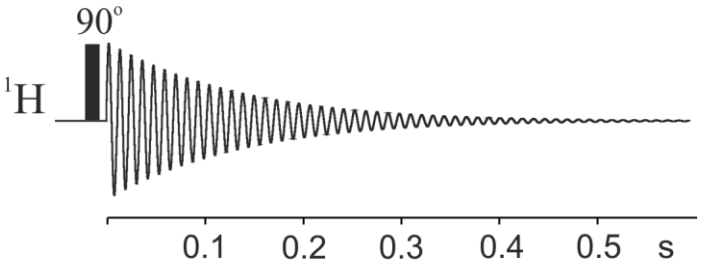
Spectral simplification

How could we get a “perfect” pure shift spectrum?



How do we get a conventional NMR spectrum?

^{1}H NMR experiment

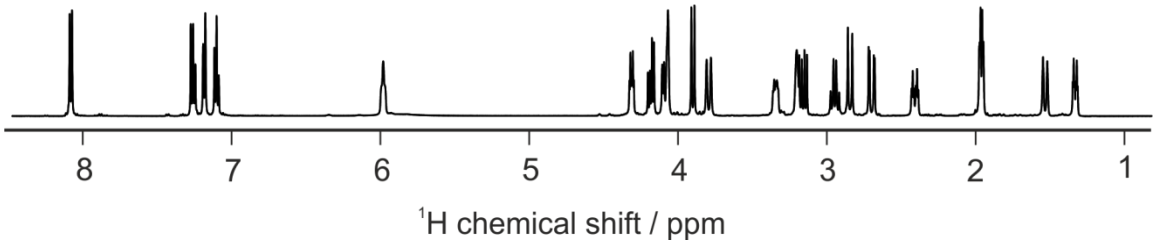


Evolution during FID

δ_H	J_{HX}	J_{HH}
✓	✓	✓

FT

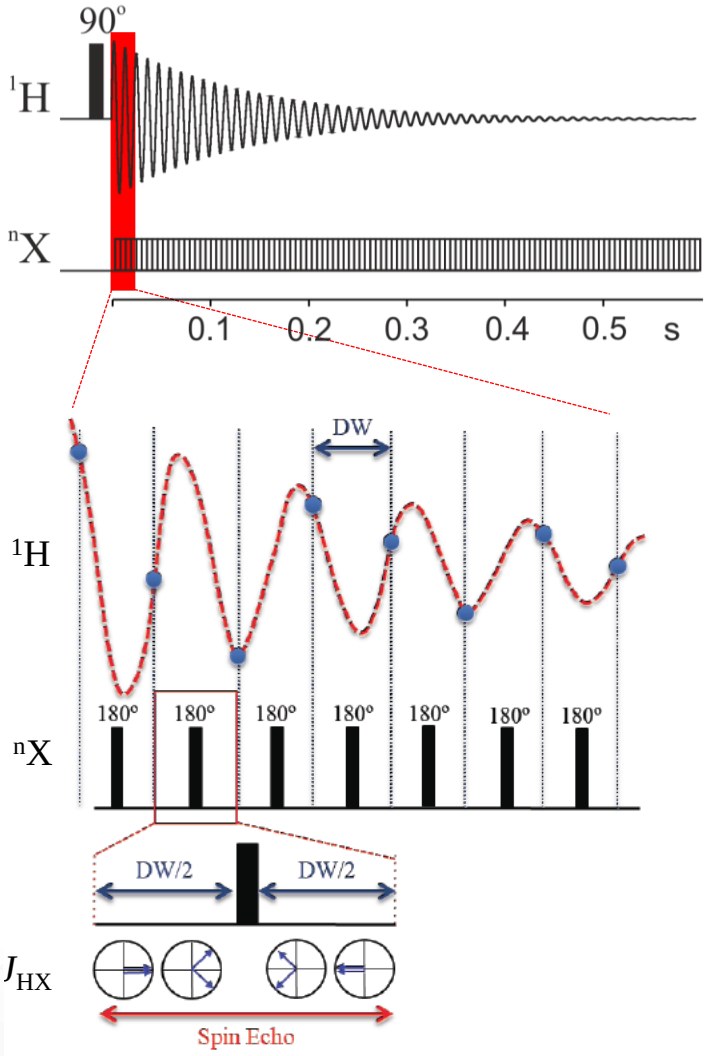
^{1}H NMR spectrum



- ✓ Chemical shifts (δ_H)
- ✓ Homonuclear couplings (J_{HH})
- ✓ Heteronuclear couplings (J_{HX})

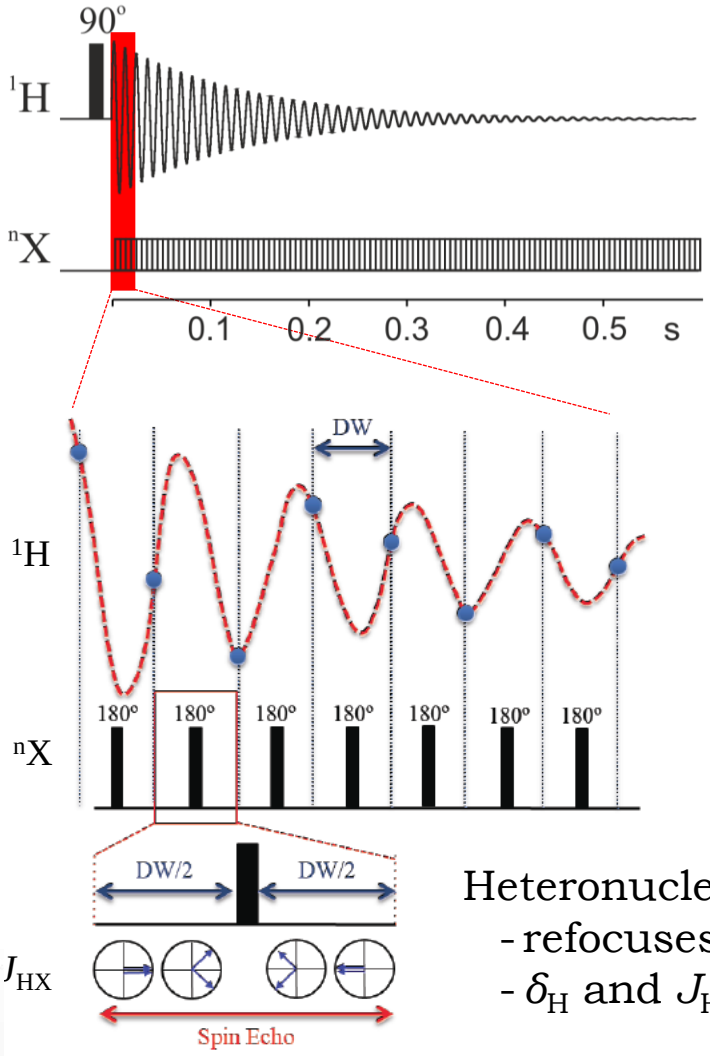
How do we get heteronuclear decoupled NMR spectrum?

$^1H\{^nX\}$ NMR experiment



How do we get heteronuclear decoupled NMR spectrum?

$^1H\{^nX\}$ NMR experiment



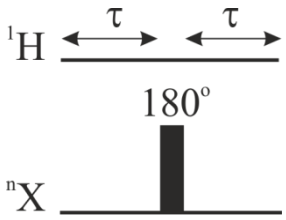
Evolution during FID

δ_H	J_{HX}	J_{HH}
✓	✖	✓

Sampling interval (DW) ~ 50 µs

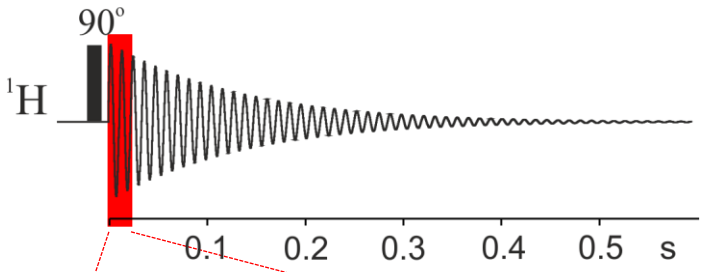
Hard 180° ^nX pulse ~ 20 µs

Heteronuclear spin echo
- refocuses J_{HX}
- δ_H and J_{HH} evolve



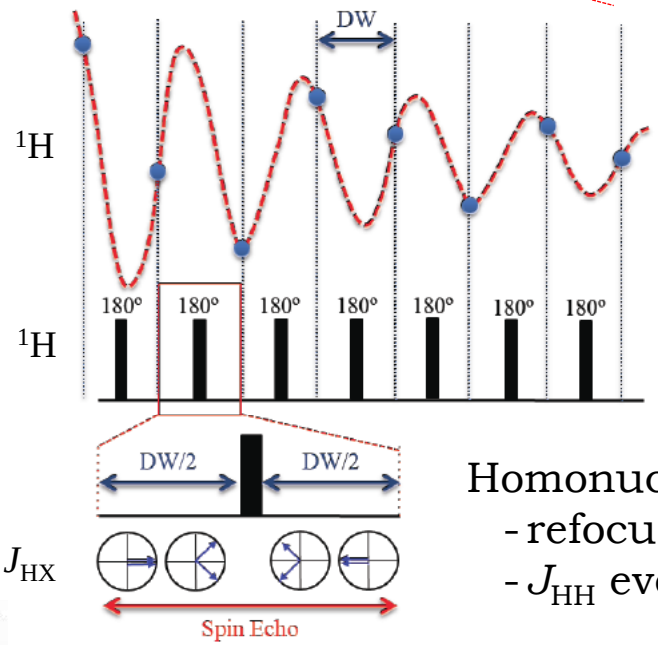
How could we get a "perfect" homodecoupled NMR spectrum?

Ideal $^1H\{^1H\}$ NMR experiment



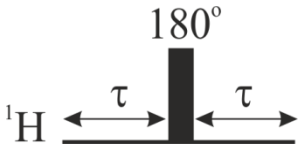
Evolution during FID

δ_H	J_{HH}
✓	✘



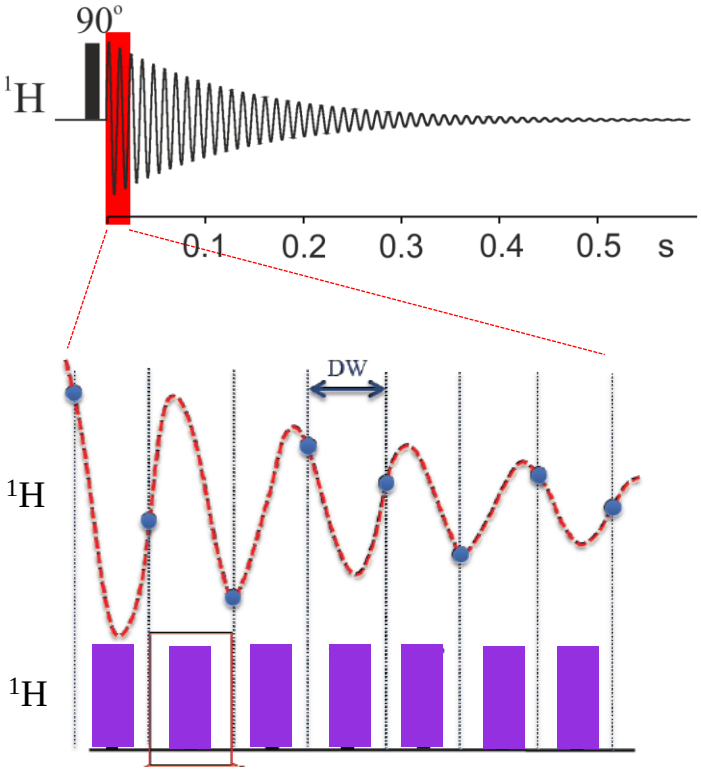
Undesired effect

Homonuclear spin echo
- refocuses δ_H
- J_{HH} evolve



How could we get a “perfect” homodecoupled NMR spectrum?

Ideal $^1H\{^1H\}$ NMR experiment



Evolution during FID

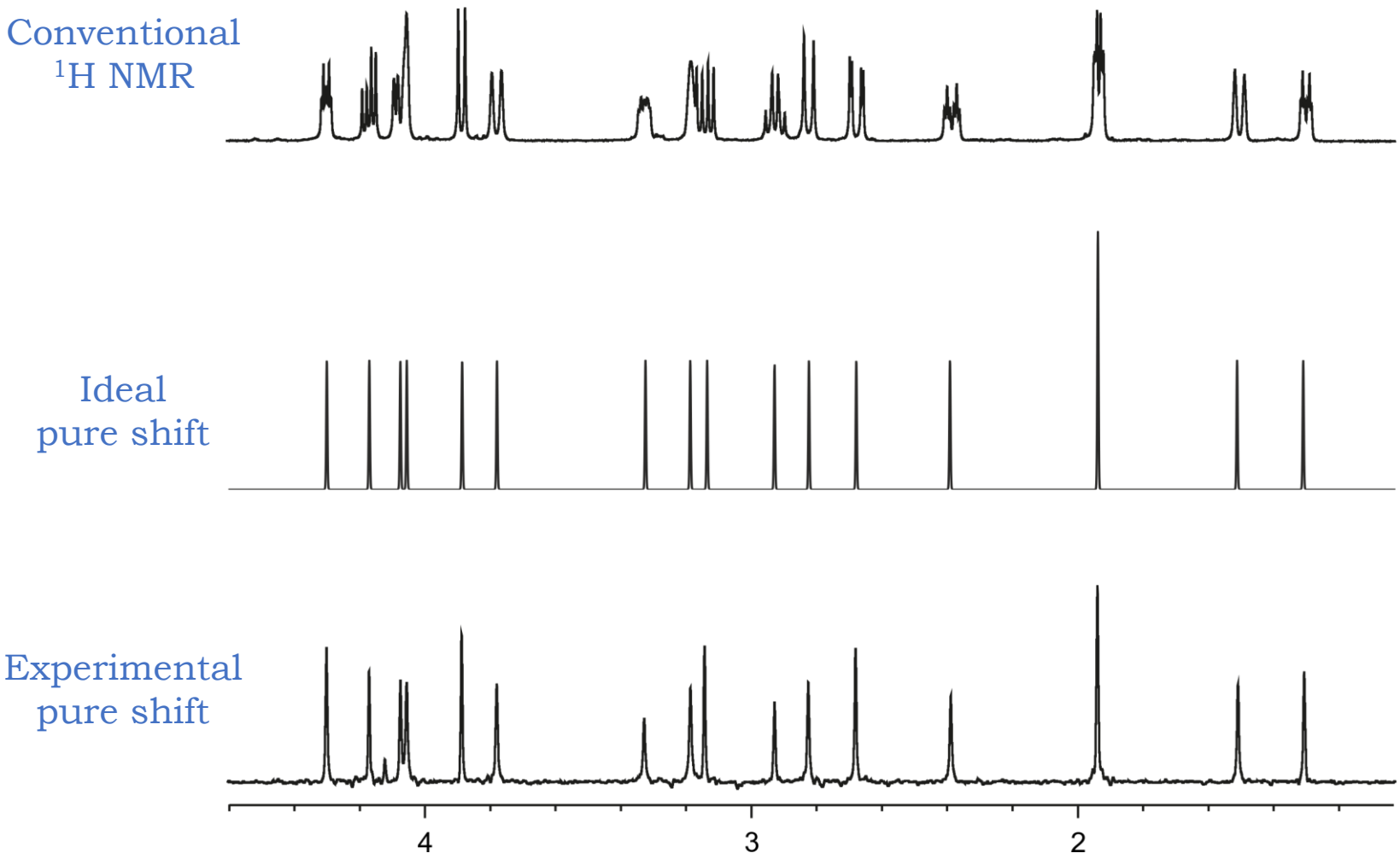
δ_H	J_{HH}
✓	✓

Not (currently) available

We would need a decoupling element:

- refocuses J_{HH}
- leaves δ_H to evolve
- last few μs

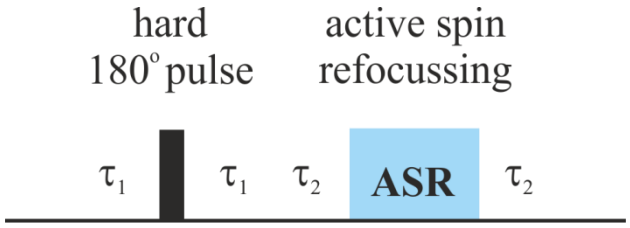
How far are we from a “perfect” pure shift spectrum?



How do we get an experimental pure shift NMR spectrum?

Homodecoupling element

J-refocussing element



J_{HH} is refocused while δ_H evolves
(for *active* spins only)

Active spin refocussing

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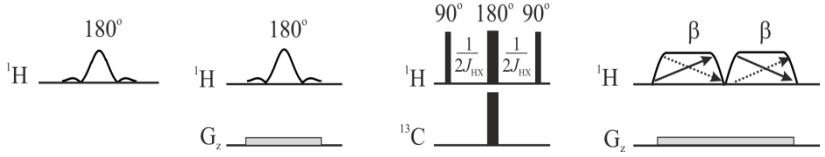
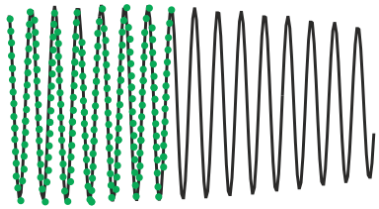


Homodecoupled FID

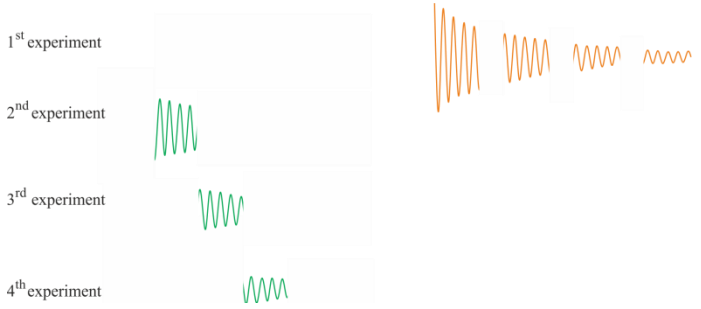
Chunking data acquisition



Chunk duration (τ_c) << $1/J_{HH}$

Acquisition methods

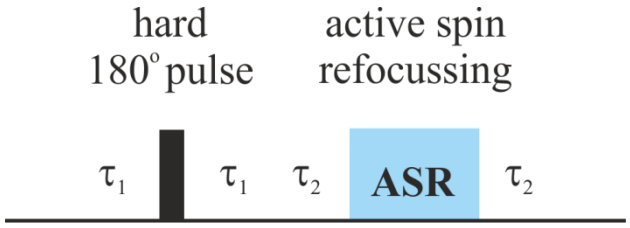
Interferogram Real-time



How do we get an experimental pure shift NMR spectrum?

Homodecoupling element

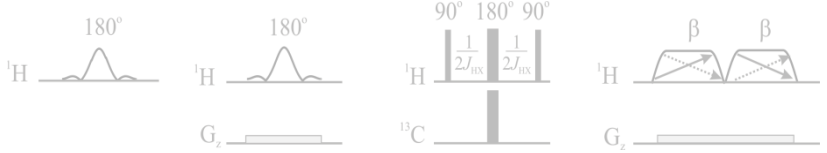
J-refocussing element



J_{HH} is refocused while δ_H evolves
(for *active* spins only)

Active spin refocussing

BS ZS BIRD PSYCHE



Homodecoupled FID

Chunking data acquisition

Chunk duration (τ_c) << $1/J_{HH}$

Acquisition methods

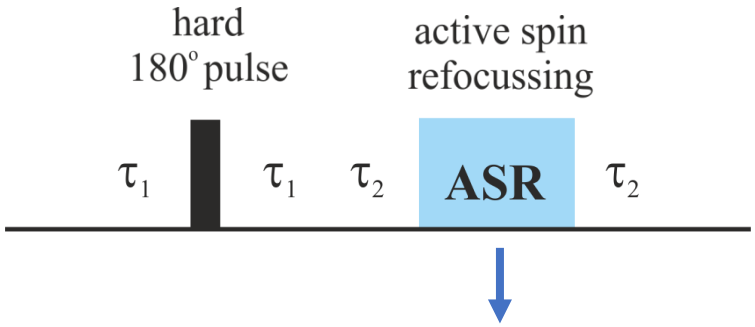
Interferogram Real-time

How do we remove the effect of J_{HH} couplings only?

We need a **decoupling element** that:

- refocuses J_{HH}
- leaves δ_H to evolve

J-refocussing element



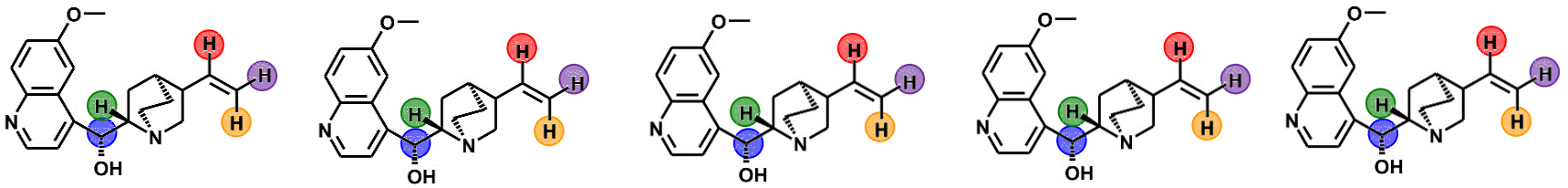
Divides the available spins into:

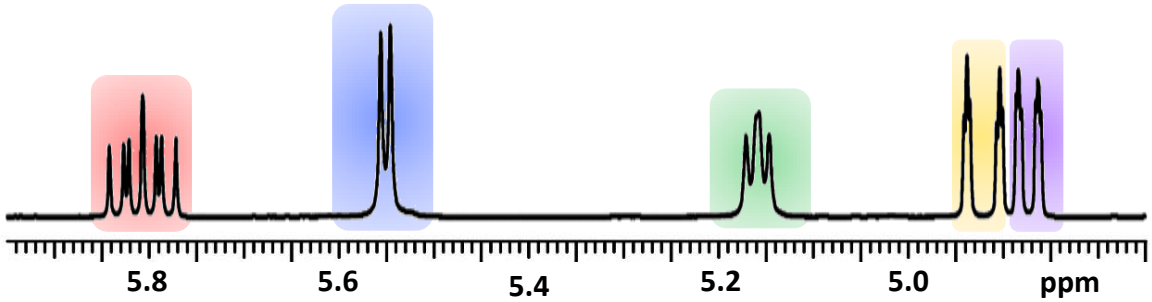
- *active* (observed)
- *passive* spins (non observed)

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

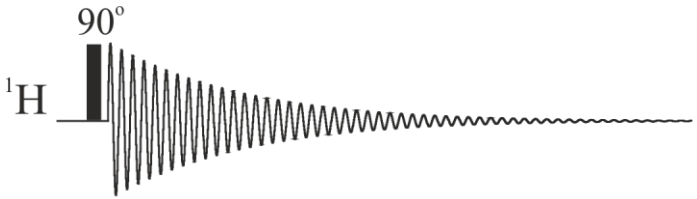
The concept of *active* and *passive* spins

Conventional ^1H NMR



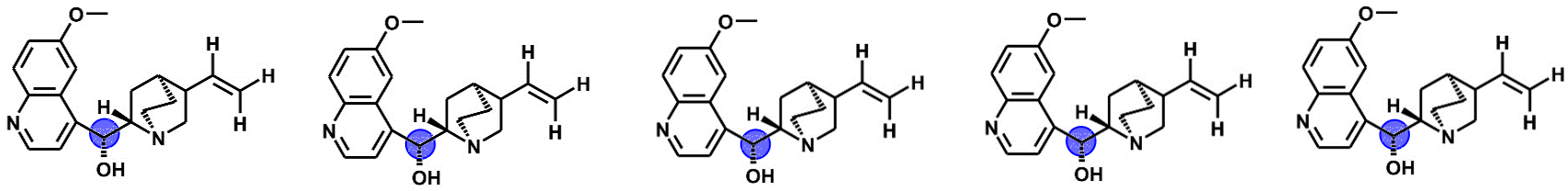


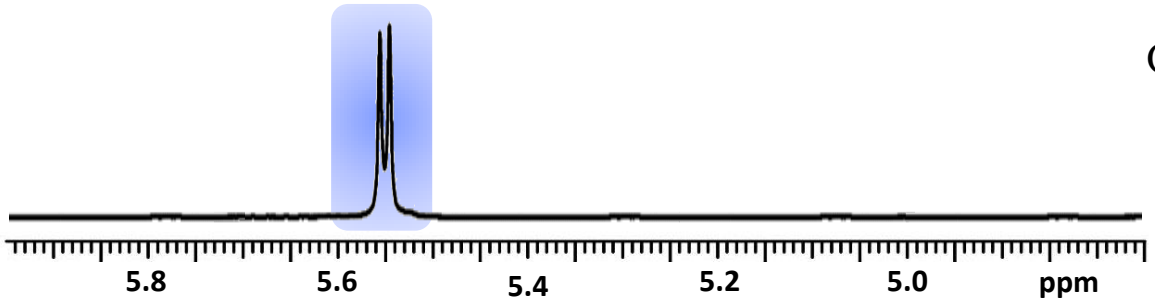
All spins are *active* (observed)



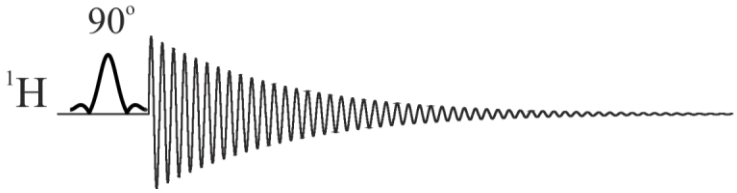
The concept of *active* and *passive* spins

Band-selective ^1H NMR





Only blue spins are *active* (observed)



Divides the available spins into
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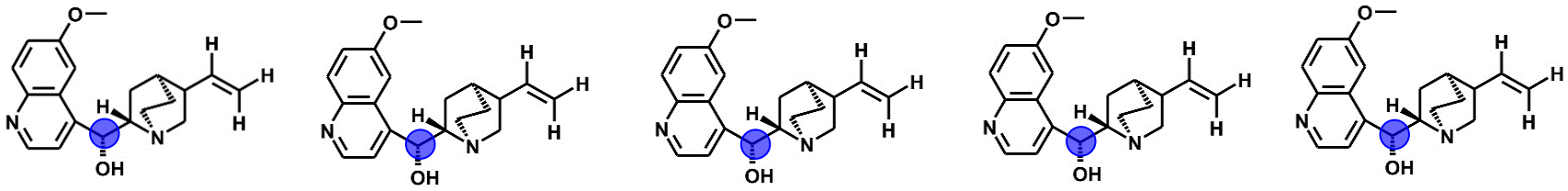
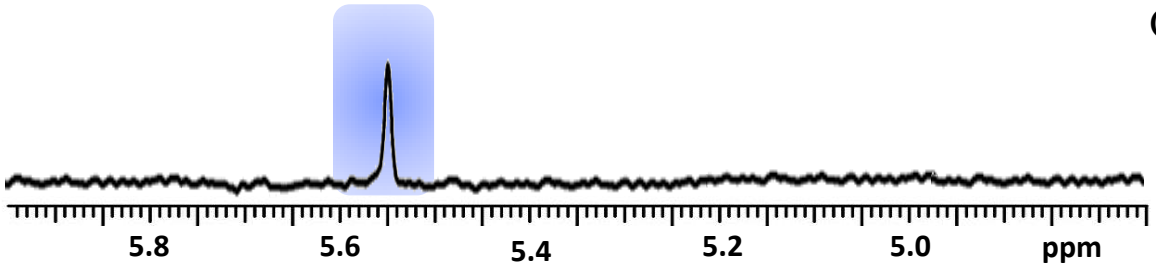
- *passive* spins (non observed)

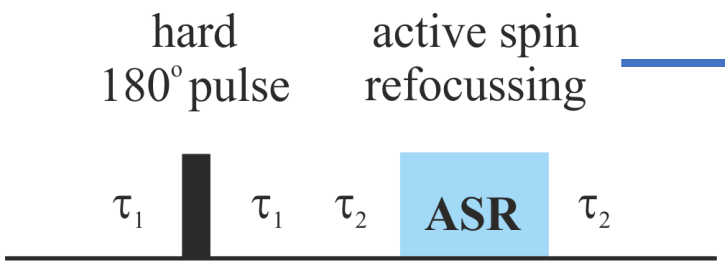
The concept of *active* and *passive* spins

Band-selective pure shift ^{1}H NMR





Only blue spins are *active* (observed)



Divides the available spins into
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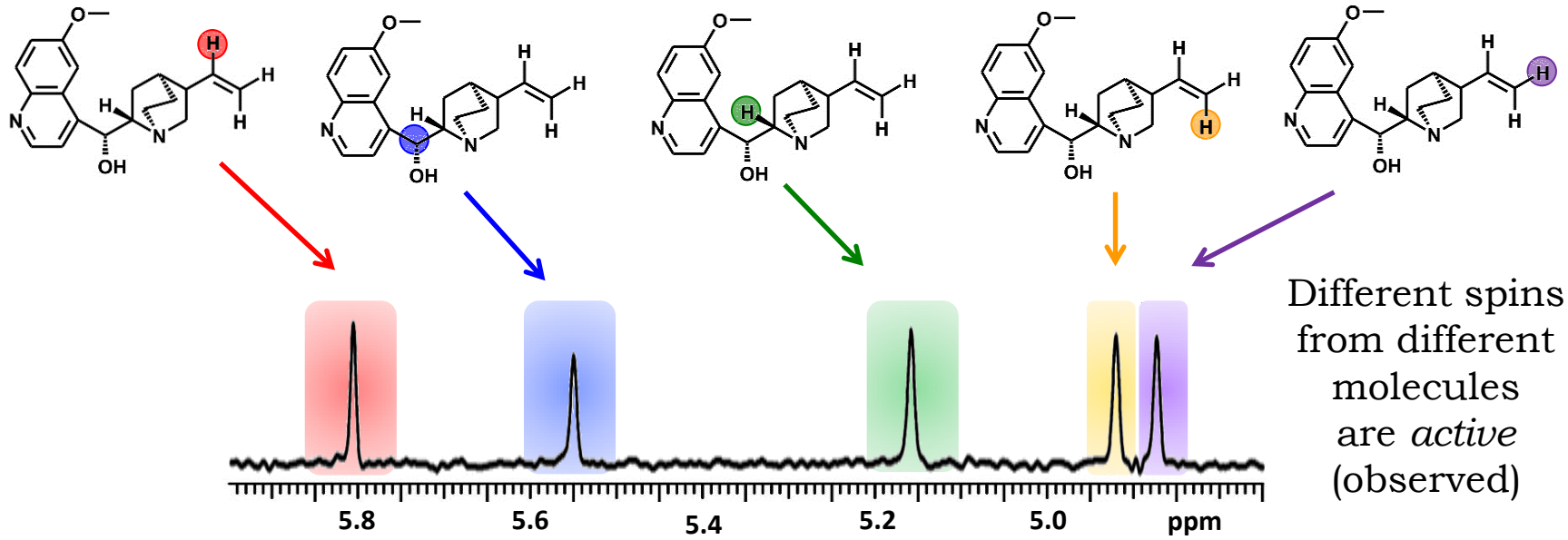
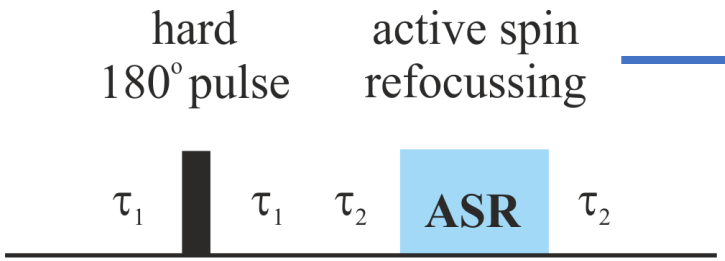
- *passive* spins (non observed)

The concept of *active* and *passive* spins

Pure shift ^{1}H NMR



Different spins from different molecules are *active* (observed)



Divides the available spins into
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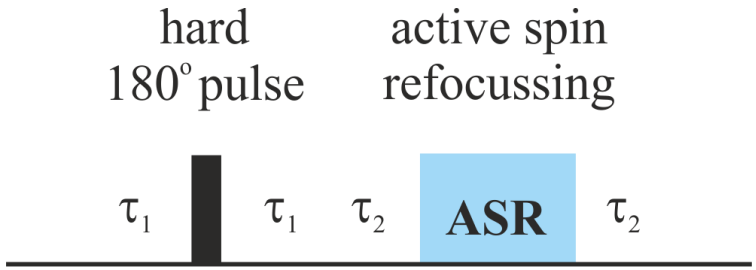
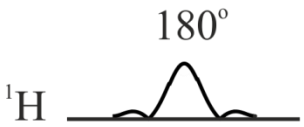
- *passive* spins (non observed)

Active spin refocussing (ASR) elements

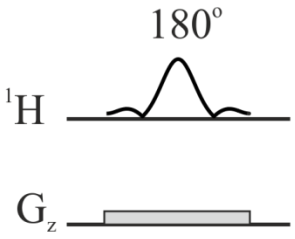


Band-selective



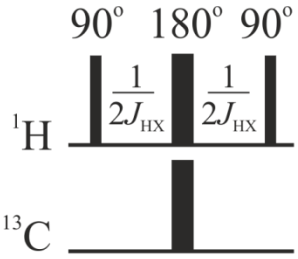
Shift selective 180° rotation

Zangger-Sterk



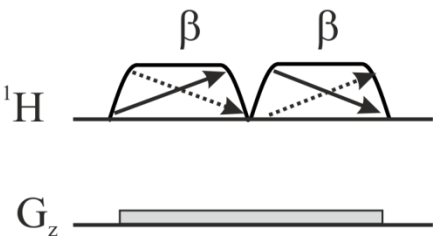
Slice and shift selective 180° rotation

BIRD



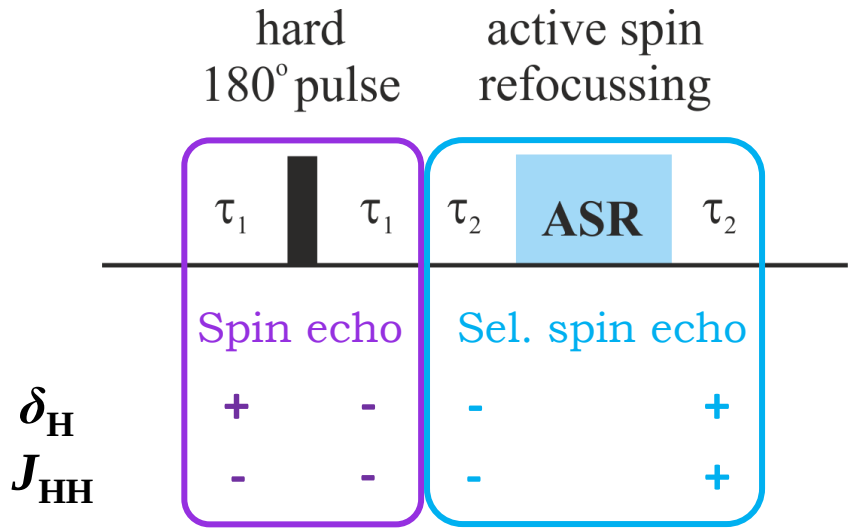
180° rotation of protons coupled to ^{13}C

PSYCHE

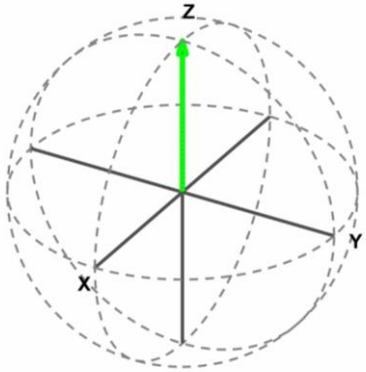


Flip a fraction $\sin^2\beta$ of spins

General mechanism for *J*-refocussing



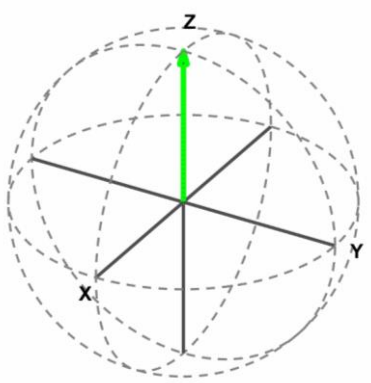
Spin echo



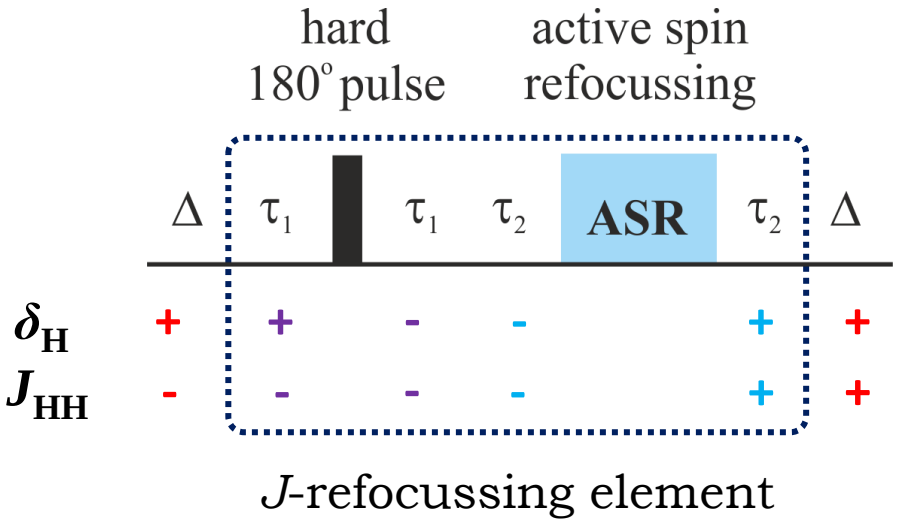
refocuses δ_H but not J_{HH}

refocuses both δ_H and J_{HH} (for active spin only)

Sel. spin echo



General mechanism for *J*-refocussing



J-refocussing element

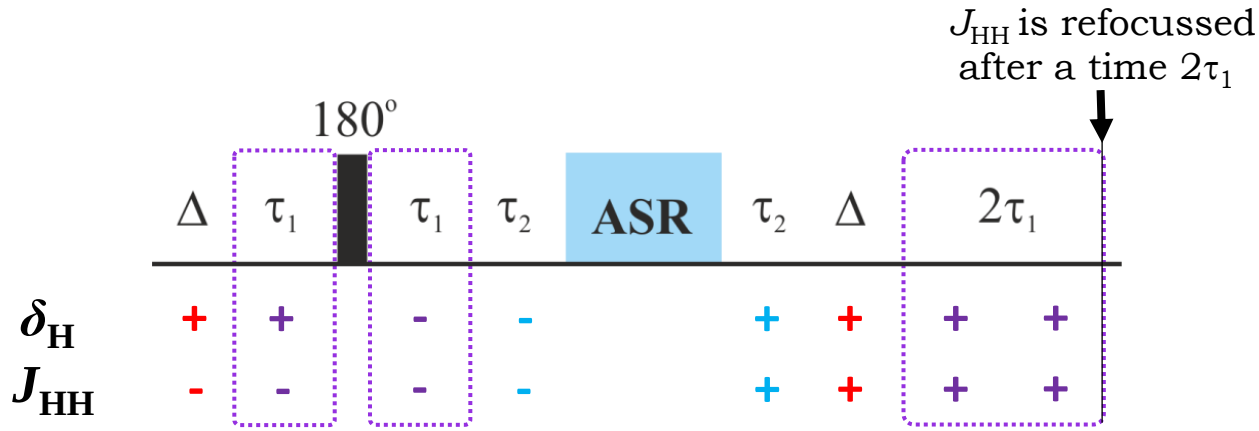
δ_H evolves

J_{HH} is refocused

(for active spin only)

Controlling *J*-refocussing time position

If $\tau_1 \neq 0$



If $\tau_1 = 0$

The timing of the *J*-refocussing element is carefully designed to have full control of when J_{HH} is refocussed (by changing τ_1)

How do we get an experimental pure shift NMR spectrum?

Homodecoupling element

J-refocussing element

hard 180° pulse

active spin refocussing

J_{HH} is refocused while δ_H evolves
(for *active* spins only)

Active spin refocussing

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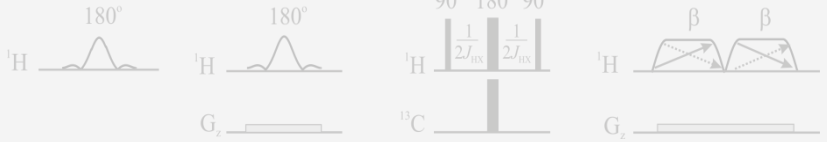
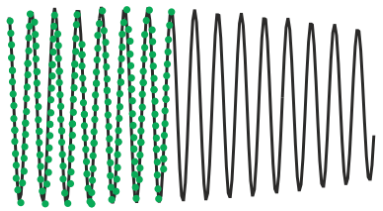


Homodecoupled FID

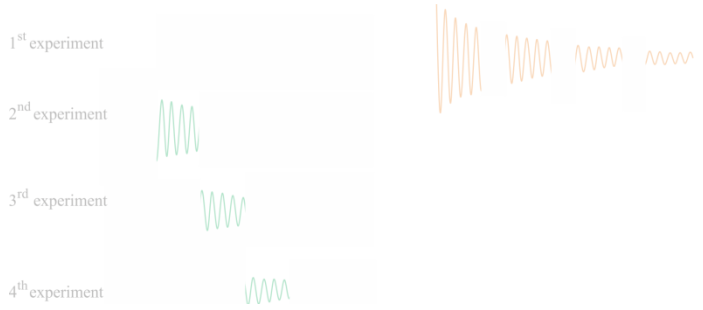
Chunking data acquisition



Chunk duration (τ_c) << $1/J_{HH}$

Acquisition methods

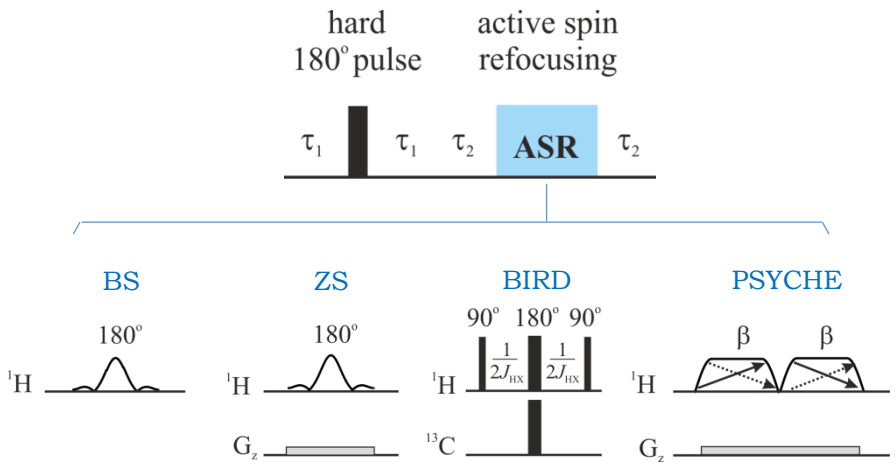
Interferogram Real-time



How do we remove the effect of J_{HH} coupling during FID?

We need to apply a homodecoupling element **after each acquisition point**

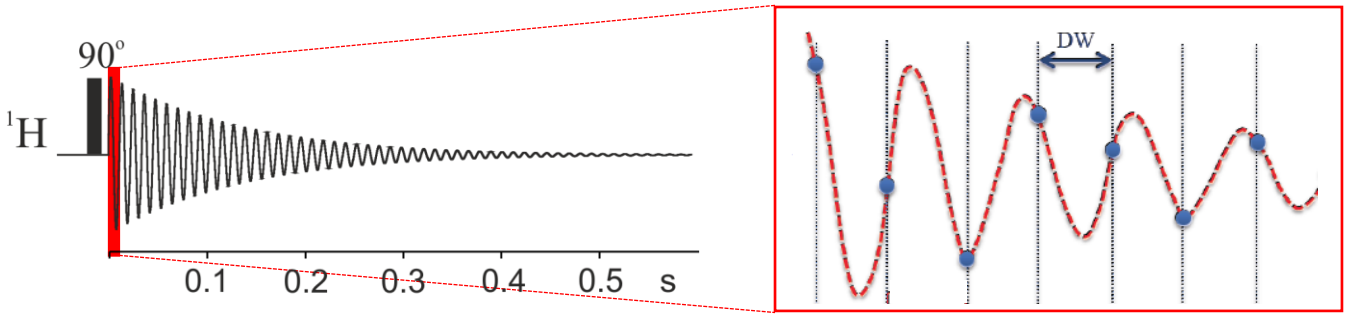
J-refocussing element



Not (currently) possible

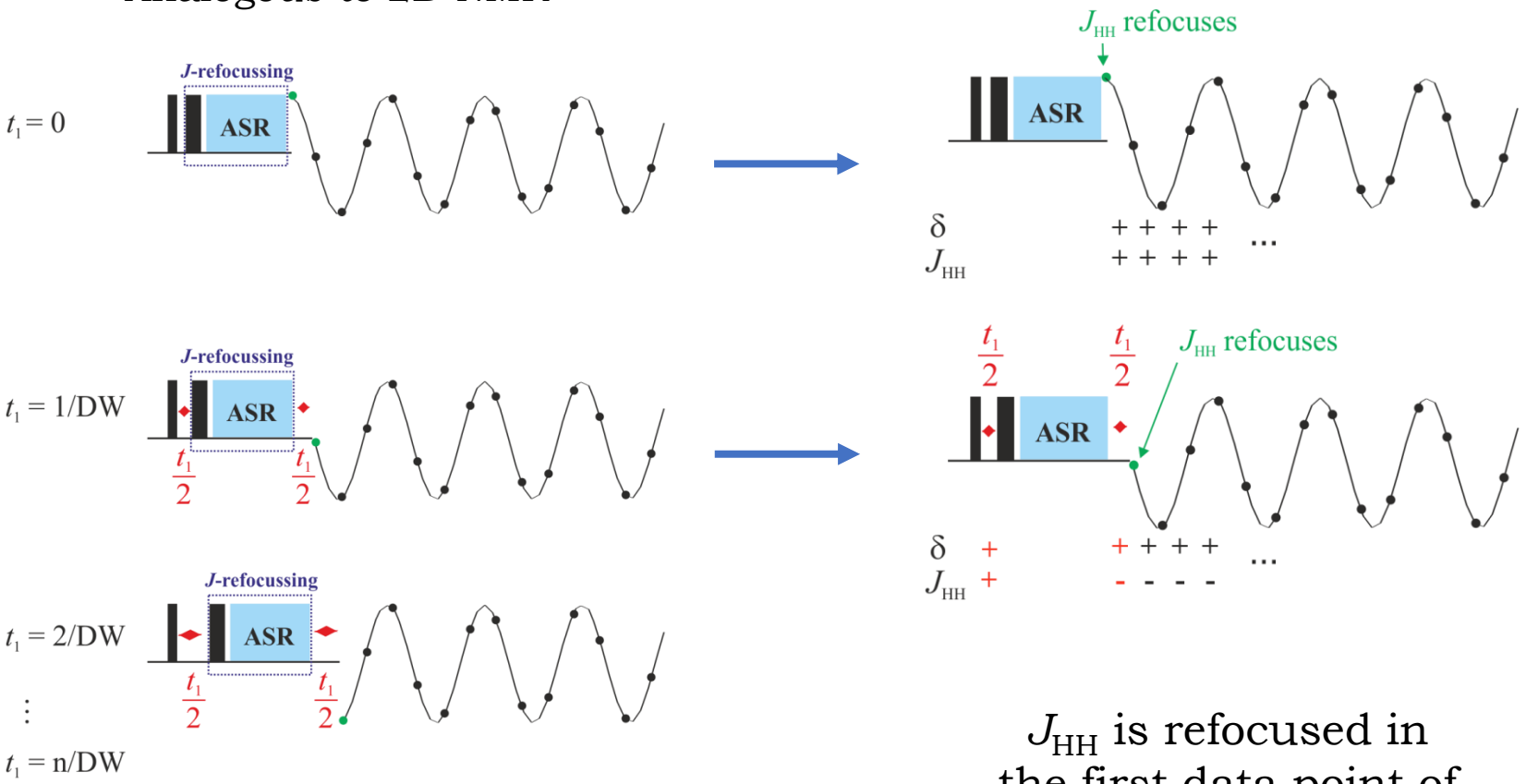
ASR duration (ms)	1-100	1-100	5-10	20-40

Sampling interval (dwell time) ~ 50 μs



Point-by-point data acquisition (first approach)

Analogous to 2D NMR

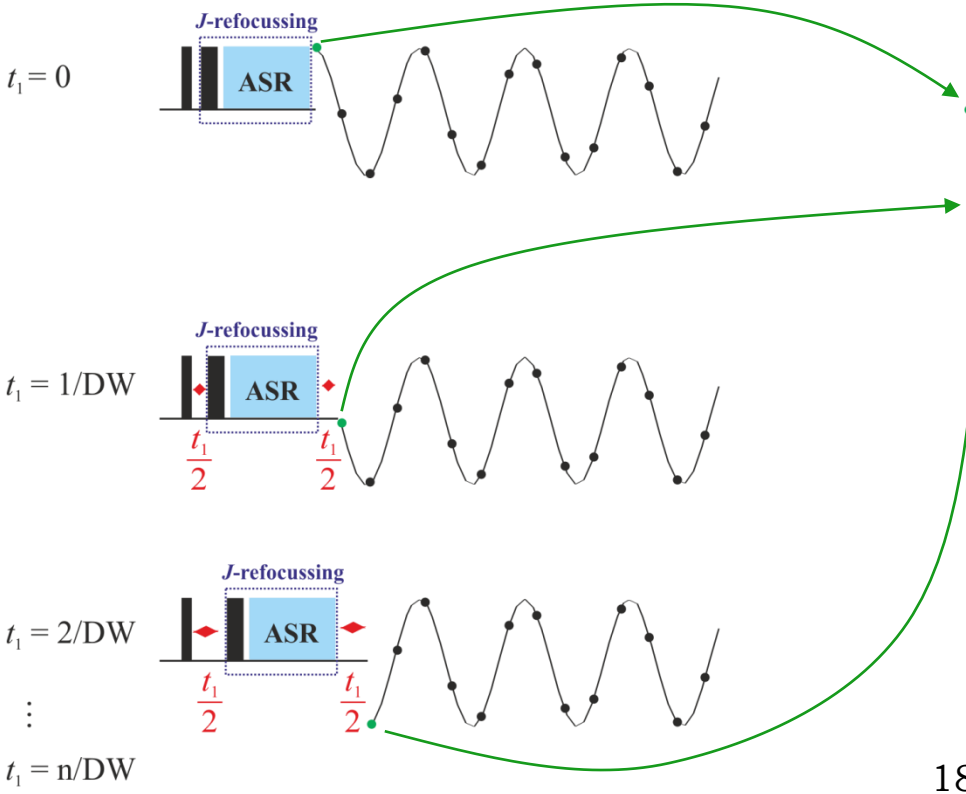


J_{HH} is refocused in the first data point of each increment

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

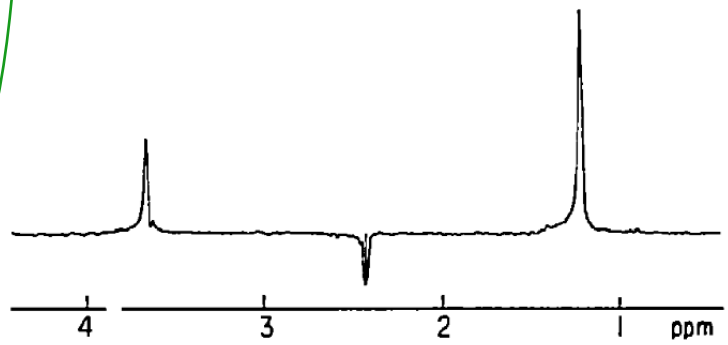
Point-by-point data acquisition (first approach)

Analogous to 2D NMR



Reconstructed pure shift FID

FT



182 MHz ^{1}H pure shift spectrum of ethanol

Extremely long (impractical)

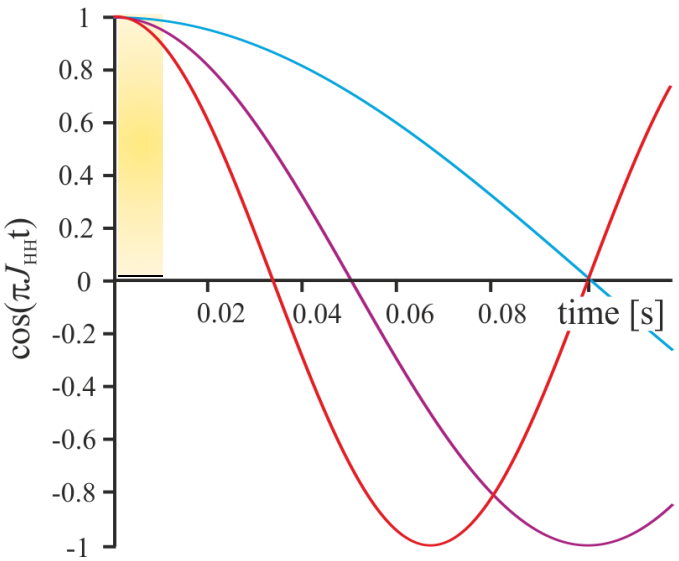
Experiment time ~ 24h
(8192 t_1 increments)

FID data points = 8192
(2.5 Hz resolution)

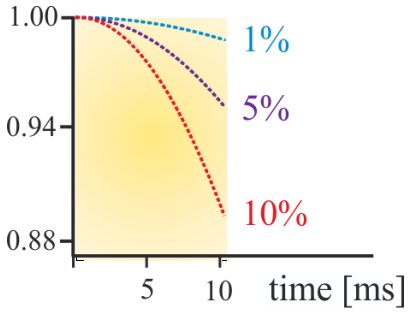
Chem. Phys. Lett. **93**, 504 (1982)

Exploiting the relative slowness of J_{HH} evolution

J_{HH} evolution for a AX spin system

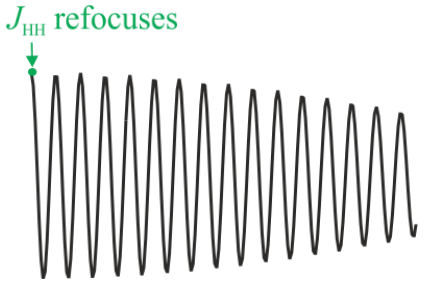


J_{HH}= 5 Hz
J_{HH}= 10 Hz
J_{HH}= 15 Hz

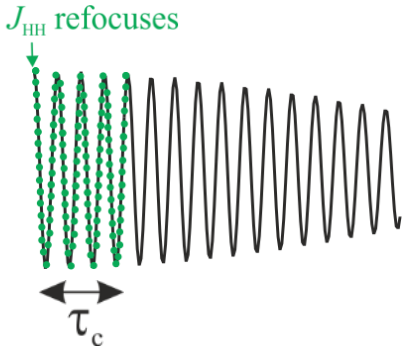


J_{HH} evolution during the chunk is negligible

Point-by-point data acquisition



Chunking data acquisition

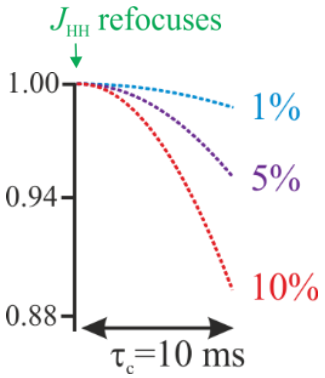


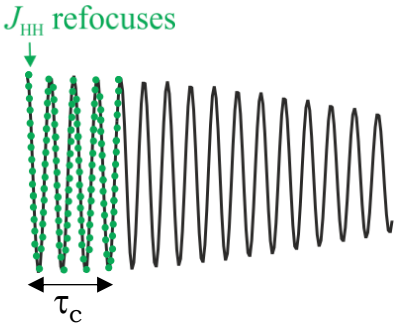
chunk duration (τ_c) << $1/J_{HH}$

(~200 data points per chunk)

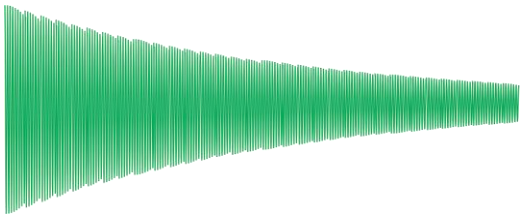
J. Magn. Reson. **124**, 486 (1997)

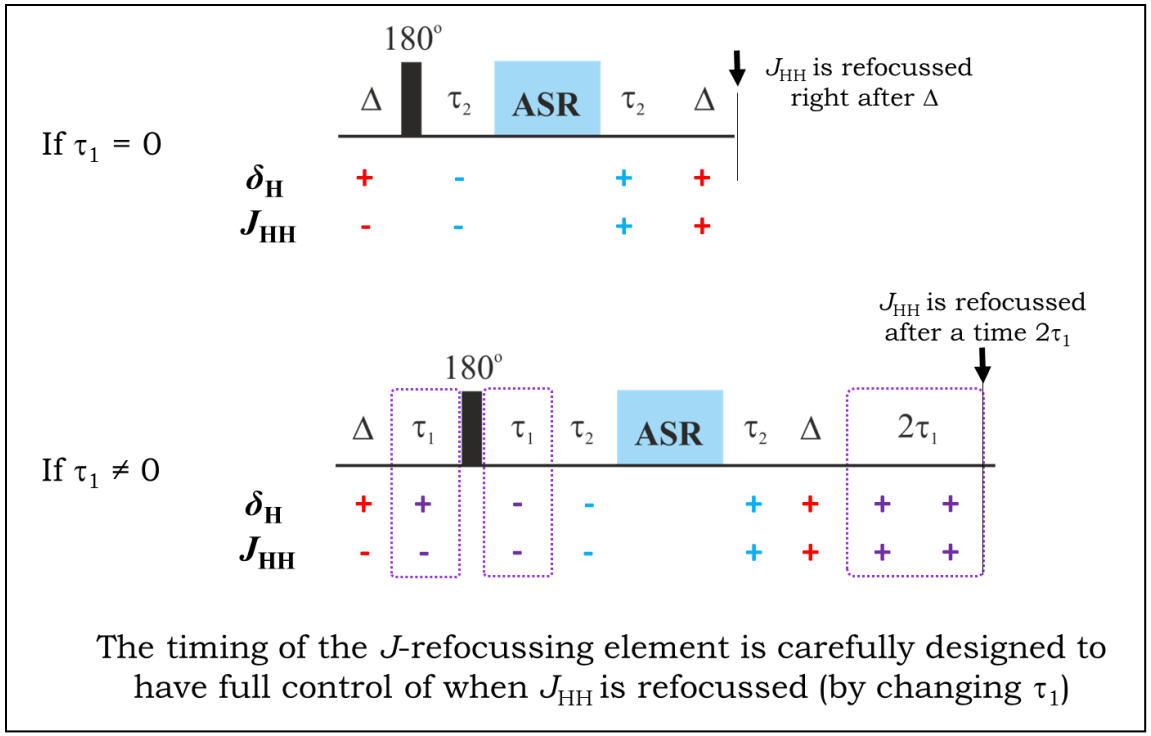
Chunking data acquisition (speeding things up)





concatenation

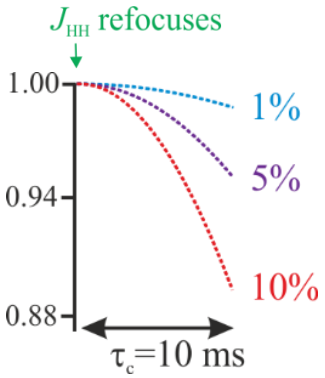


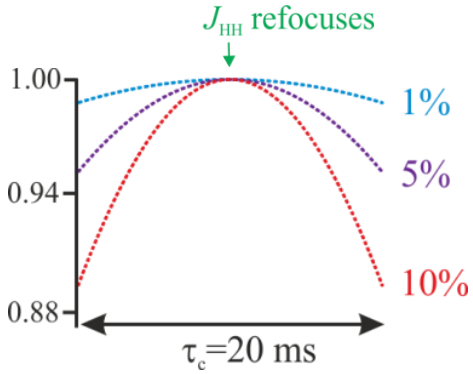


The timing of the *J*-refocussing element is carefully designed to have full control of when J_{HH} is refocussed (by changing τ_1)

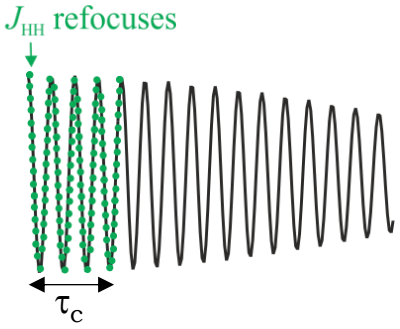
Angew. Chem. Int. Ed. **49**, 3901 (2010)

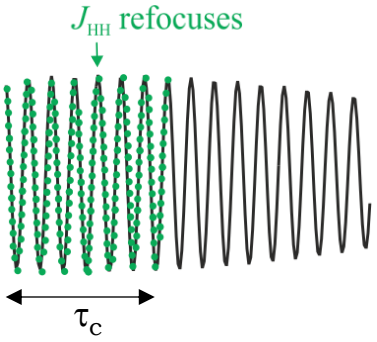
Chunking data acquisition (speeding things up)



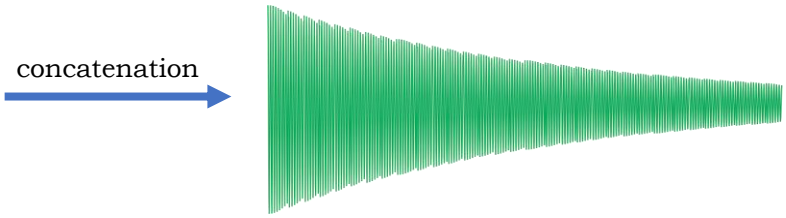


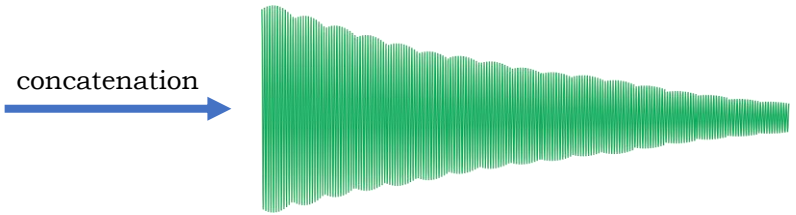
Refocussing J_{HH} in the middle of the chunk





Allows to acquire chunks twice longer



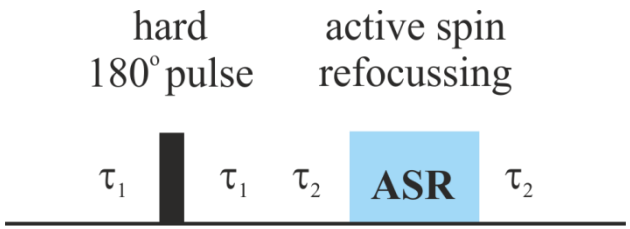


Reducing experiment time

(half number of chunks are needed for achieving the same FID resolution)

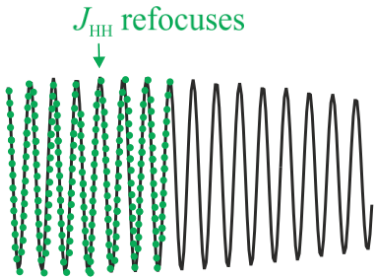
Pure shift key ideas

J-refocussing element



J_{HH} is refocused while δ_H evolves
(for active spin only)

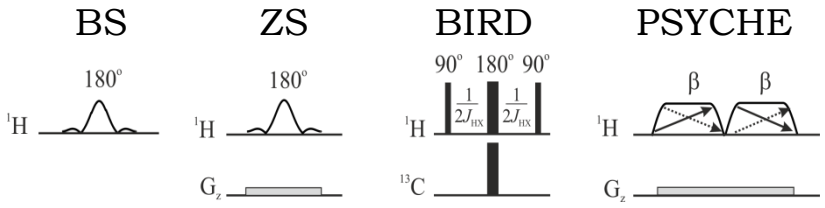
Chunking data acquisition



Chunk duration (τ_c) << $1/J_{HH}$
J_{HH} refocused in the middle

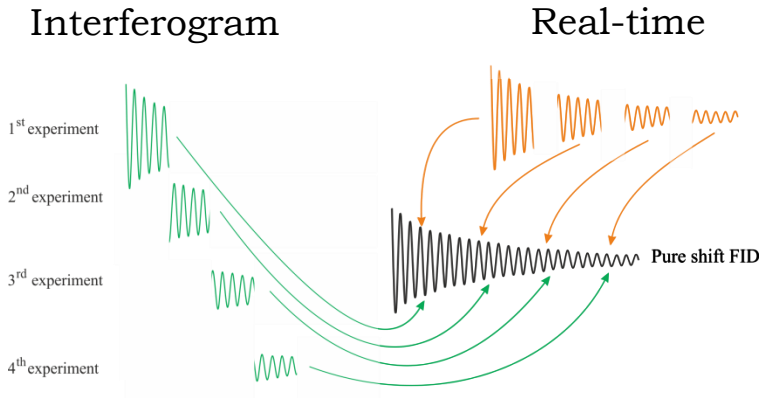
Pure shift methods

Active spin refocussing



Divides the spins into *active* (observed) and *passive* spins (non observed)

Acquisition methods



Pure shift key ideas

J-refocussing element

J_{HH} is refocused while δ_H evolves
(for active spin only)

Chunking data acquisition

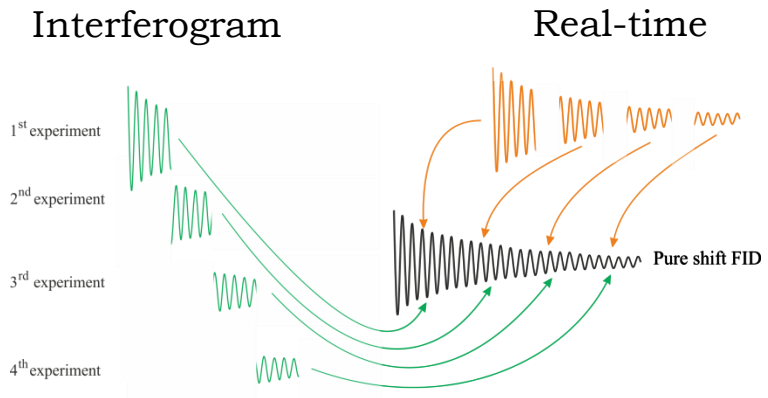
Chunk duration (τ_c) << $1/J_{HH}$
J_{HH} refocused in the middle

Pure shift methods

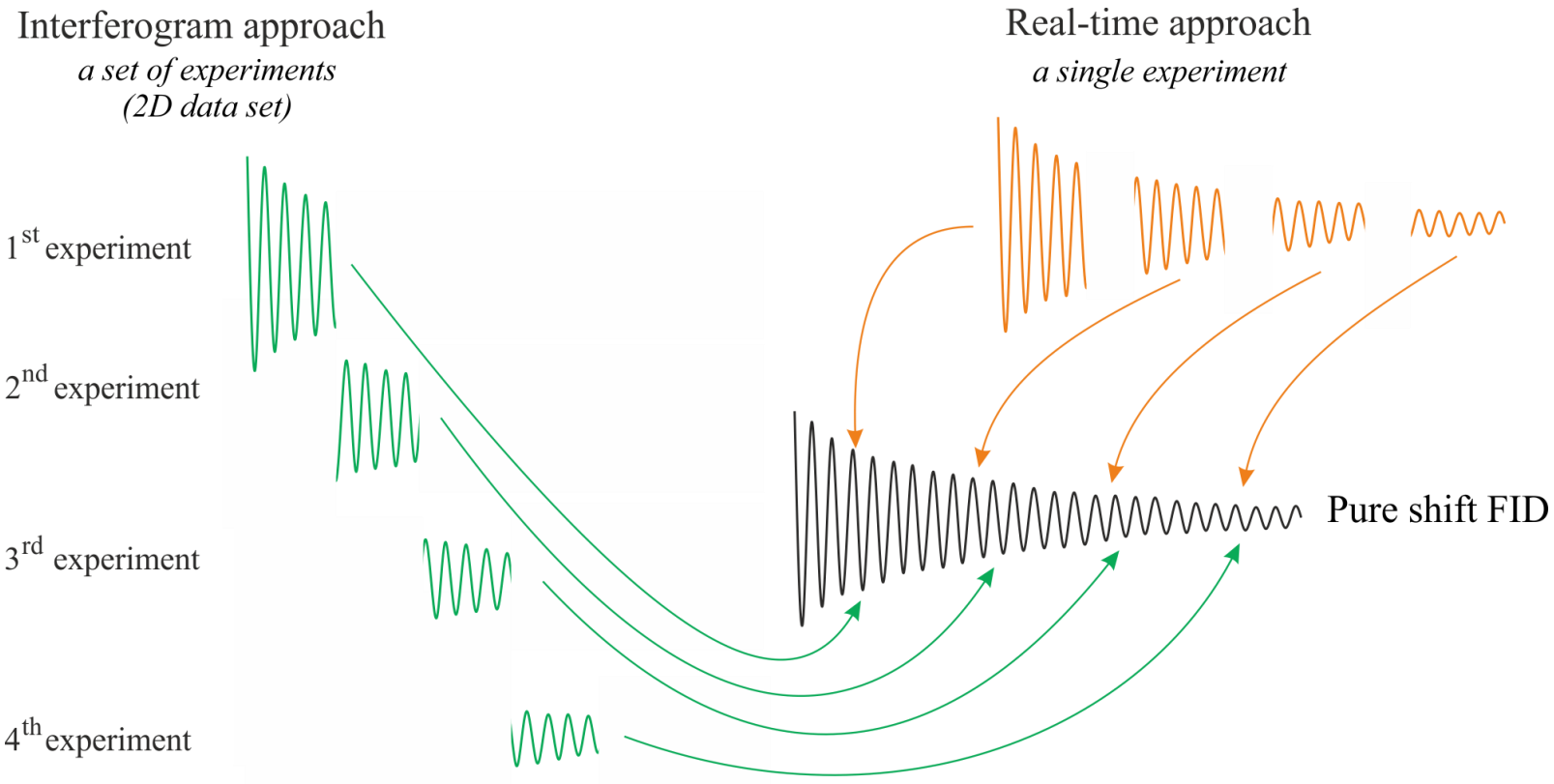
Active spin refocussing

Divides the spins into *active* (observed) and *passive* spins (non observed)

Acquisition methods



Pure shift acquisition methods

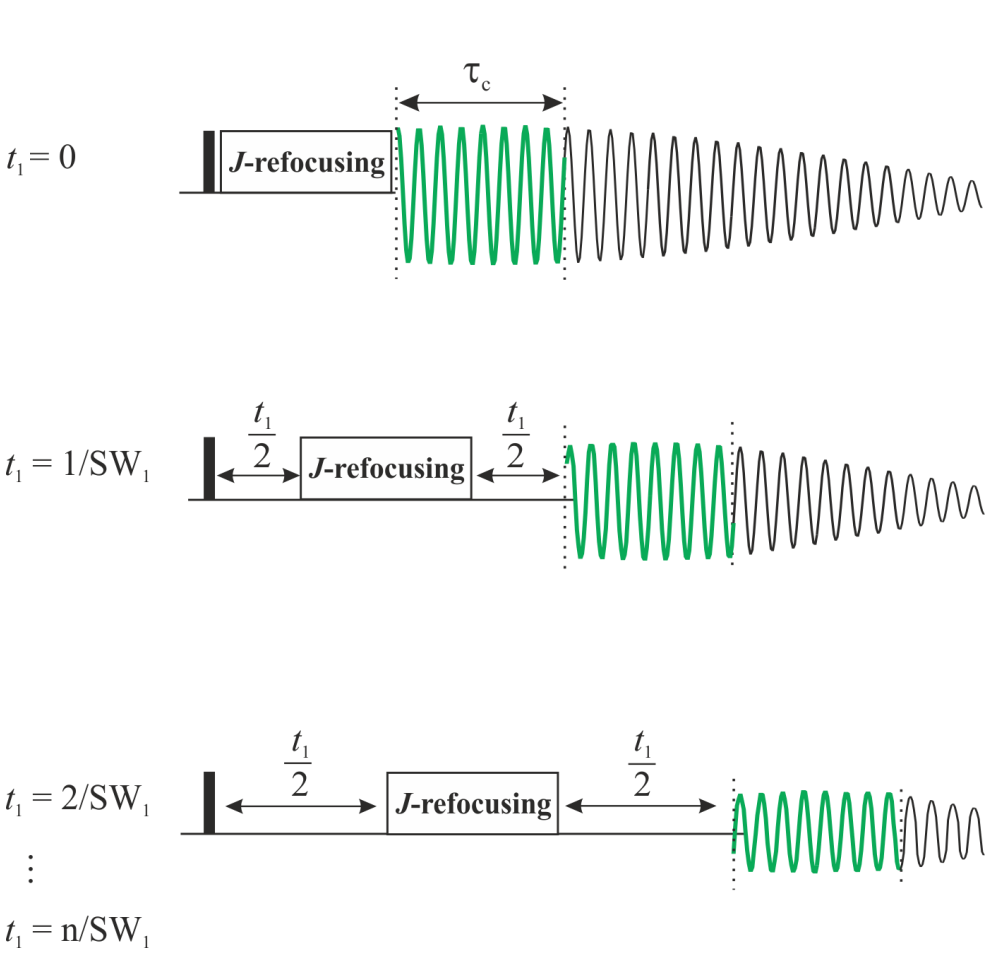


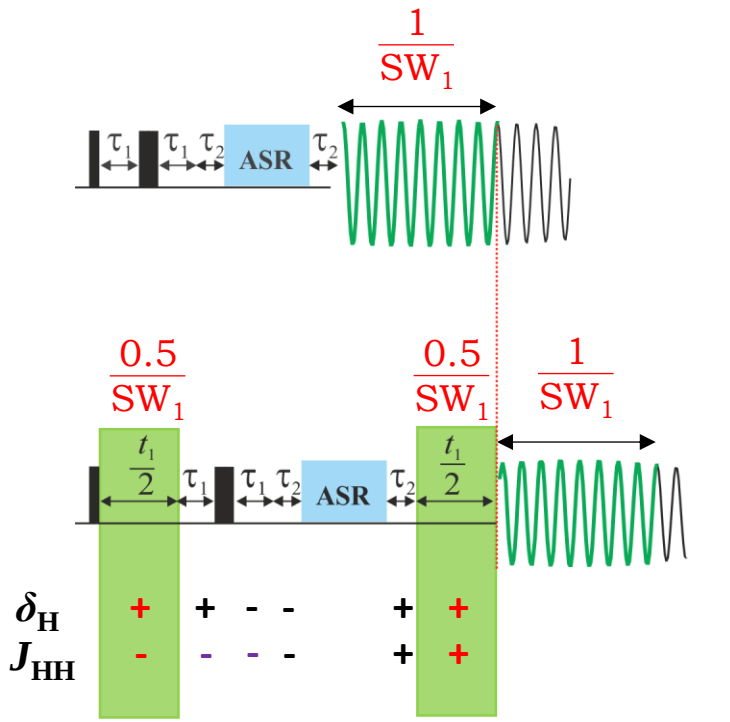
Chunk duration (τ_c) << $1/J_{HH}$ (τ_c~10-20 ms)

J_{HH}-evolution refocused in the middle of the chunk

Interferogram pure shift experiments – 2D acquisition

Analogous to 2D NMR





During t_1 δ_H evolves & J_{HH} is refocused

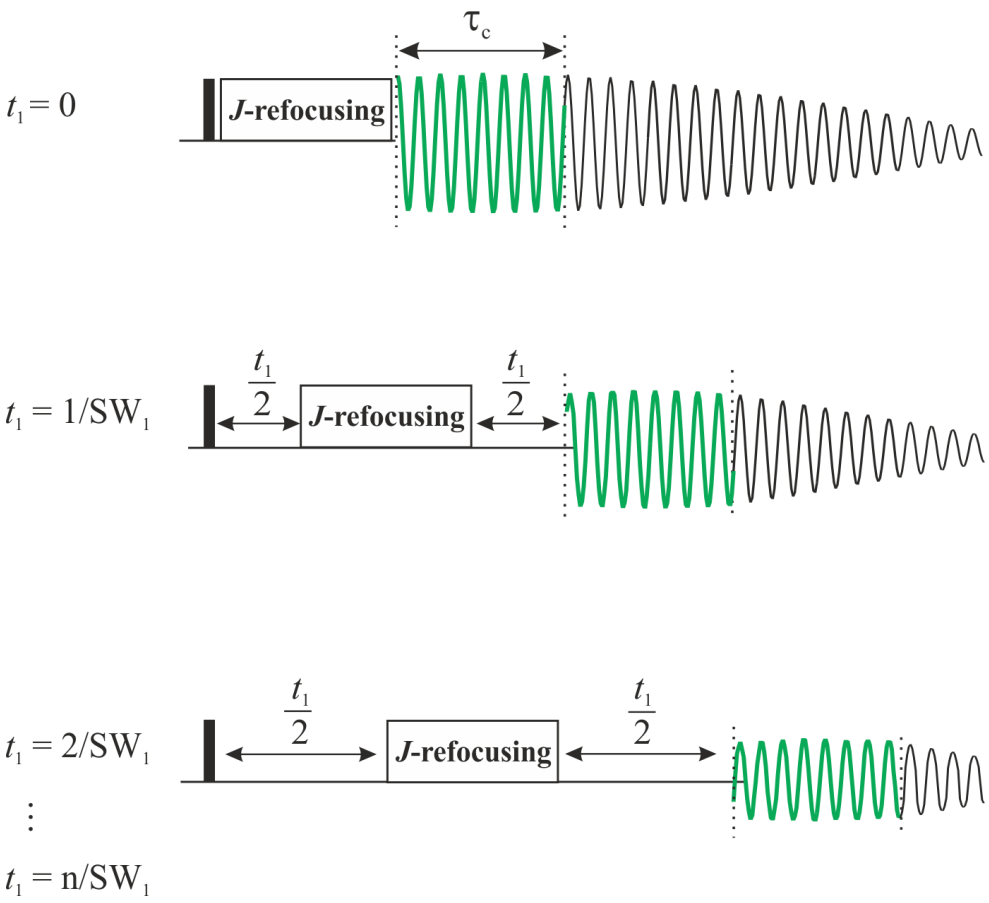
Increment in t_1 delay ($1/SW_1$) is set to the duration of the chunk

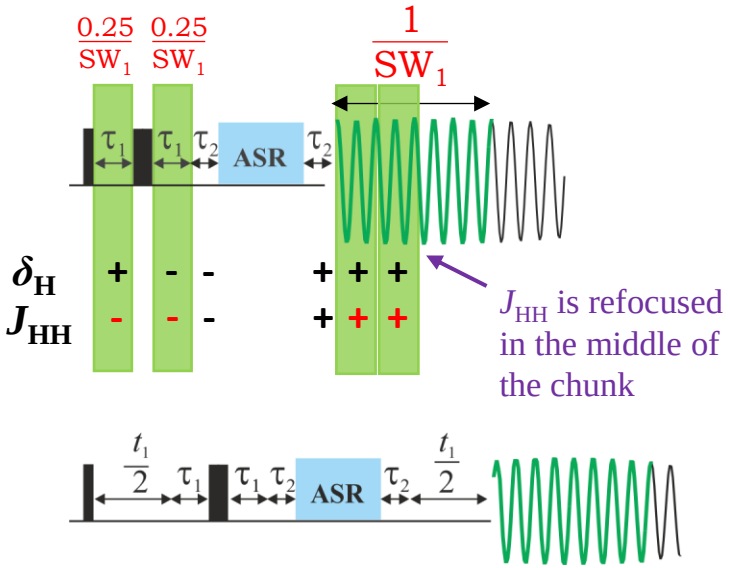
$\tau_c = 1/SW_1$

J. Magn. Reson. **124**, 486 (1997); *Angew. Chem. Int. Ed.* **49**, 3901 (2010)

Interferogram pure shift experiments – 2D acquisition

Analogous to 2D NMR





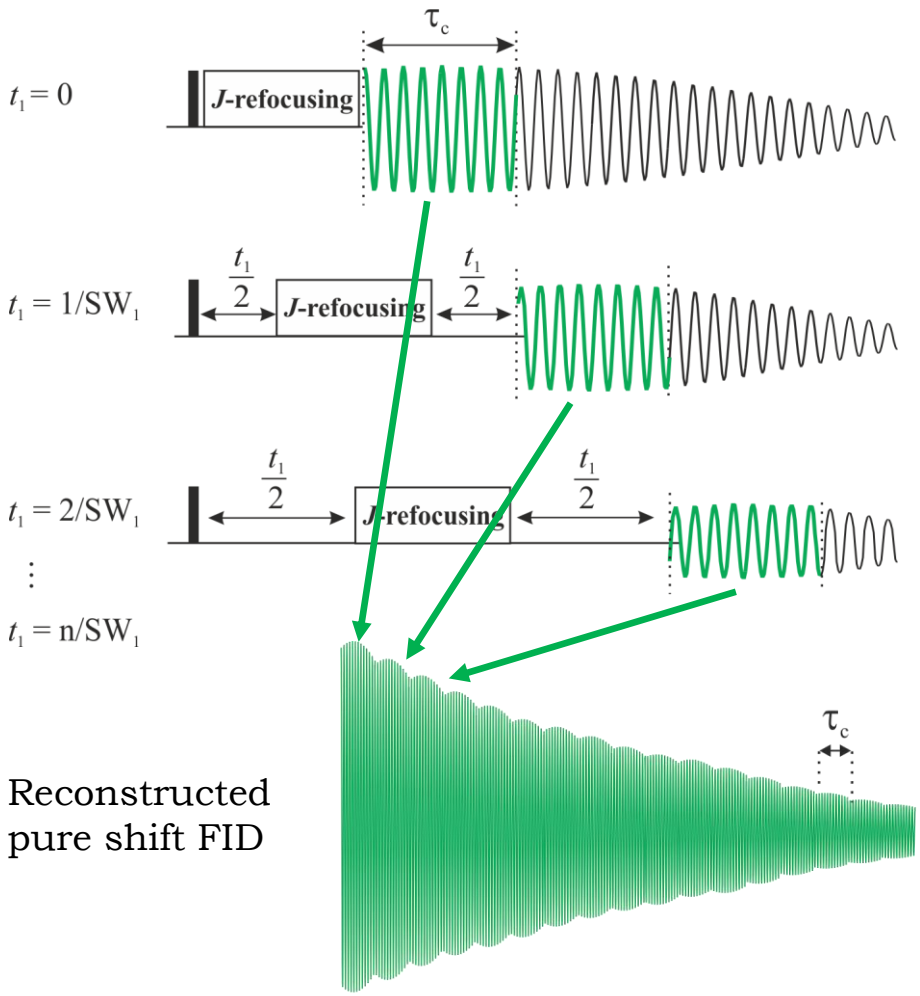
τ_1 is normally set to ensure that J_{HH} is refocused at the midpoint of each chunk

Increment in t_1 delay ($1/SW_1$) is set to the duration of the chunk

$\tau_c = 1/SW_1$

J. Magn. Reson. **124**, 486 (1997); *Angew. Chem. Int. Ed.* **49**, 3901 (2010)

Interferogram pure shift experiments – 2D acquisition



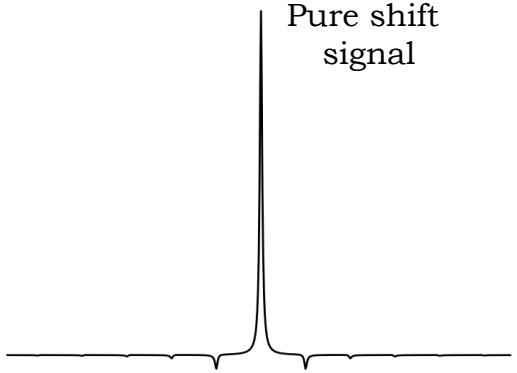
Reconstructed pure shift FID

Special data processing is needed

Extract first chunk of each increment

Assemble them sequentially (reconstructed pure shift FID)

FT

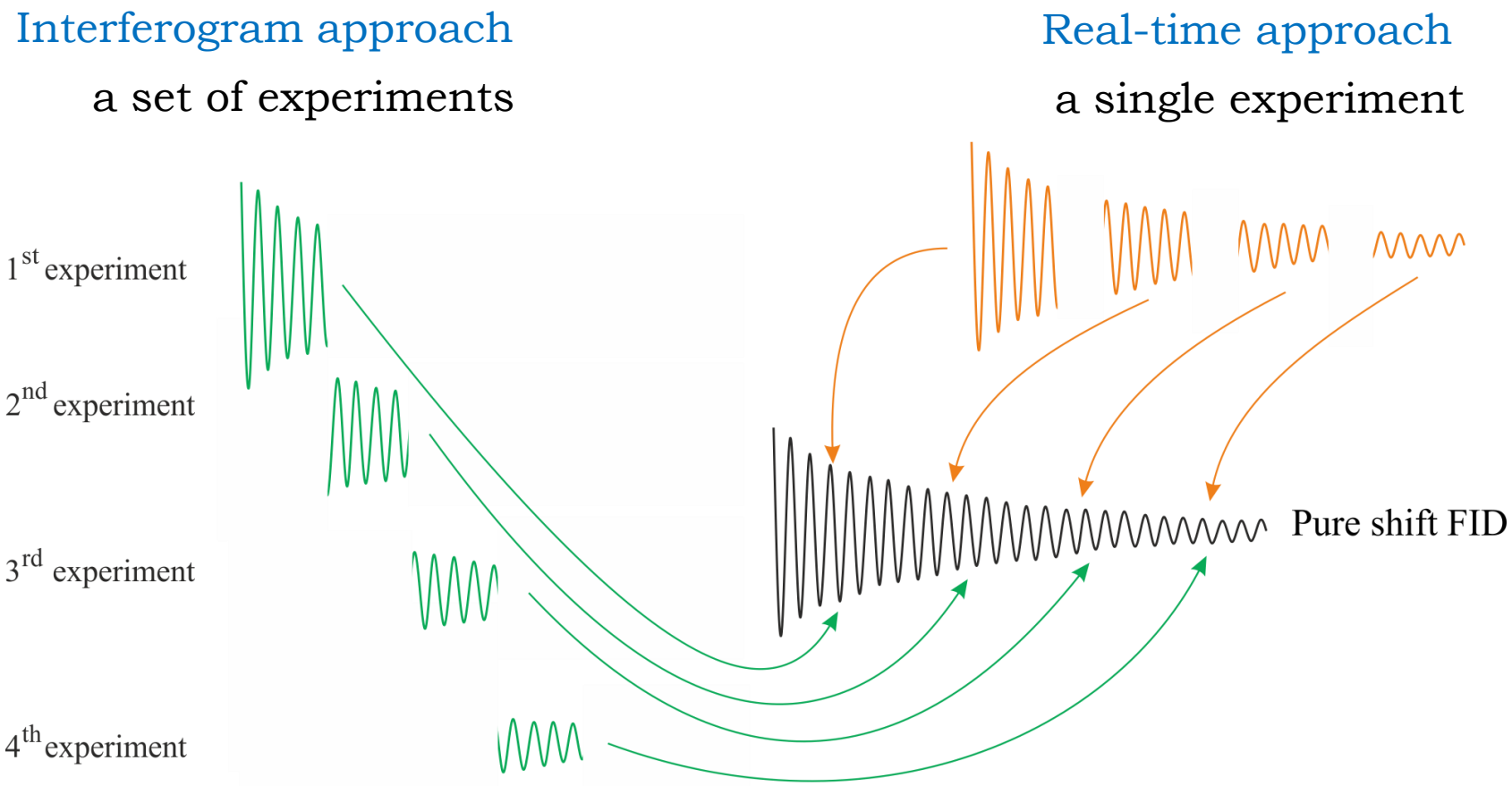


chunking artefacts

Acquiring pure shift data in chunks of duration τ_c gives rise to *J*-sidebands ("chunking artefacts") with a spacing $1/\tau_c$ in the spectrum

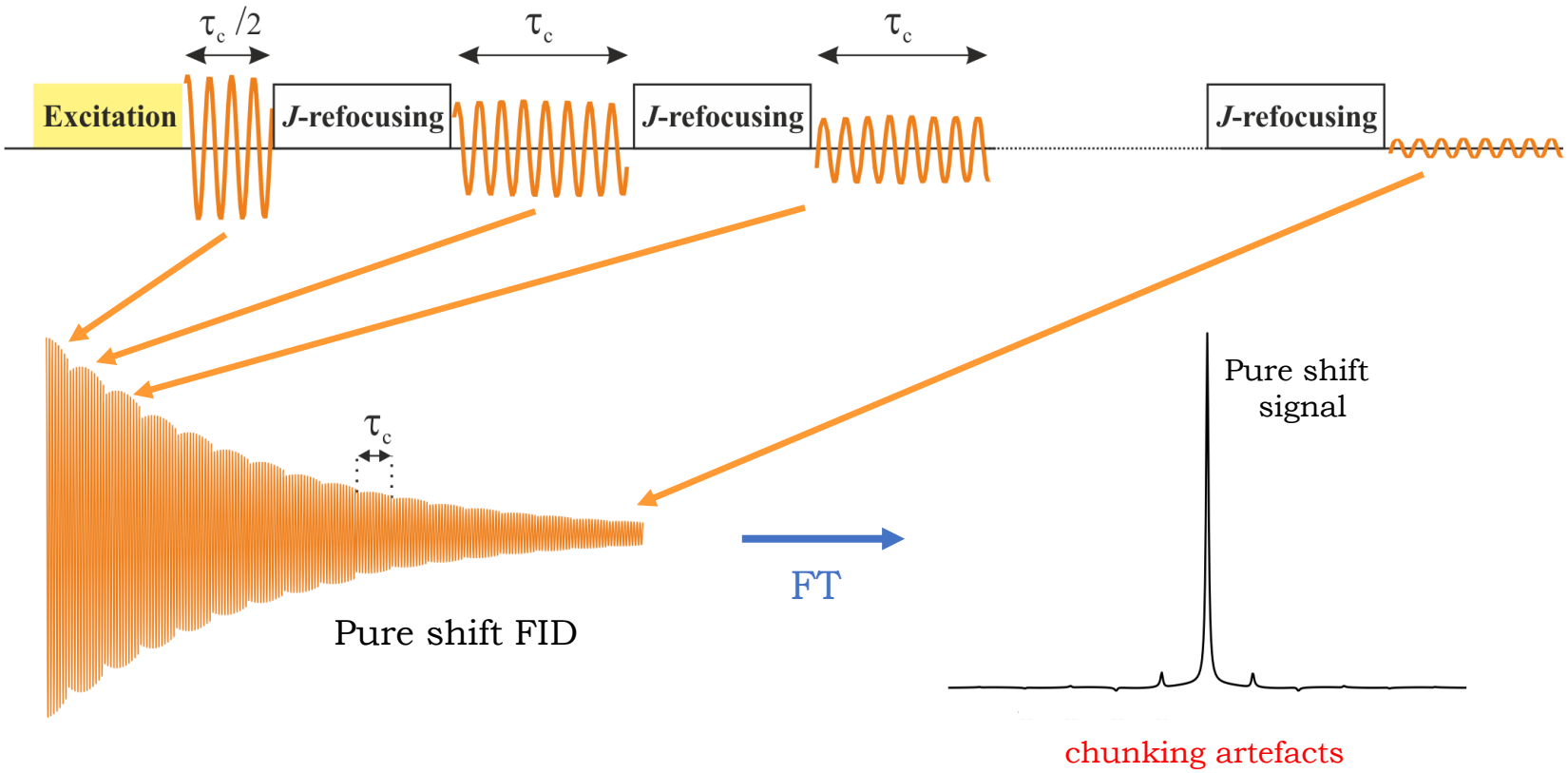
J. Magn. Reson. **124**, 486 (1997); *Angew. Chem. Int. Ed.* **49**, 3901 (2010)

Speeding things up



Real-time pure shift experiments – 1D acquisition

Single shot acquisition



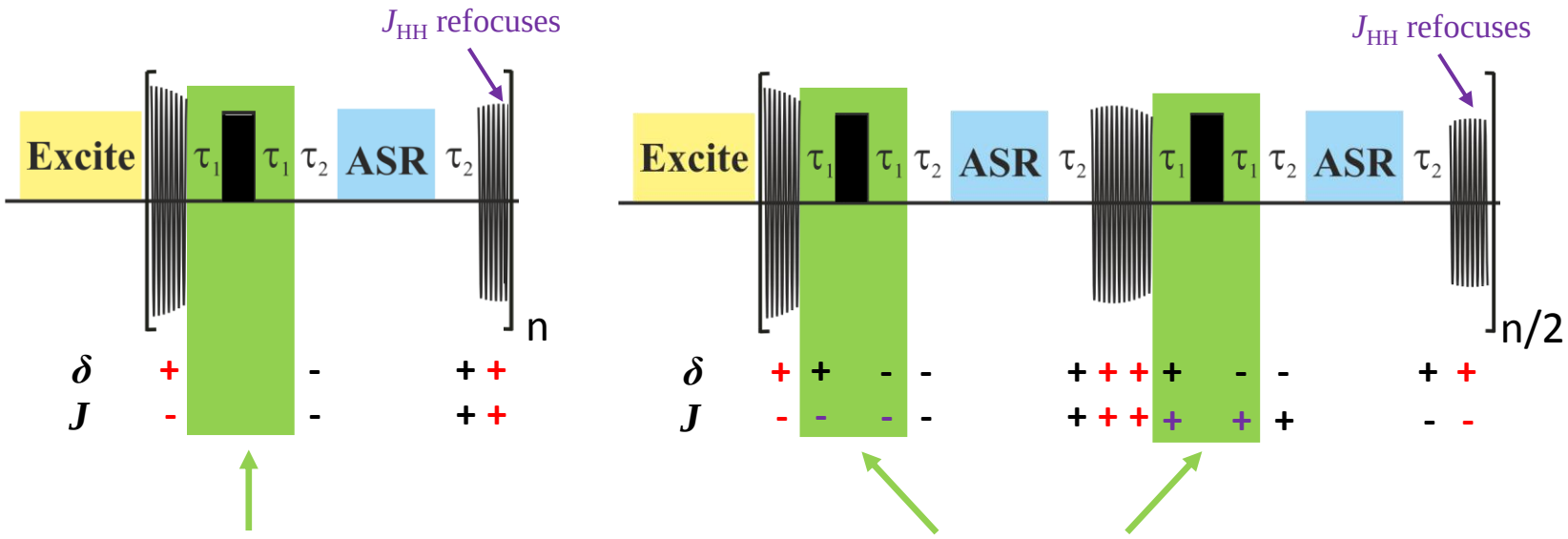
Pure shift FID acquired directly (special data processing is **NOT** needed)

Acquiring pure shift data in chunks of duration τ_c gives rise to *J*-sidebands with a spacing $1/\tau_c$ in the spectrum

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

Real-time pure shift experiments – 1D acquisition

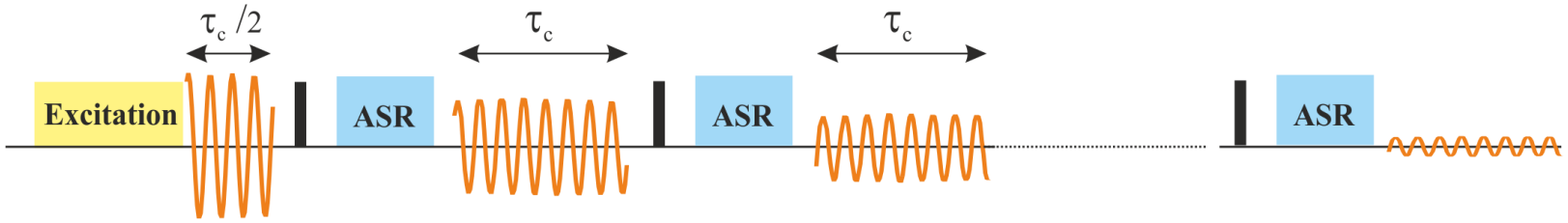
J-refocussing in real time



If τ_1=0
J_{HH} is refocused
at the midpoint
of each chunk
(except the first one)

If $\tau_1 \neq 0$
J_{HH} is refocused
at the midpoint
of every other chunk

Resolution in real-time pure shift spectra



Digital resolution

Increasing the number of chunks

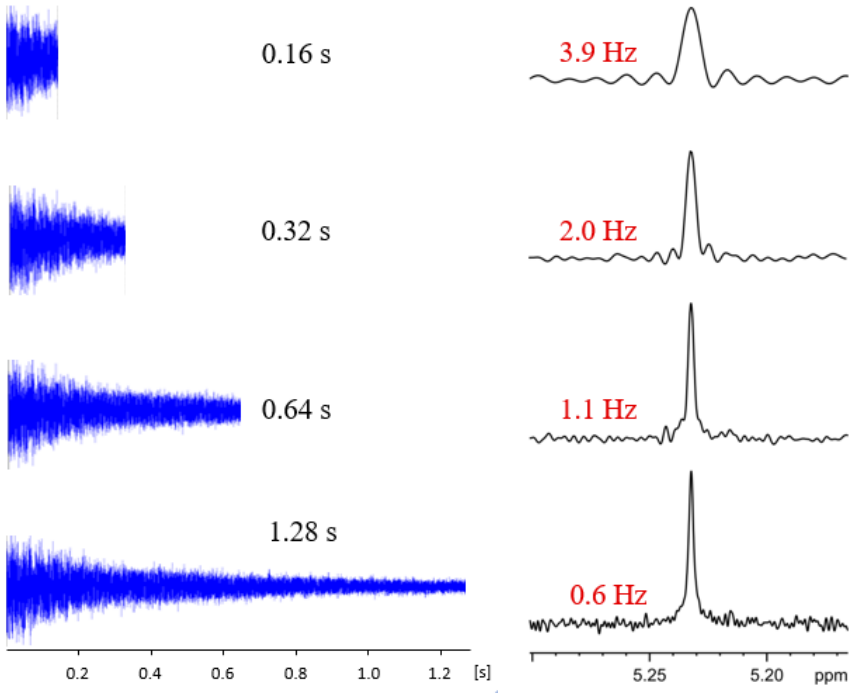
↓

Improves digital resolution

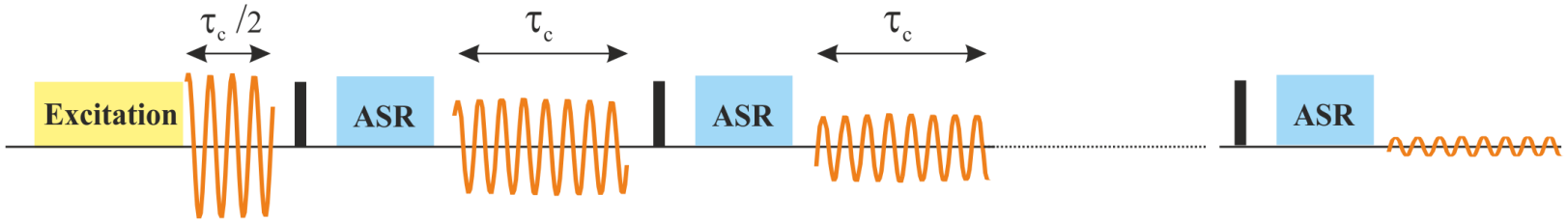
↓

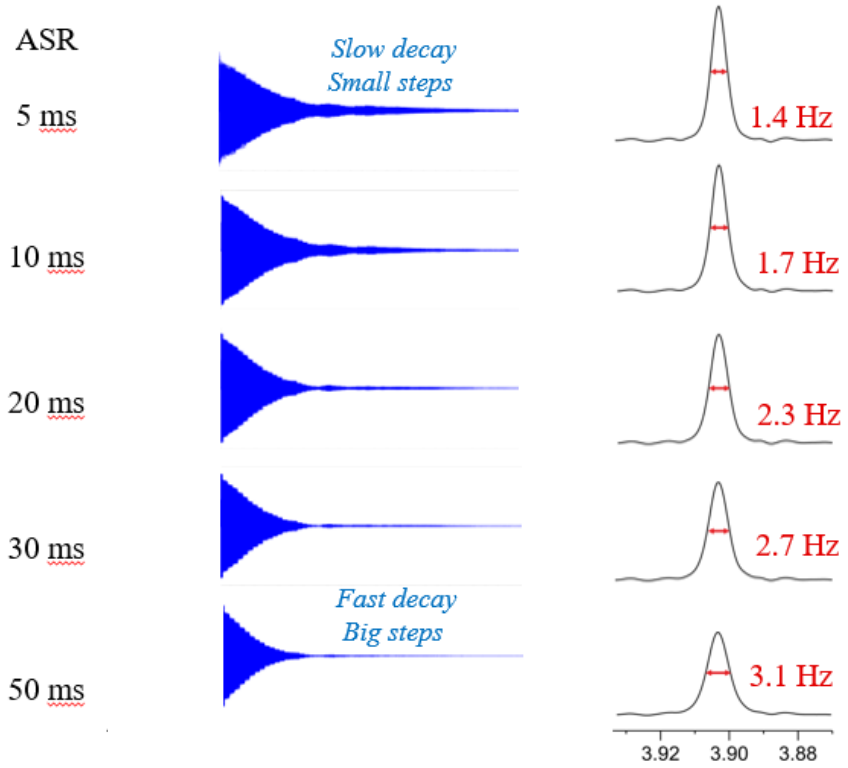
Problems with irreproducibility from chunk to chunk occurs

number of chunks	number of FID points	length of the FID	line-width at half height
8	3200	0.16 s	3.9 Hz
16	6400	0.32 s	2.0 Hz
32	12800	0.64 s	1.1 Hz
64	25600	1.28 s	0.6 Hz



Resolution in real-time pure shift spectra





Signal resolution

Longer *J*-refocusing (ASR) elements

↓

More signal loss by relaxation

↓

FID to decay faster (broader signals)

+

Generates discontinuity from chunk to chunk (bigger chunking artefacts)

Pros and cons

Interferogram approach

- A set of experiments
- Low SNR /experiment time
- Special data processing
- Chunking artefacts
- Smooth FID decay
- High spectral quality

Real-time approach

- A single experiment
- High SNR /experiment time
- Direct Fourier transformed
- Chunking artefacts
- FID discontinuities
- Variable spectral quality

Pure shift key ideas

J-refocussing element

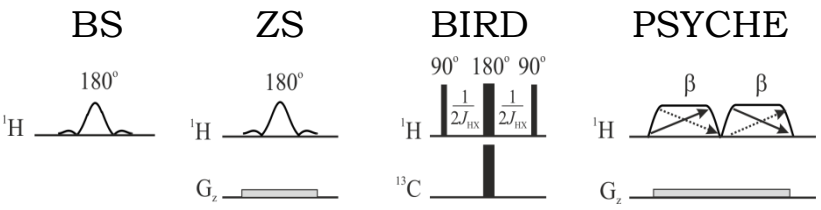
J_{HH} is refocused while δ_H evolves
(for active spin only)

Chunking data acquisition

Chunk duration (τ_c) << $1/J_{HH}$
J_{HH} refocused in the middle

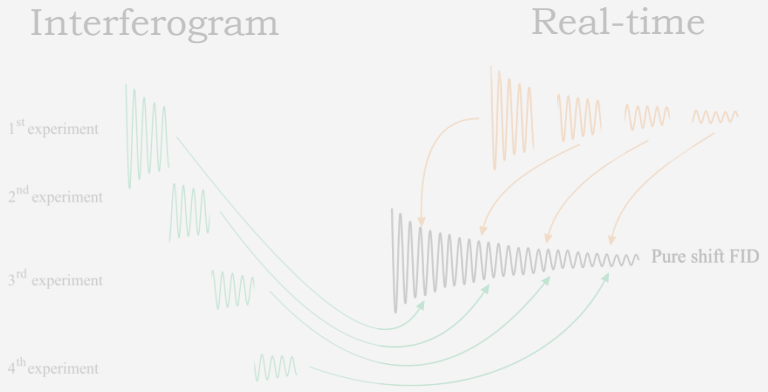
Pure shift methods

Active spin refocussing



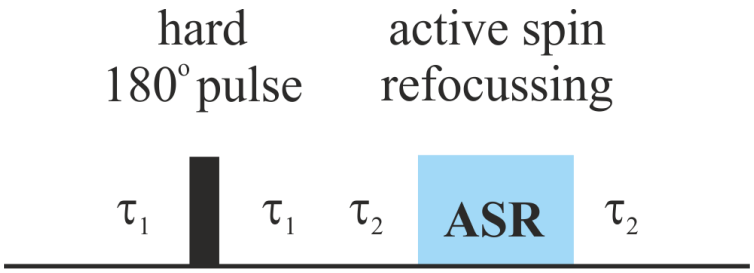
Divides the spins into *active* (observed) and *passive* spins (non observed)

Acquisition methods

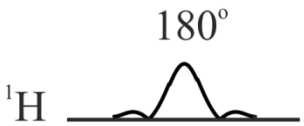


Active spin refocussing (ASR) elements

Divides the spins into *active* (observed) and *passive* spins (non observed)

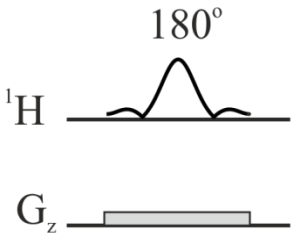


Band-selective



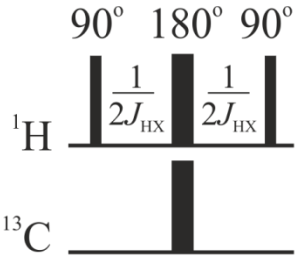
Shift selective
180° rotation

Zangger-Sterk



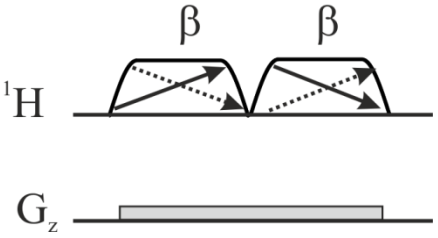
Slice and shift
selective
180° rotation

BIRD



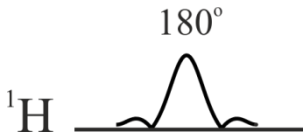
180° rotation
of protons
coupled to ^{13}C

PSYCHE

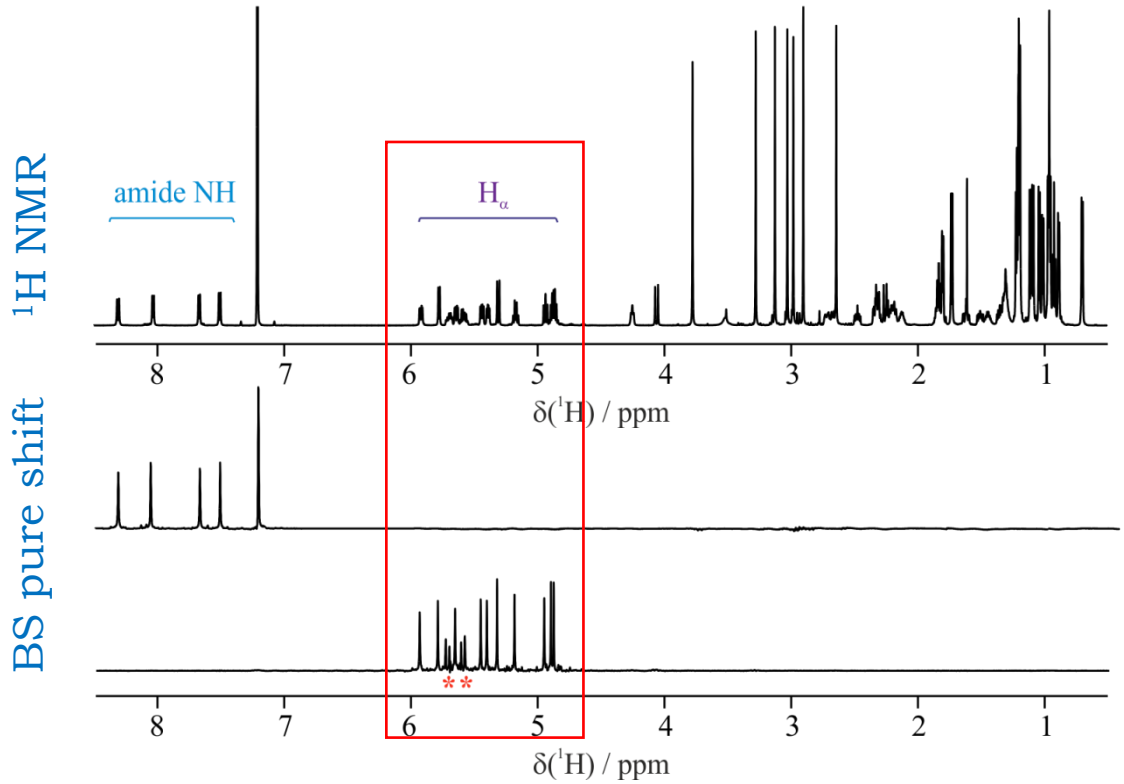


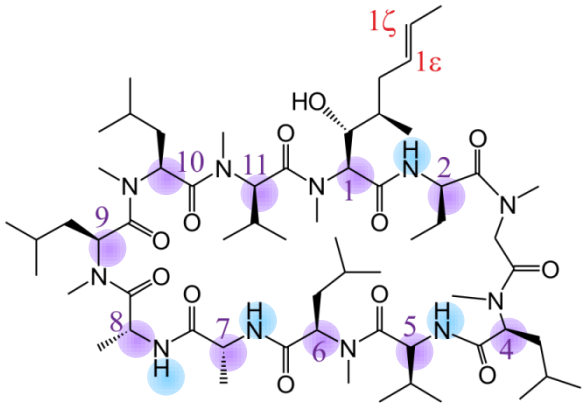
Flip a fraction
$\sin^2\beta$ of spins

Band-selective – BS, HOBS, BASH and BASHD



- The selective 180° pulse refocuses only protons within its bandwidth (*active* spins)
- One (frequency selection) or several resonances (band-selection or multiple-frequency selection) can be homodecoupled

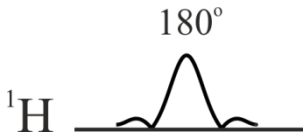




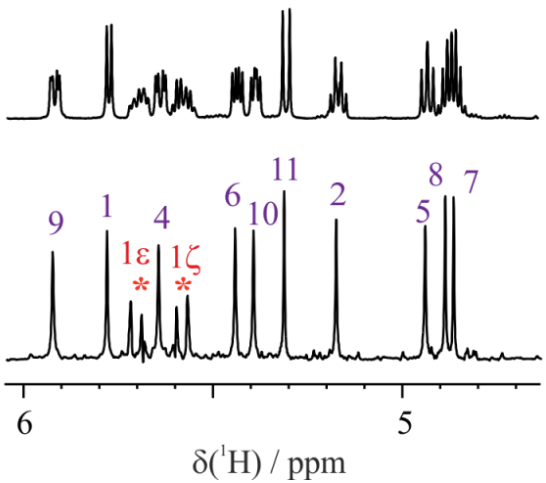
Cyclosporine

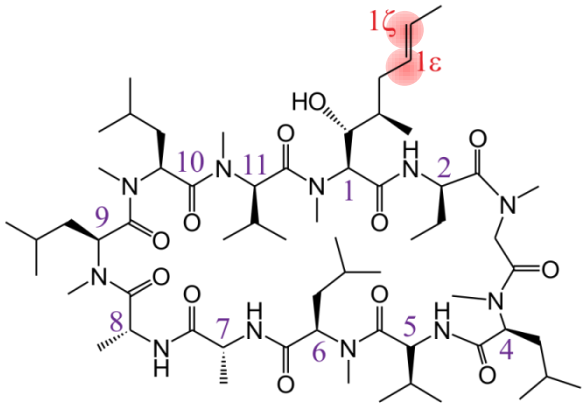
Chem. Eur. J. **19**, 17283 (2013); *J. Magn. Reson.* **241**, 97 (2014); *Chem. Commun.* **50**, 25127 (2014)

Band-selective – BS, HOBS, BASH and BASHD



- The selective 180° pulse refocuses only protons within its bandwidth (*active* spins)
- One (frequency selection) or several resonances (band-selection or multiple-frequency selection) can be homodecoupled
- Need to avoid exciting coupled protons
- Suitable for the analysis of molecules with well-separated regions (peptides and proteins) and isomeric mixtures

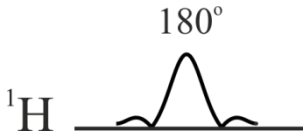




Cyclosporine

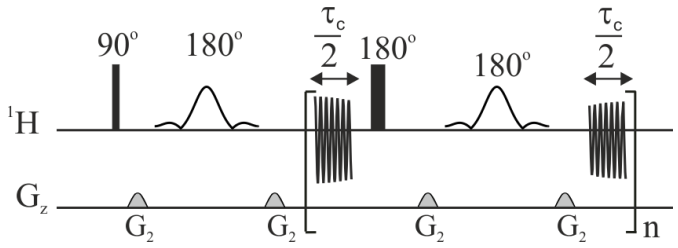
Chem. Eur. J. **19**, 17283 (2013); *J. Magn. Reson.* **241**, 97 (2014); *Chem. Commun.* **50**, 25127 (2014)

Band-selective pure shift methods

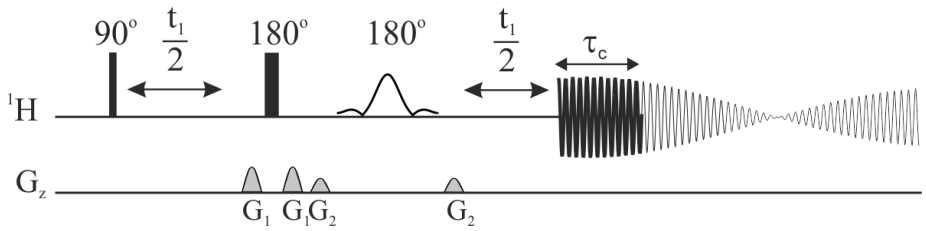


- Compatible with both real-time and interferogram acquisition

Real-time BS experiment

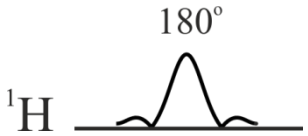


Interferogram BS experiment

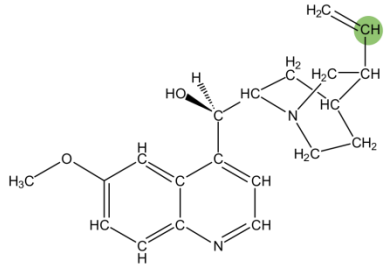


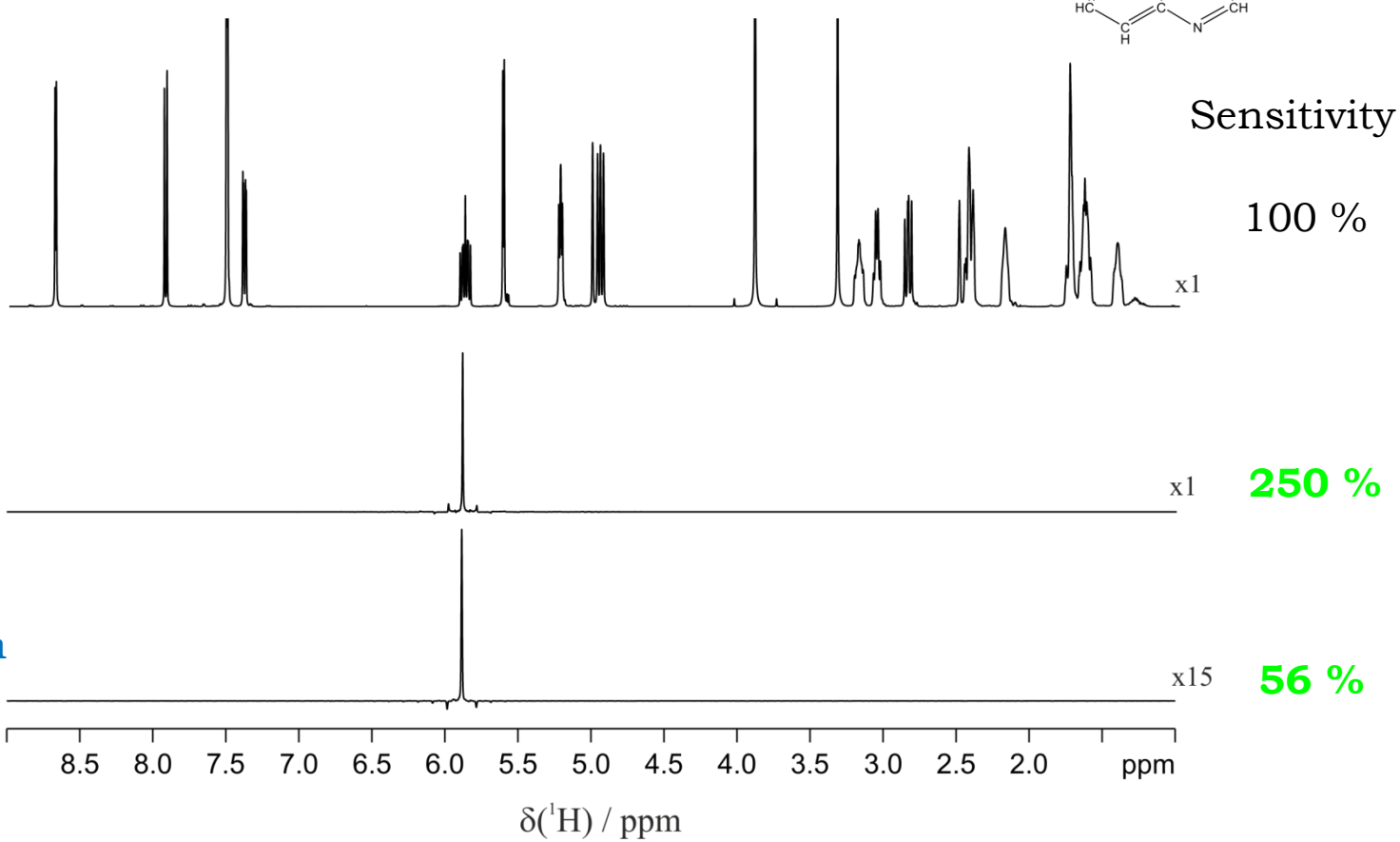
Chem. Eur. J. **19**, 17283 (2013); *J. Magn. Reson.* **241**, 97 (2014); *Chem. Commun.* **50**, 25127 (2014)

Sensitivity in band-selective pure shift spectra



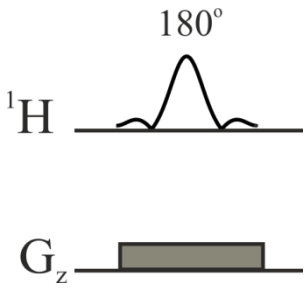
- Excellent sensitivity





Chem. Eur. J. **19**, 17283 (2013); *J. Magn. Reson.* **241**, 97 (2014); *Chem. Commun.* **50**, 25127 (2014)

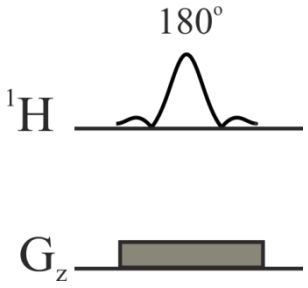
Zangger-Sterk (ZS)



- Simultaneous application of a selective 180° pulse and a weak pulse field gradient
- Slice and shift selection
- Each *active* spin is refocused in a narrow region (slice) of the sample
- Coupled spins cannot be refocused within the same slice

J. Magn. Reson. **124**, 486 (1997)

Zanger-Sterk (ZS)

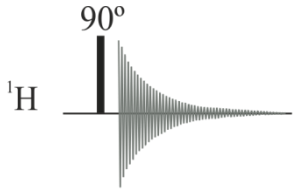


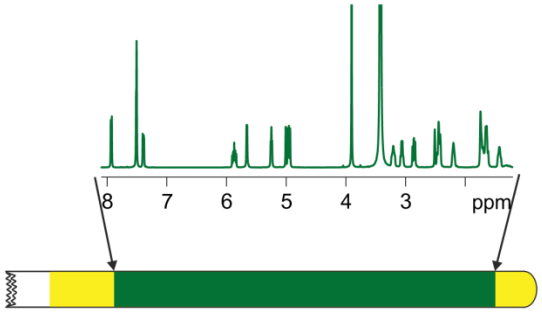
- Simultaneous application of a selective 180° pulse and a weak pulse field gradient
- **Slice and shift selection**
- Each *active* spin is refocused in a narrow region (slice) of the sample
- Coupled spins cannot be refocused within the same slice

J. Magn. Reson. **124**, 486 (1997)

Broadband excitation – shift selection – band selection

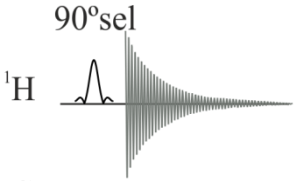
Broadband

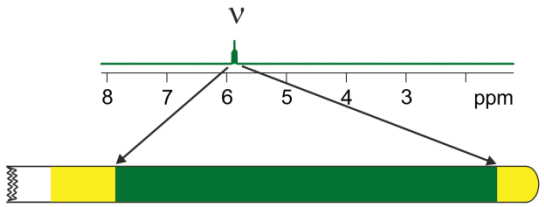




All frequencies are excited in the whole active volume

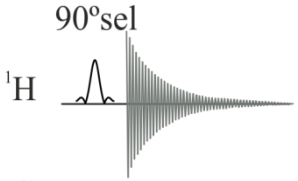
Frequency selection

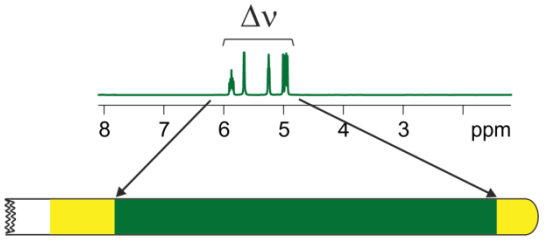




A narrow range of frequencies is excited in the whole active volume

Band selection

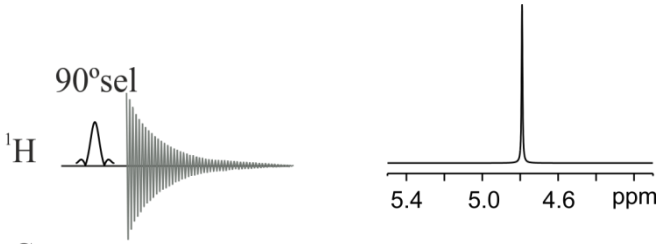


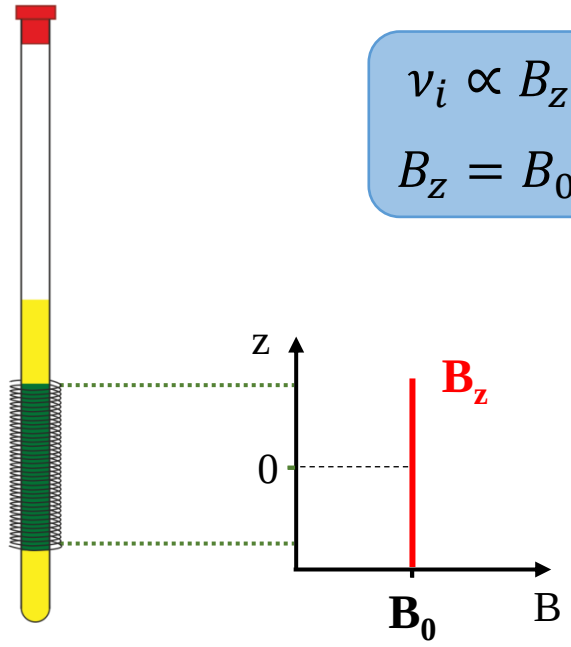


A wide range of frequencies is excited in the whole active volume

Shift selection – slice and shift selection

Shift selection

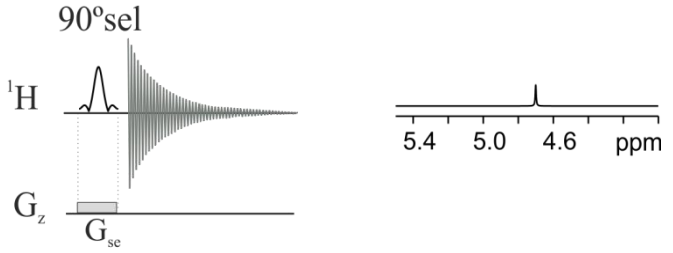


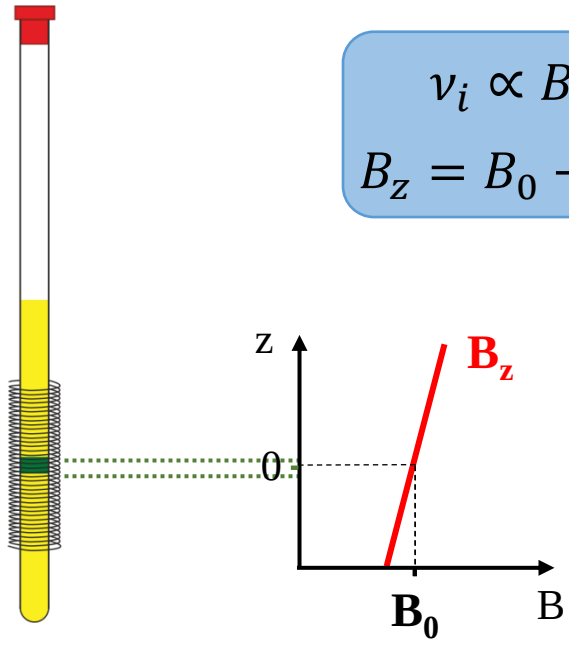


$$\nu_i \propto B_z$$
$$B_z = B_0$$

In absence of PFG B_z is constant along z-axis

Slice and shift selection



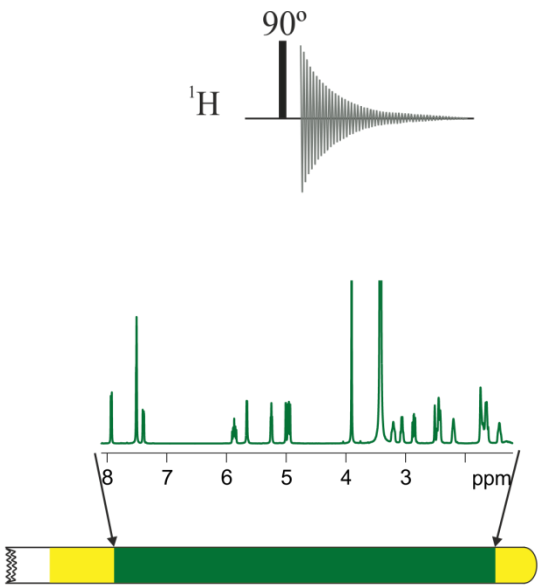


$$\nu_i \propto B_z$$
$$B_z = B_0 + zG$$

In presence of PFG B_z varies linearly along z-axis

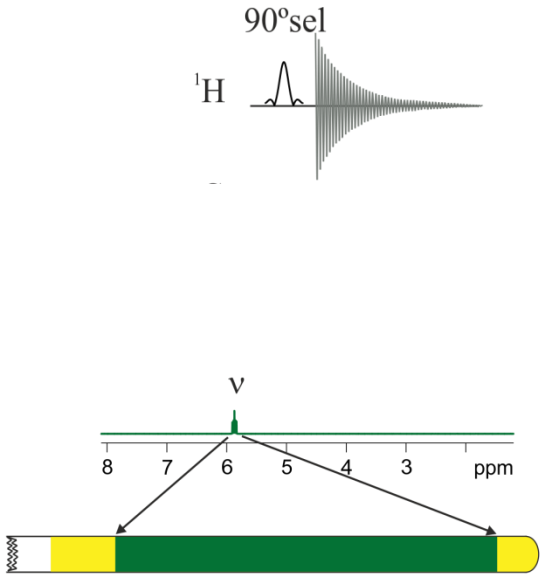
Broadband excitation – shift selection – band selection

Broadband



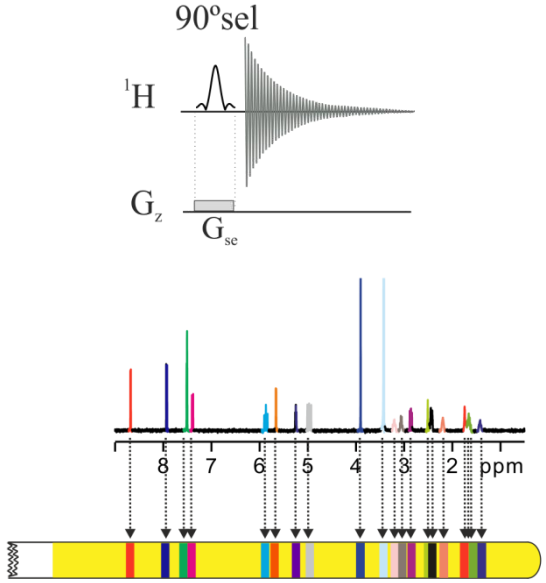
All frequencies are excited in the whole active volume

Shift selection



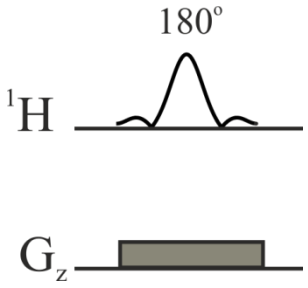
A narrow range of frequencies is excited in the whole active volume

Slice and shift selection

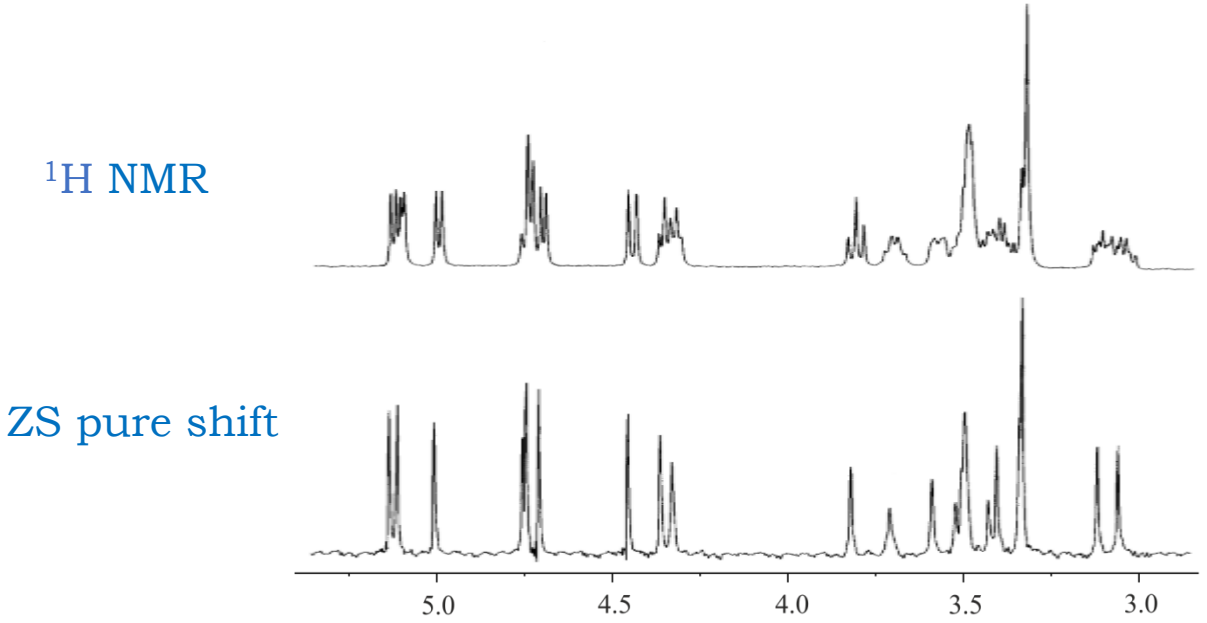


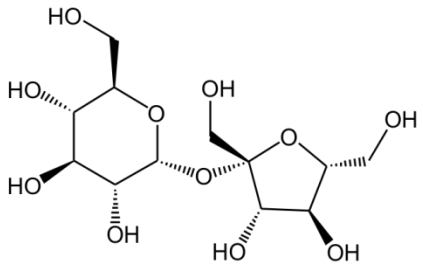
Different frequencies are excited in different parts of the active volume

Zangger-Sterk (ZS)



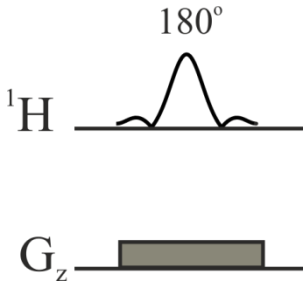
- Simultaneous application of a selective 180° pulse and a weak pulse field gradient
- Slice and shift selection
- Each active spin is excited in a narrow region (slice) of the sample
- Coupled spins cannot be refocused within the same slice
- Broadband pure shift spectrum





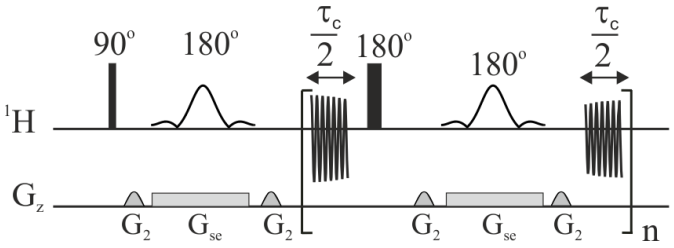
J. Magn. Reson. **124**, 486 (1997)

Zangger-Sterk pure shift methods

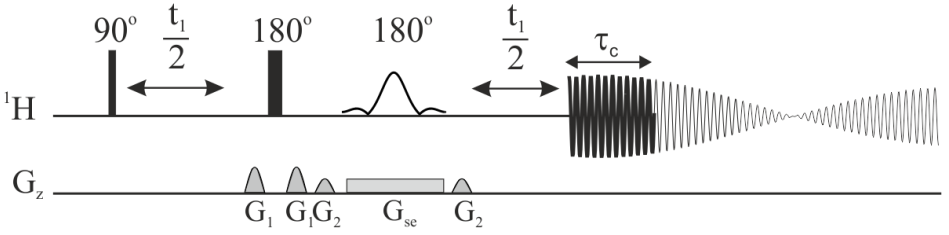


- Compatible with both real-time and interferogram acquisition

Real-time ZS experiment

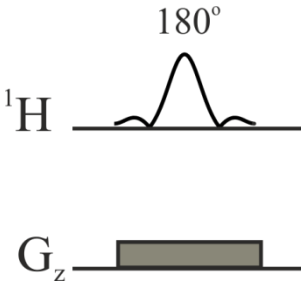


Interferogram ZS experiment

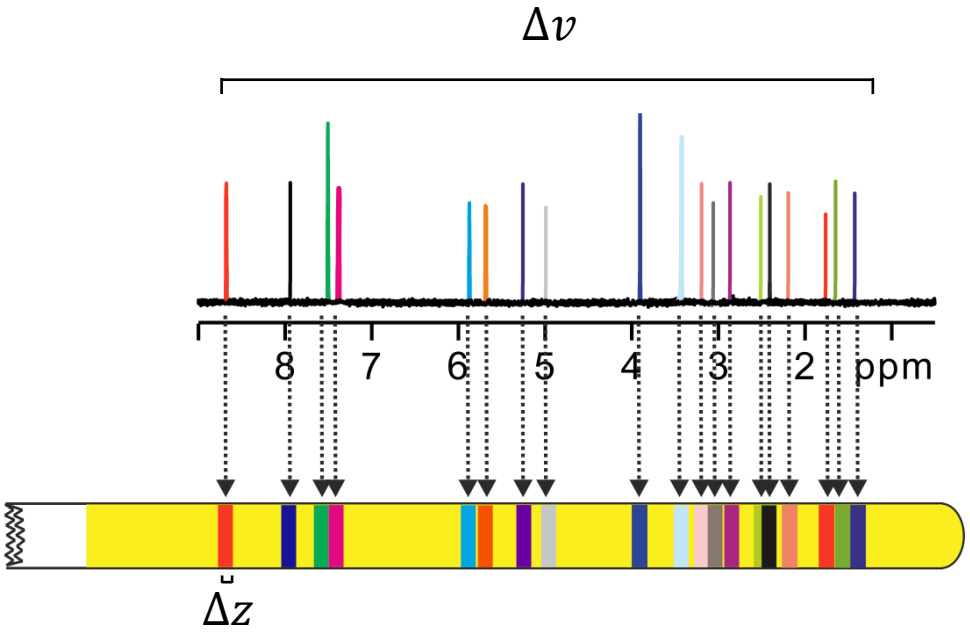


J. Magn. Reson. **124**, 486 (1997); Angew. Chem. Int. Ed. **52**, 7143 (2013)

Sensitivity in Zangger-Sterk pure shift spectra



- *Active* spins only come from a slice
- Low sensitivity
- Proportional to the slice thickness



Slice thickness:

$$\Delta z = \frac{\Delta\omega}{\gamma G}$$

Gradient strength:

$$G = \frac{\Delta v}{L\gamma}$$

Bandwidth of the selective pulse ($\Delta\omega$) dictated by the separation of the closest coupled spins

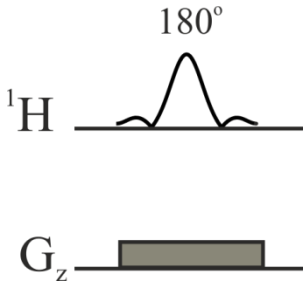
Selectivity and spectral range required will determine the sensitivity

Selectivity $\leftrightarrow$ $\Delta\omega$

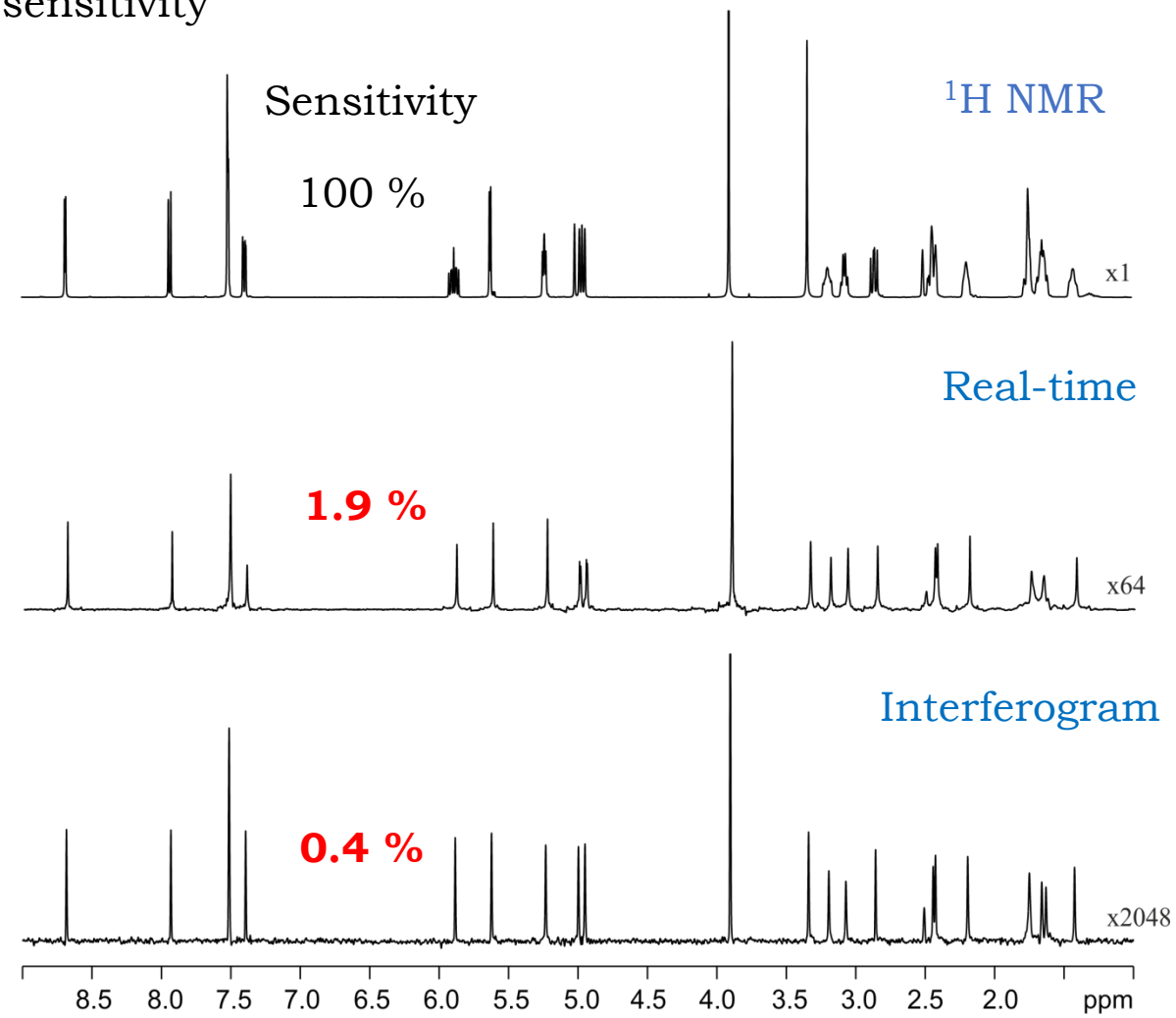
Δv $\leftrightarrow$ G

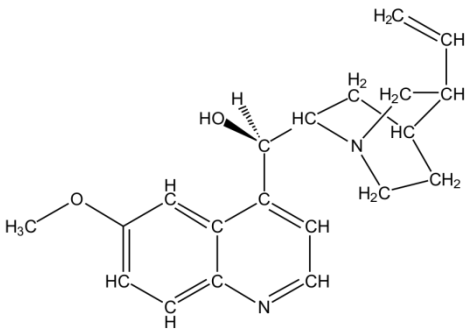
Δz $\leftrightarrow$ **SNR**

Sensitivity in Zangger-Sterk pure shift spectra

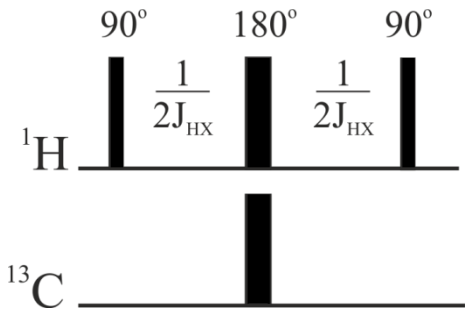


- Low sensitivity

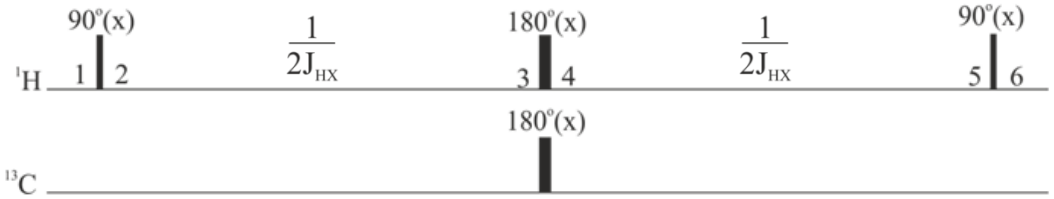


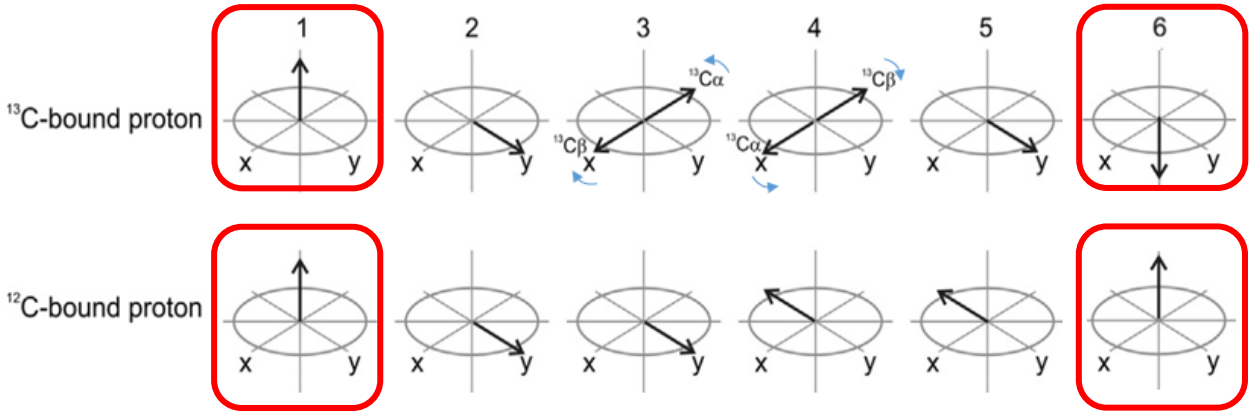


Bilinear rotation decoupling (BIRD)



- Protons are *active* if attached to ^{13}C (or ^{15}N) and *passive* if not
- BIRD^{x} inverts only protons directly coupled to ^{13}C (or ^{15}N)



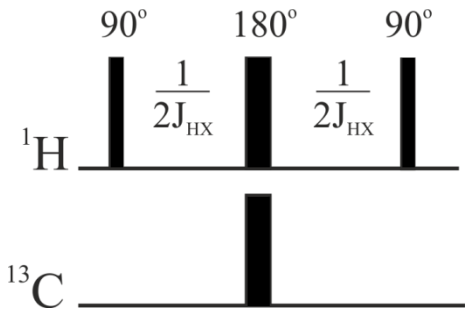


Active spins inverted

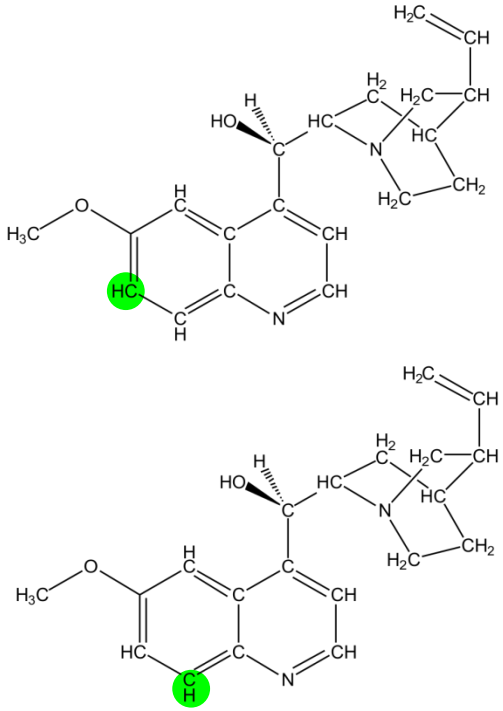
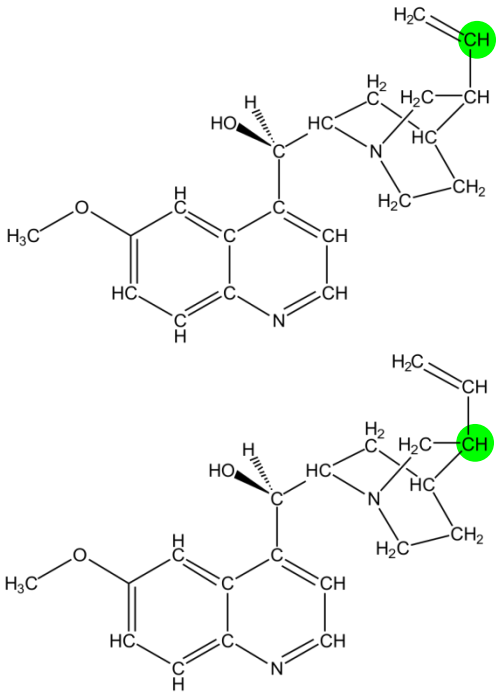
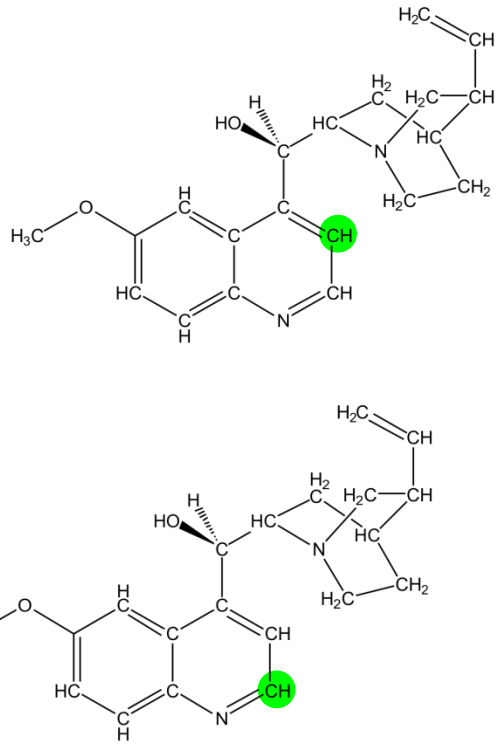
Passive spins "unaffected"

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

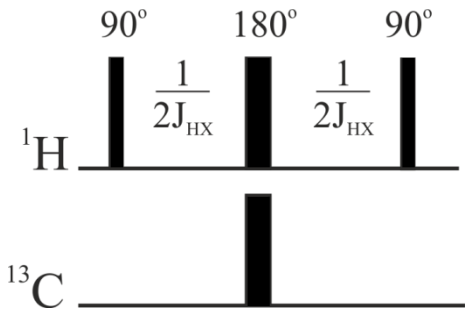
Bilinear rotation decoupling (BIRD)



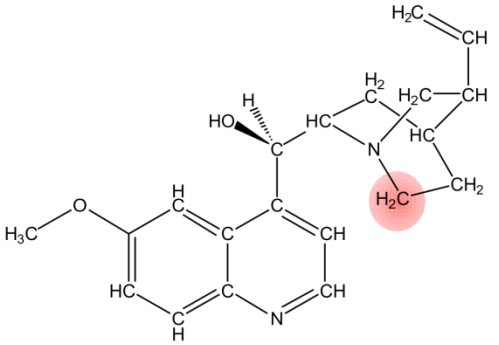
- Protons are *active* if attached to ^{13}C (or ^{15}N) and *passive* if not
- BIRD^{x} inverts only protons directly coupled to ^{13}C (or ^{15}N)
- Isotopic dilution ensures that their coupled partners are not inverted

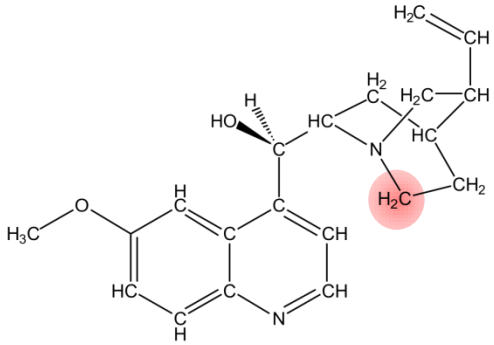




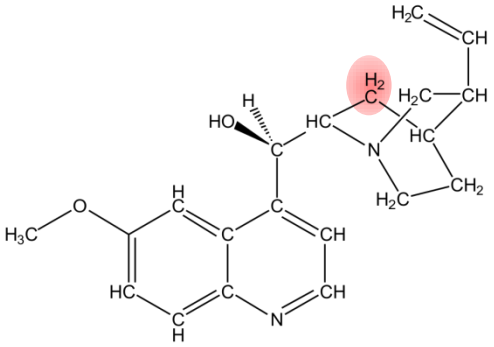
Bilinear rotation decoupling (BIRD)

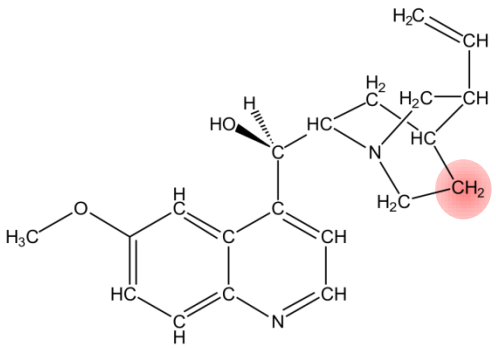


- Protons are *active* if attached to ^{13}C (or ^{15}N) and *passive* if not
- BIRD^{x} inverts only protons directly coupled to ^{13}C (or ^{15}N)
- Isotopic dilution ensures that their coupled partners are not inverted
- Protons attached to the same ^{13}C are not decoupled from one another – geminal protons appear as doublets

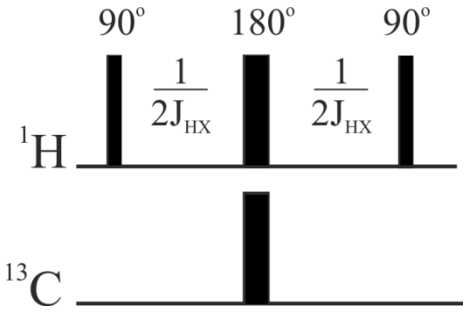








Bilinear rotation decoupling (BIRD)



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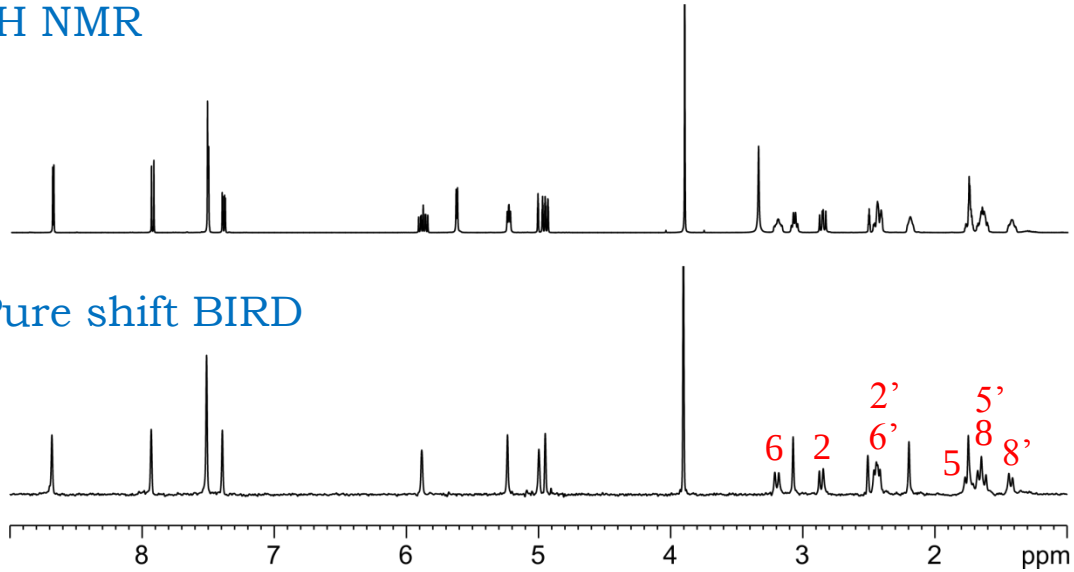
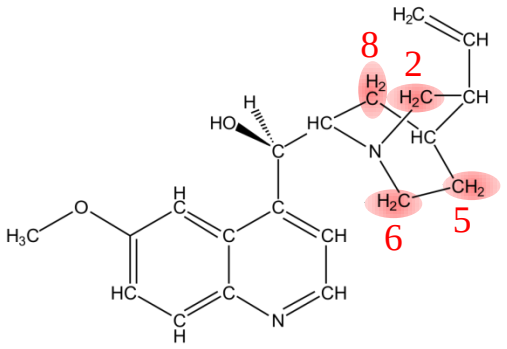
- BIRD^{x} inverts only protons directly coupled to ^{13}C (or ^{15}N)
- Isotopic dilution ensures that their coupled partners are not inverted
- Protons attached to the same ^{13}C are not decoupled from one another – geminal protons appear as doublets

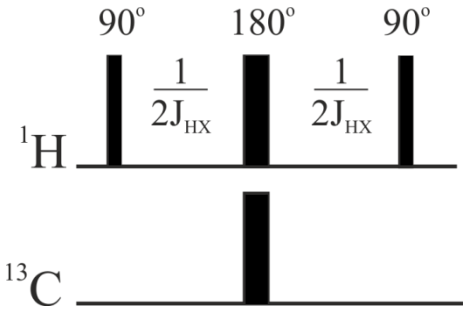
^{1}H NMR

Pure shift BIRD



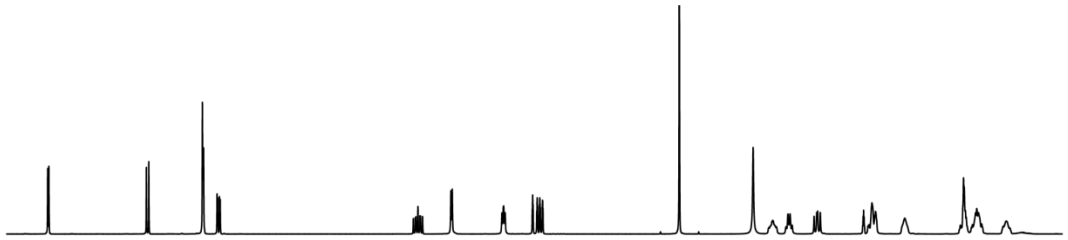


Sensitivity in BIRD pure shift spectra



- Compatible with both real-time and interferogram acquisition
- Low sensitivity
- Limited by the natural abundance at 1.1 % ^{13}C (0.37 % in ^{15}N)

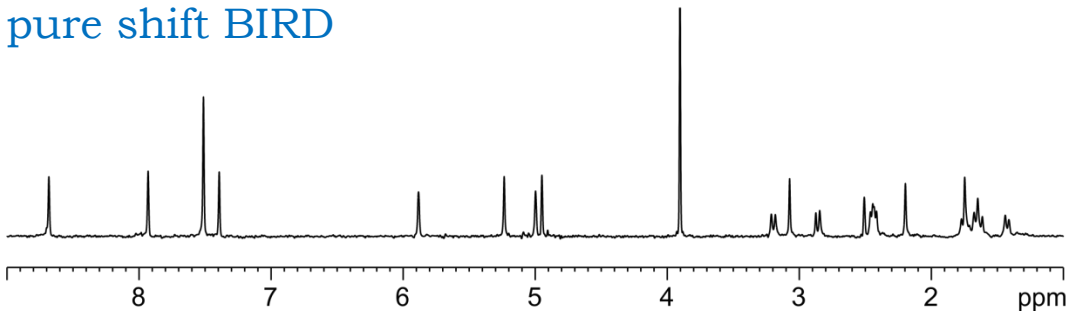
^{1}H NMR



Sensitivity

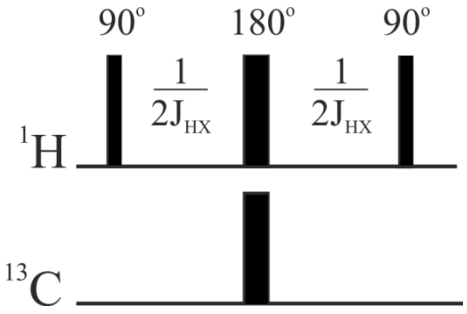
100 %

Real-time pure shift BIRD



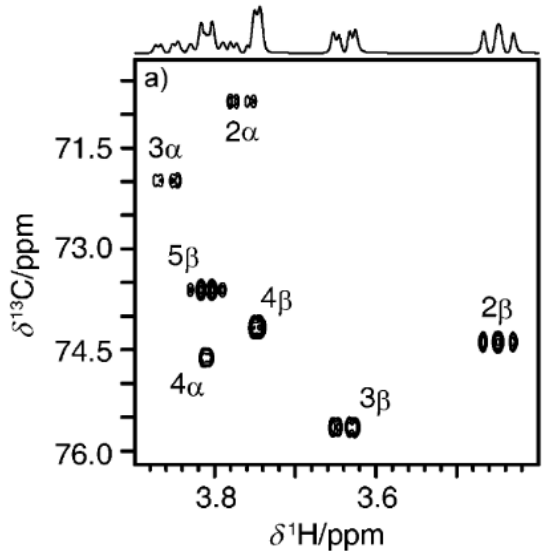
0.8 %

Sensitivity in BIRD pure shift spectra



- Compatible with both real-time and interferogram acquisition
- Low sensitivity
- Limited by the natural abundance at 1.1 % ^{13}C (0.37 % in ^{15}N)
- No sensitivity penalty in HSQC experiments

Conventional ^{1}H-^{13}C HSQC

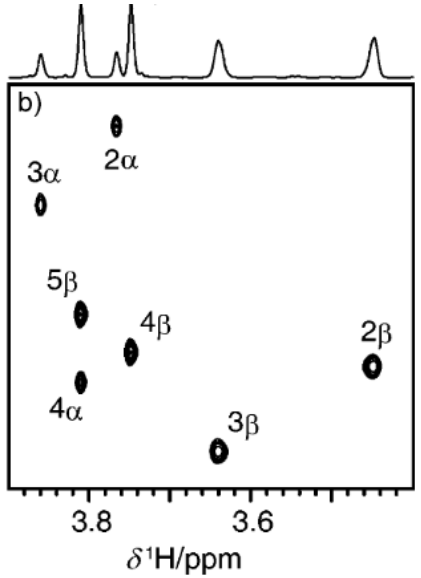


Sensitivity

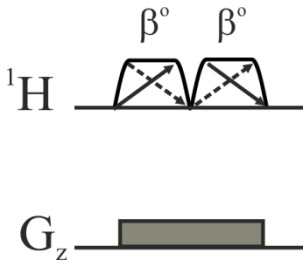
100 %

Real-time pure shift ^{1}H-^{13}C HSQC

180 %



Pure shift yield by chirp excitation (PSYCHE)



- Simultaneous application of a low-flip angle (β) saltire chirp pulse and a weak pulse field gradient
- The refocussing of the J_{HH} couplings is achieved by the simplification of coupling patters using low flip angle pulses (similar to anti-z-COSY experiment)
- Only a fraction sin2β of spins (*active* spins) are "refocused"

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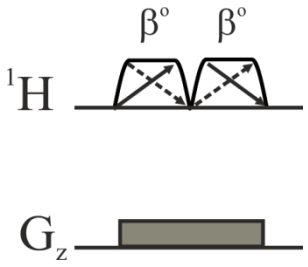
Pure shift yield by chirp excitation (PSYCHE)



- Simultaneous application of a **low-flip angle** (β) saltire chirp pulse and a weak pulse field gradient
- The refocussing of the J_{HH} couplings is achieved by the simplification of coupling patters using low flip angle pulses (similar to anti-z-COSY experiment)
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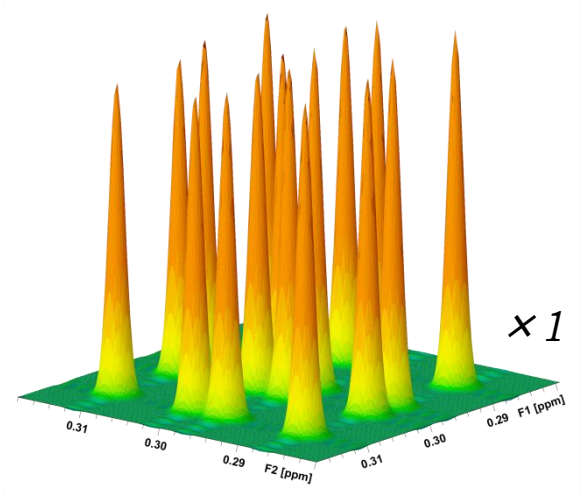
The effect of flip angle

$\beta = 90^\circ$



Diagonal: 100 %

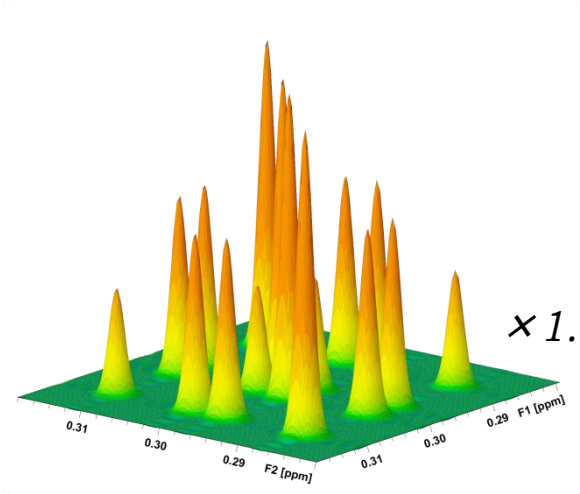
Off-diagonal: 100 %

Decoupling factor = 1

Calculations from M. Foroozandeh

The effect of flip angle

$\beta = 60^\circ$



Diagonal: 60 %

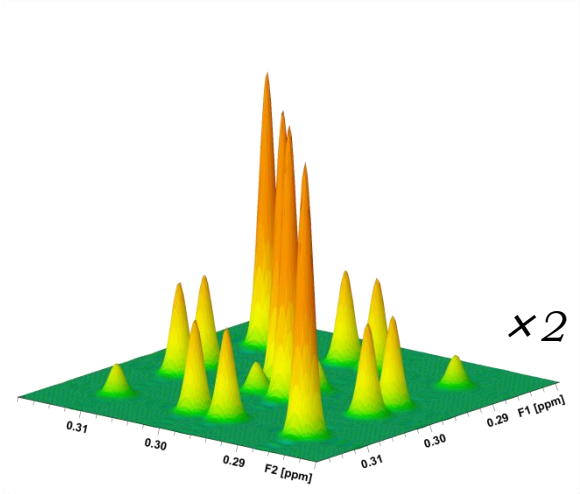
Off-diagonal: 36 %

Decoupling factor = 1.7

Calculations from M. Foroozandeh

The effect of flip angle

$\beta = 45^{\circ}$



Diagonal : 33.3 %

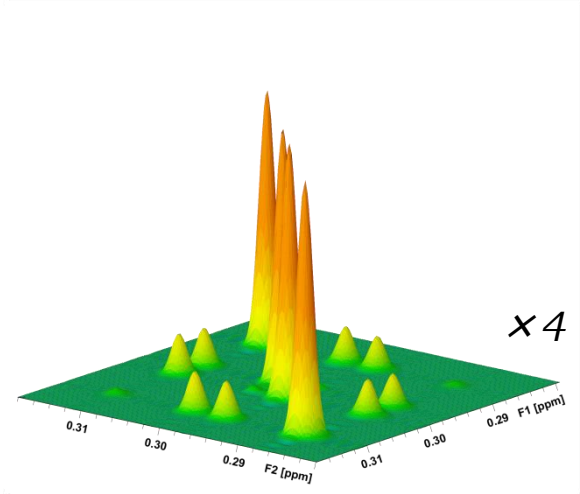
Off-diagonal : 11.1 %

Decoupling factor = 3

Calculations from M. Foroozandeh

The effect of flip angle

$\beta = 30^\circ$



Diagonal : 14.3 %

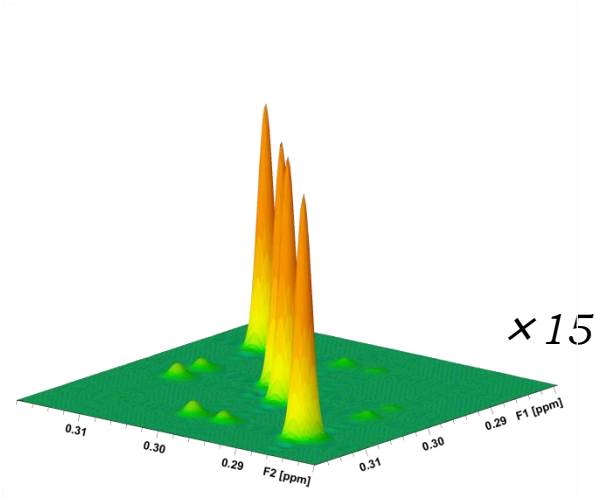
Off-diagonal : 2 %

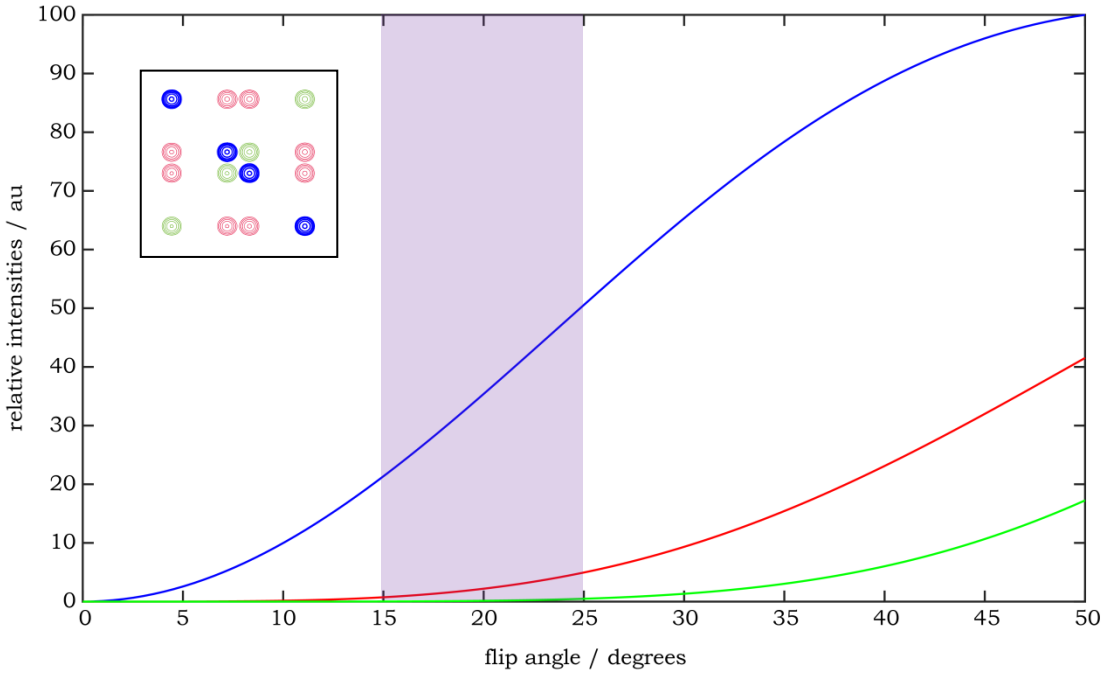
Decoupling factor = 7

Calculations from M. Foroozandeh

The effect of flip angle

$\beta = 15^\circ$





Diagonal : 3.5 %

Off-diagonal : 0.12 %

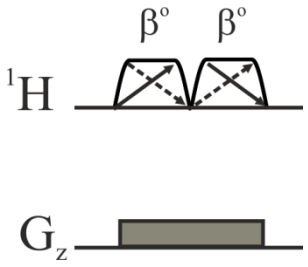
Decoupling factor = 28.6

Signal of interest
- pure shift signal

Unwanted signals
- Recoupling artefacts

Calculations from M. Foroozandeh

Pure shift yield by chirp excitation (PSYCHE)



- Simultaneous application of a low-flip angle (β) **saltire chirp pulse** and a weak pulse field gradient
- The refocussing of the J_{HH} couplings is achieved by the simplification of coupling patters using low flip angle pulses (similar to anti-z-COSY experiment)
- Only a fraction sin2β of spins (*active* spins) are "refocused"

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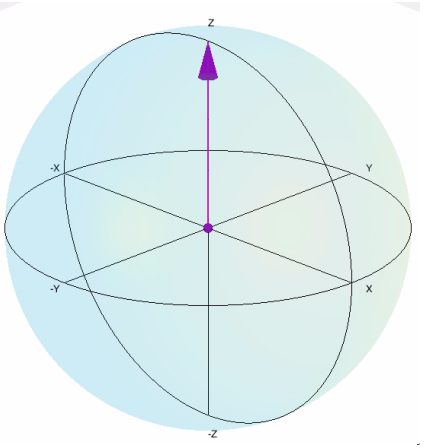
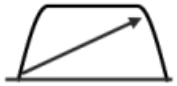
Swept-frequency (chirp) pulses

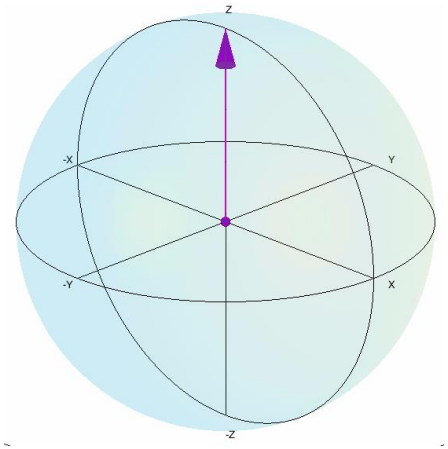
Generally they sweep the frequency across the spectral window in a linear fashion

180° chirp

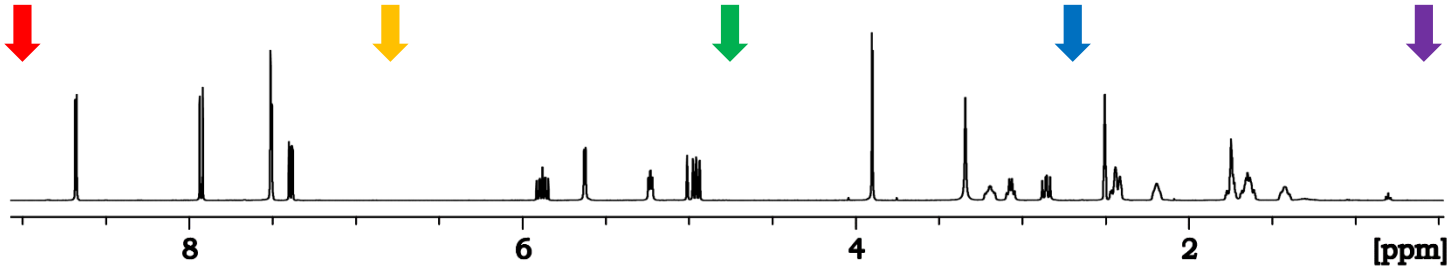


Low-flip angle chirp



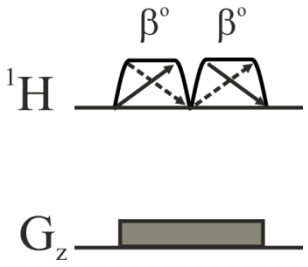


Low frequency On-resonance High frequency



Calculations from M. Foroozandeh

Pure shift yield by chirp excitation (PSYCHE)



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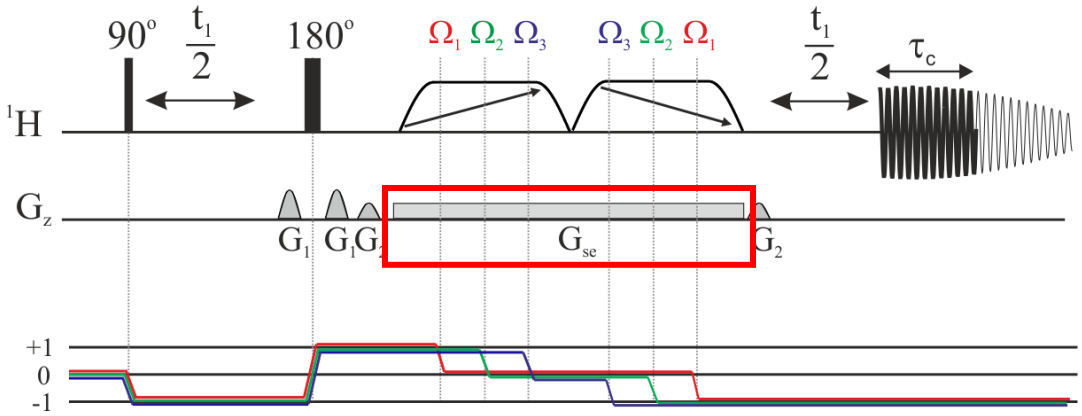
- Only a fraction sin2β of spins (*active* spins) are "refocused"



Signal of interest

- pure shift signal

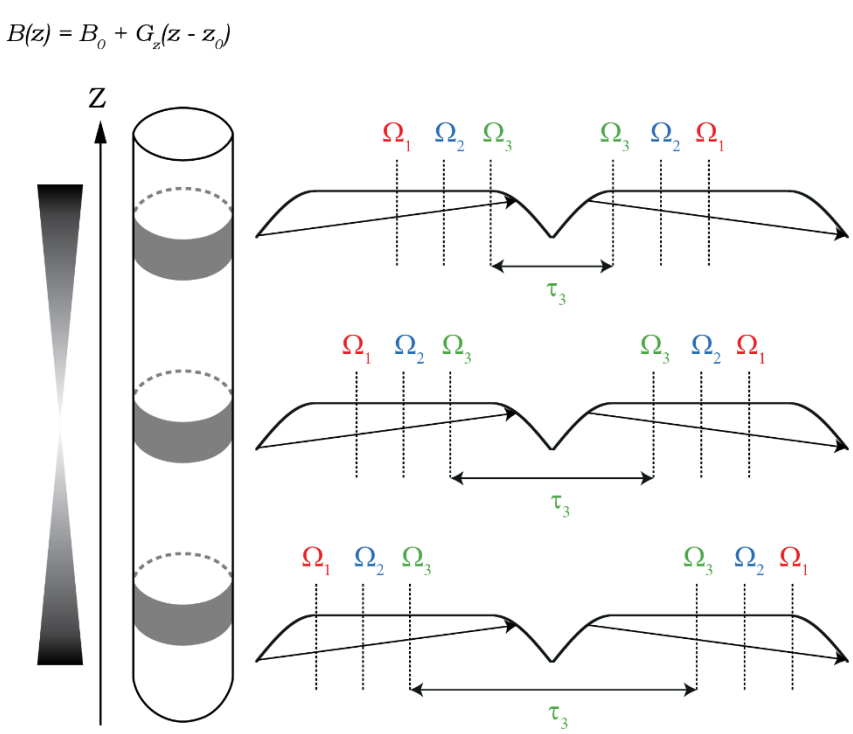
Unwanted signals

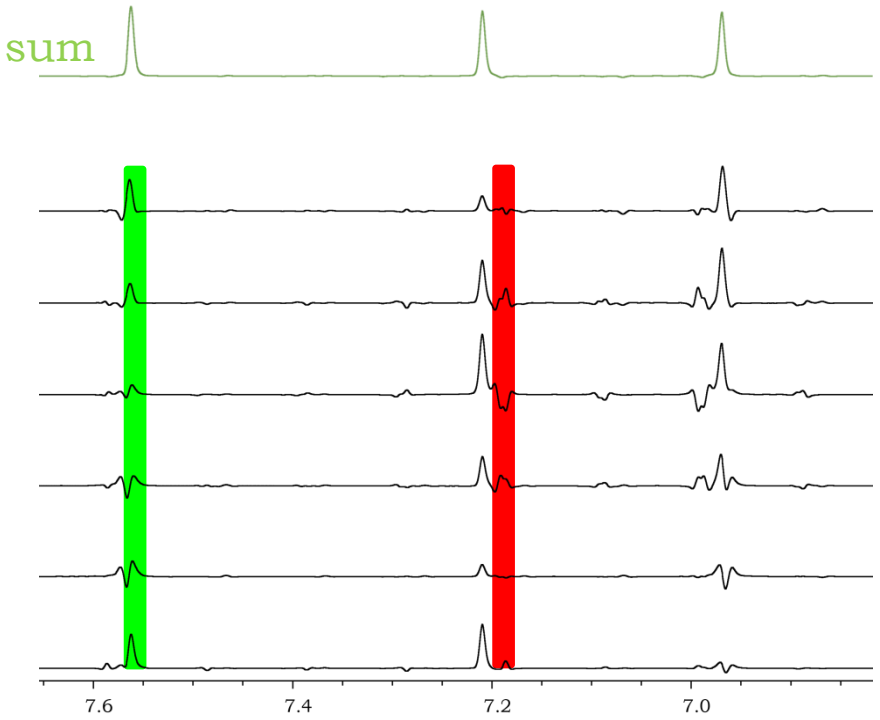
- Recoupling artef… …gnals
- Zero Quan… …gnals
- CO… …e responses
- …rong coupling signals

Spatial-temporal averaging

Spatio-temporal averaging

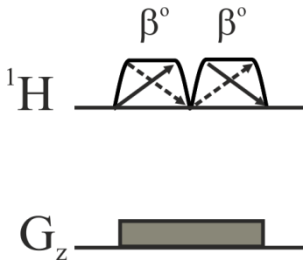
- Wanted signals (pure shift singlets) have time-invariant phase
- Unwanted signals have time-dependent phases



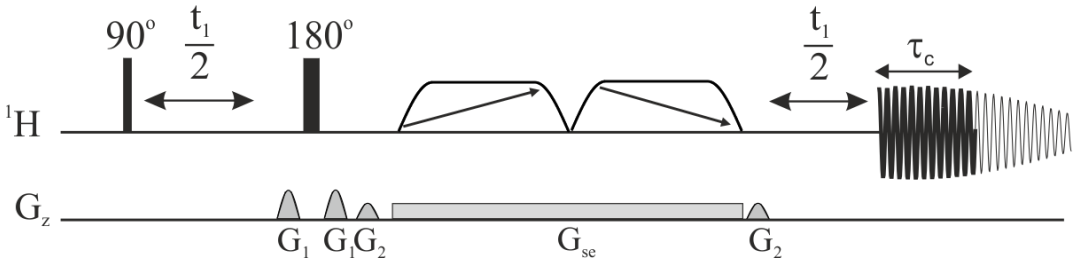


Calculations from M. Foroozandeh

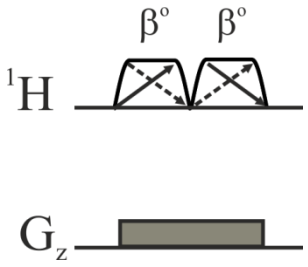
Pure shift yield by chirp excitation (PSYCHE)



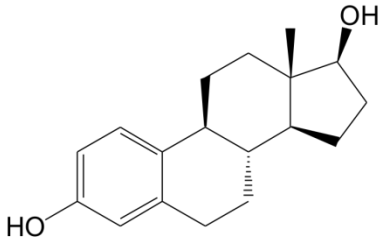
- Simultaneous application of a low-flip angle (β) saltire chirp pulse and a weak pulse field gradient
- The refocussing of the J_{HH} couplings is achieved by the simplification of coupling patters using low flip angle pulses (similar to anti-z-COSY experiment)
- Only a fraction sin2β of spins (*active* spins) are "refocused"
- Only compatible with interferogram acquisition (statistical excitation)



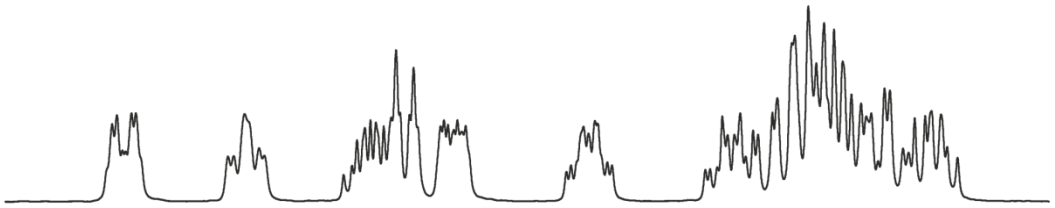
Sensitivity in PSYCHE pure shift spectra



- Sensitivity depends on the fraction of spins (*active* spins) that have been "refocused"
- It depends on the low-flip angle: sin2β



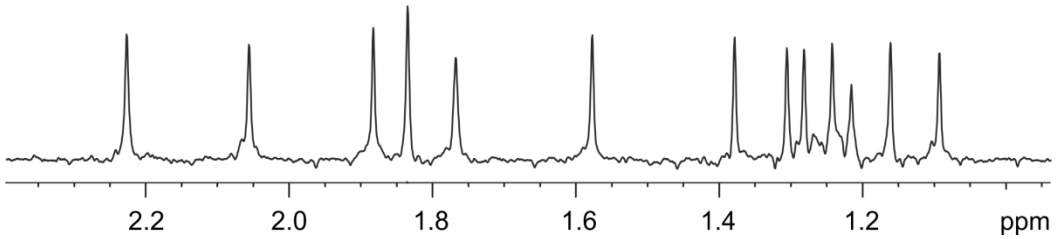
^{1}H NMR



Sensitivity

100 %

Interferogram pure shift PSYCHE

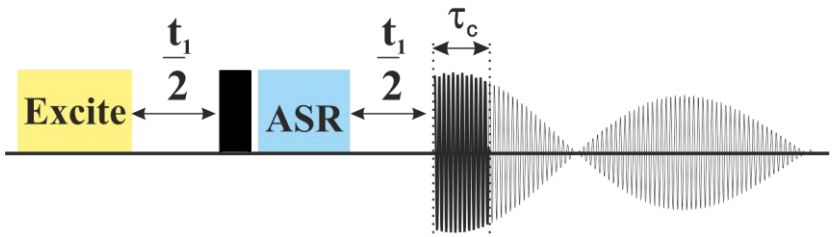


3.8 %

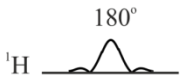
Angew. Chem. Int. Ed. **53**, 6990 (2014)

How can we combine all these elements?

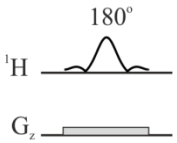
Interferogram



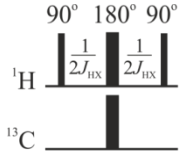
BS



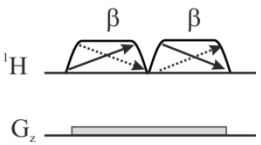
ZS



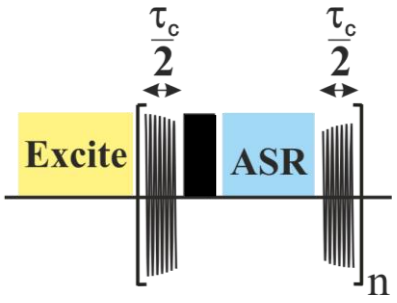
BIRD



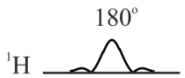
PSYCHE



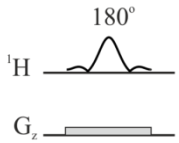
Real-time



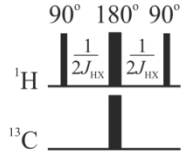
BS



ZS



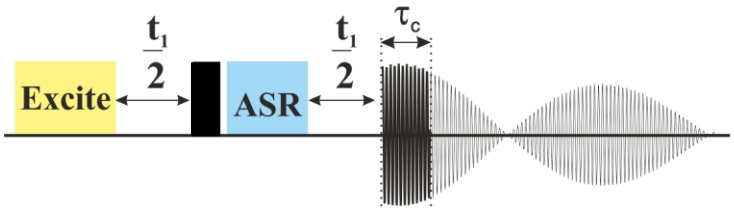
BIRD



General overview: sensitivity of each element

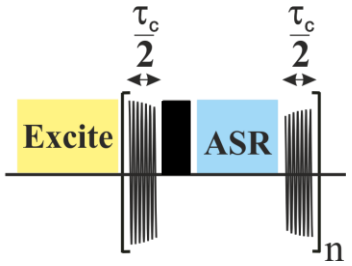
Acquisition mode

Interferogram



$$\propto \frac{1}{\sqrt{number\ of\ increments}}$$

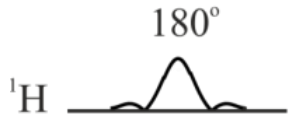
Real-time



100 %

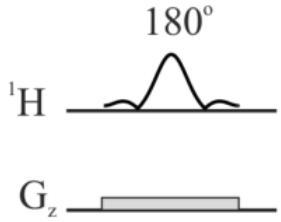
Active spin refocusing methods

BS



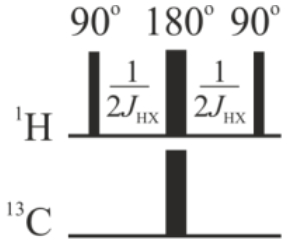
≥ 100 %

ZS



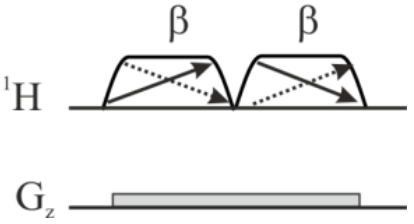
0.5 - 10 %

BIRD



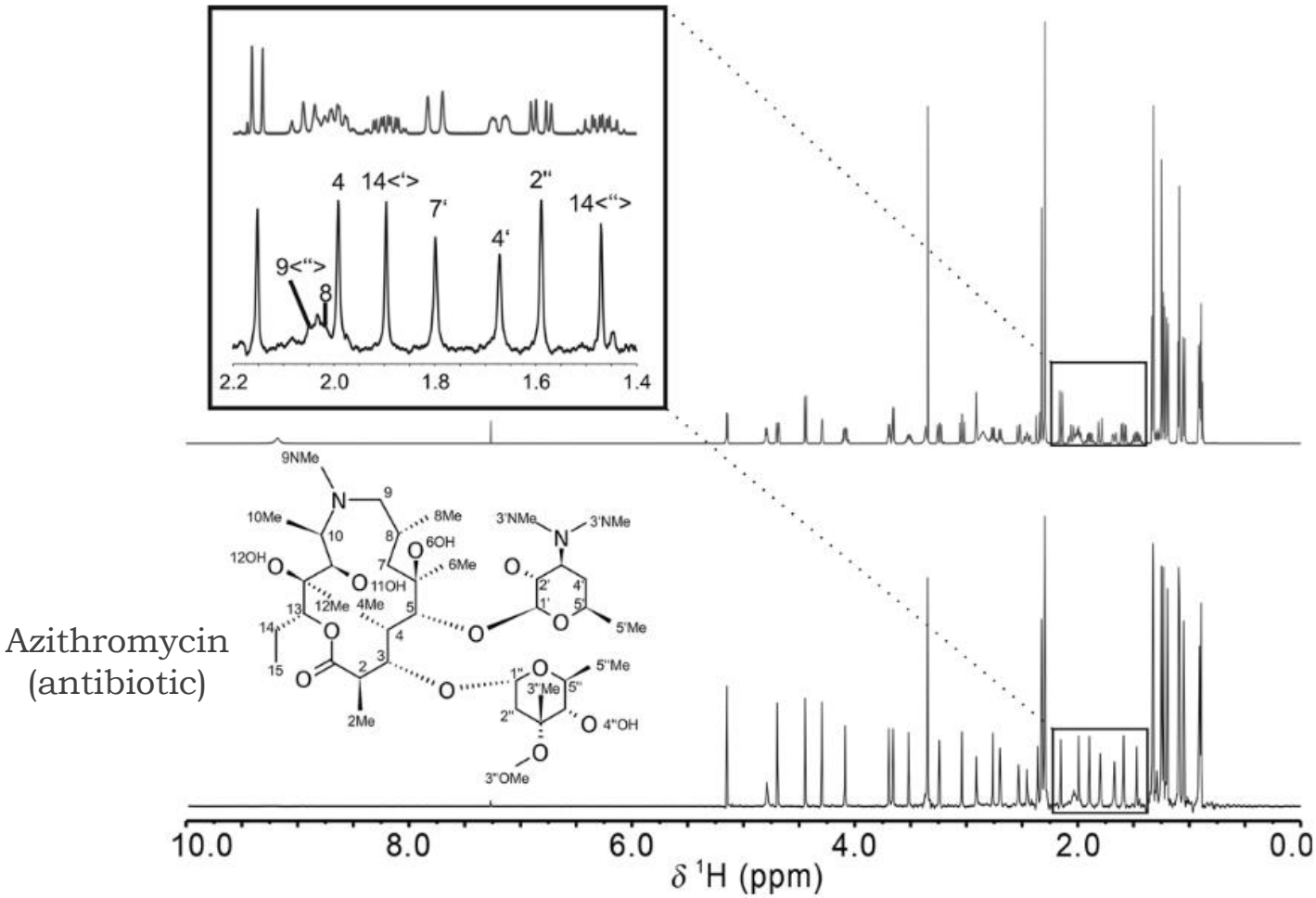
1.1 %

PSYCHE



3 - 20 %

1D pure shift NMR experiments for structure analysis of small and medium sized molecules



Azithromycin (antibiotic)

Conventional ^{1}H NMR

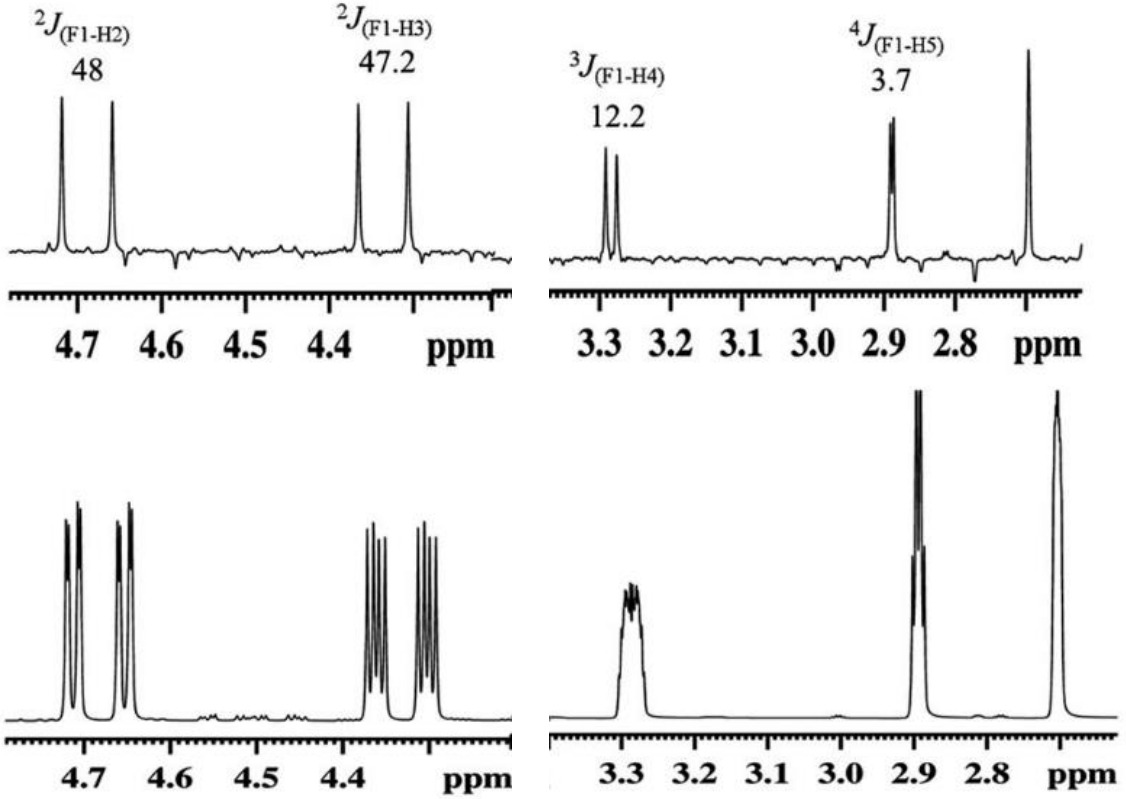
Pure shift real-time ZS

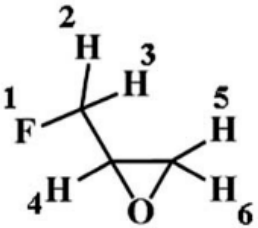
Angew. Chem. Int. Ed. **52**, 7143 (2013)

1D Pure shift NMR experiments for fast and accurate extraction of heteronuclear coupling constants

Pure shift interferogram ZS

Conventional ^{1}H NMR

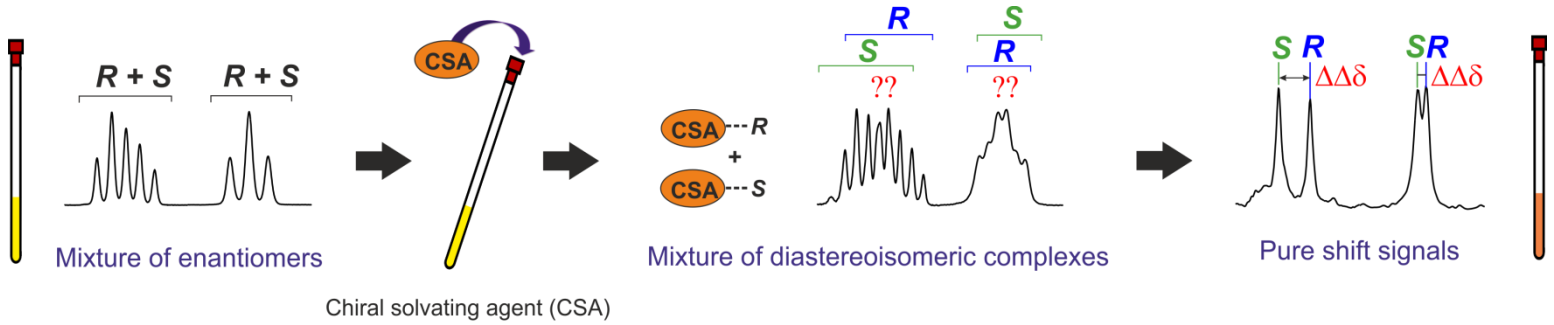




Epifluorohydrin

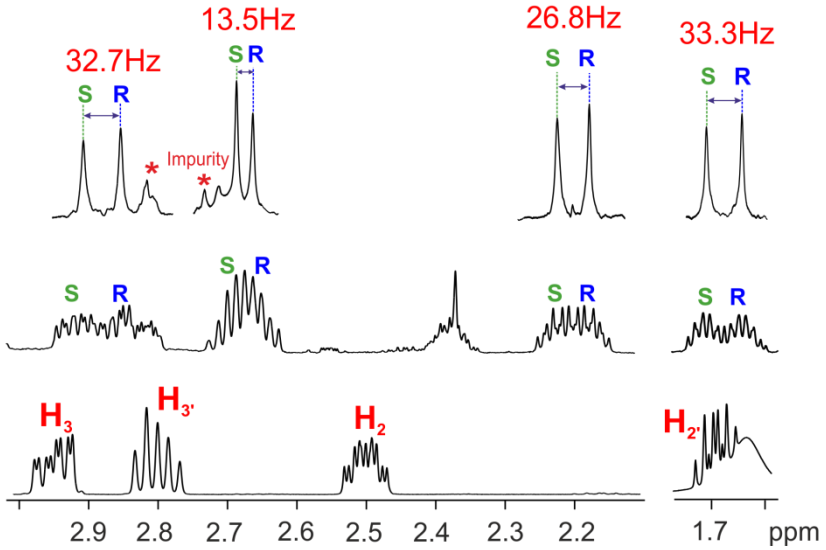
RSC Adv. **4**, 15018 (2014)

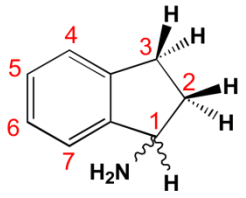
1D pure shift NMR experiments for enantiomer and diastereomer studies



Pure shift real-time BS

Conventional ^{1}H NMR





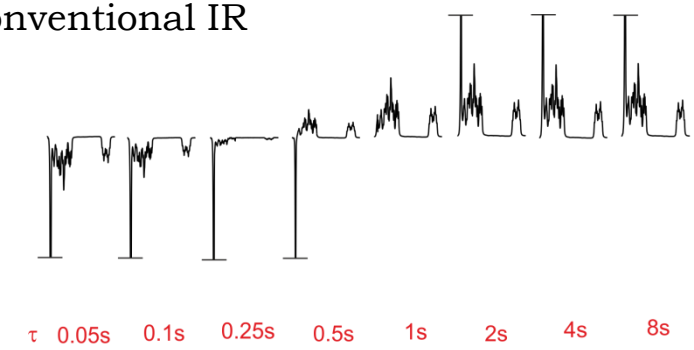
1- aminoindan (racemic mixture)

ChemPhysChem **15**, 854 (2014)

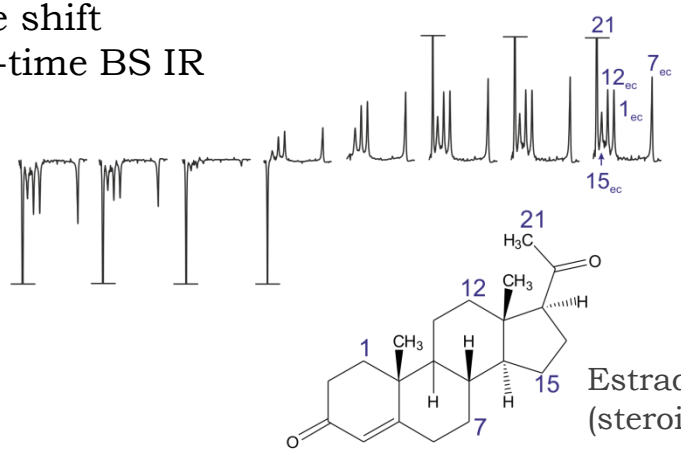
Pure shift NMR experiments to measure relaxation times in overlapped regions

Inversion-Recovery: T_1 measurement

Conventional IR



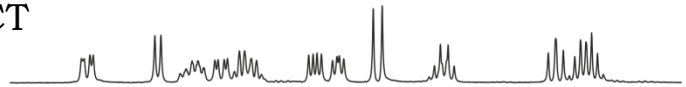
Pure shift
real-time BS IR



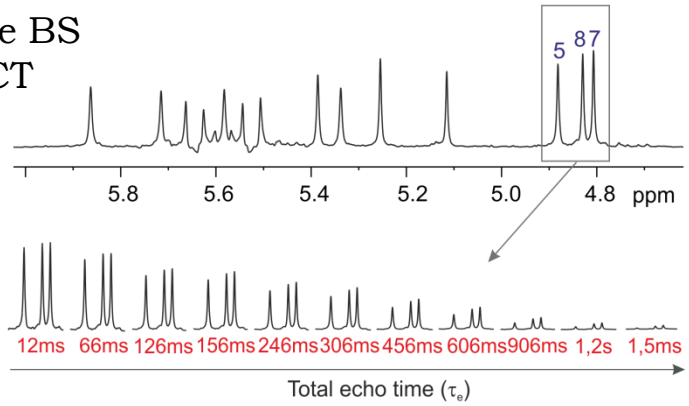
Estradiol
(steroid)

PROJECT: Determining T_2 measurement

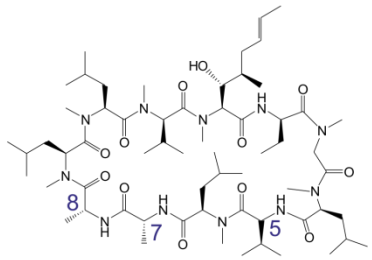
Conventional
PROJECT



Pure shift
real-time BS
PROJECT

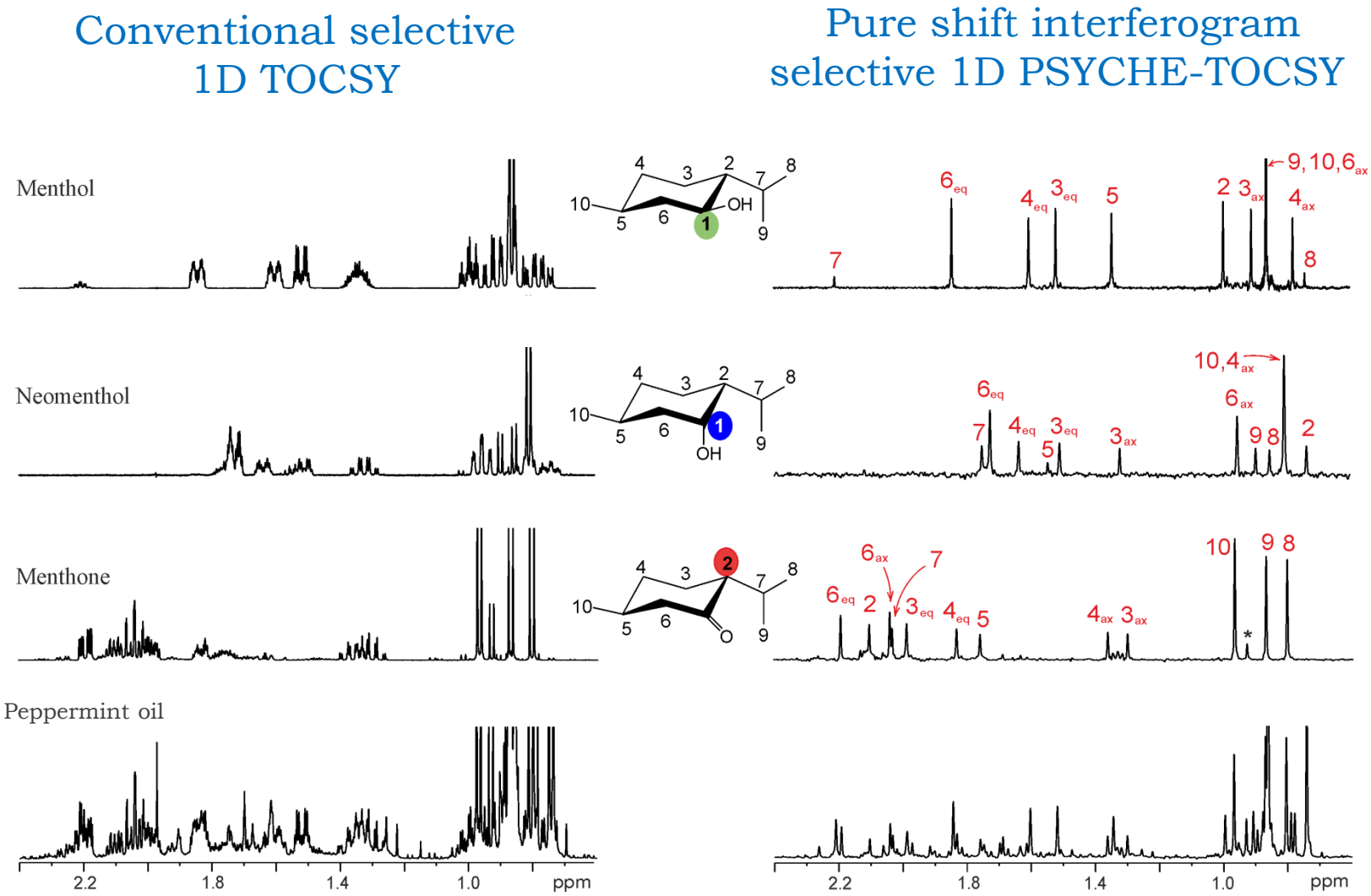


Cyclosporine A
(peptide)



J. Magn. Reson. **244**, 30 (2014)

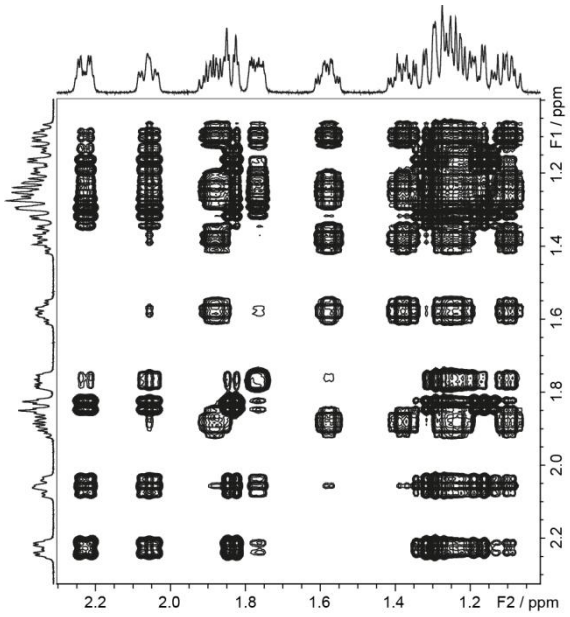
1D pure shift NMR experiments for the study of complex mixtures



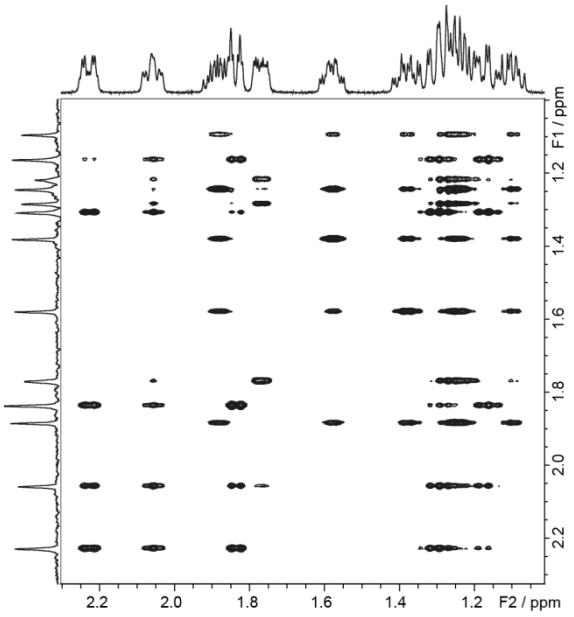
RSC Adv. **6**, 100063 (2016)

Homonuclear 2D pure shift NMR experiments for structure analysis of small and medium sized molecules

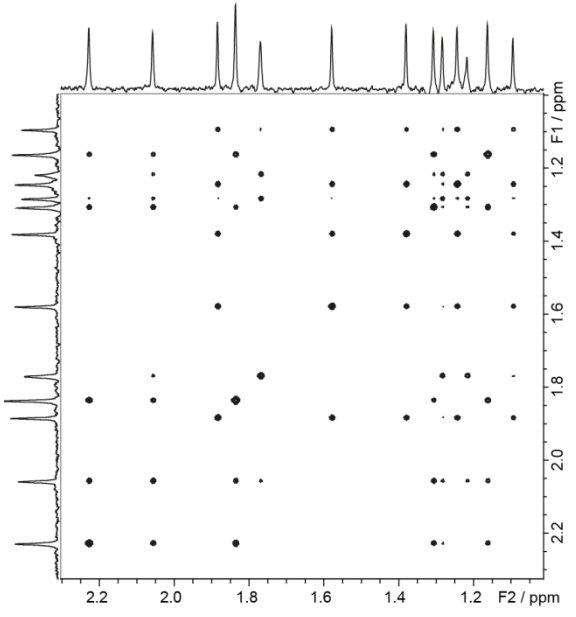
Conventional TOCSY

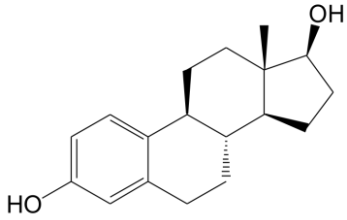


Pure shift F_1-PSYCHE TOCSY



Pure shift F_1-PSYCHE TOCSY and indirect covariance processing





Estradiol (steroid)

J. Am. Chem. Soc. **136**, 11867 (2014)

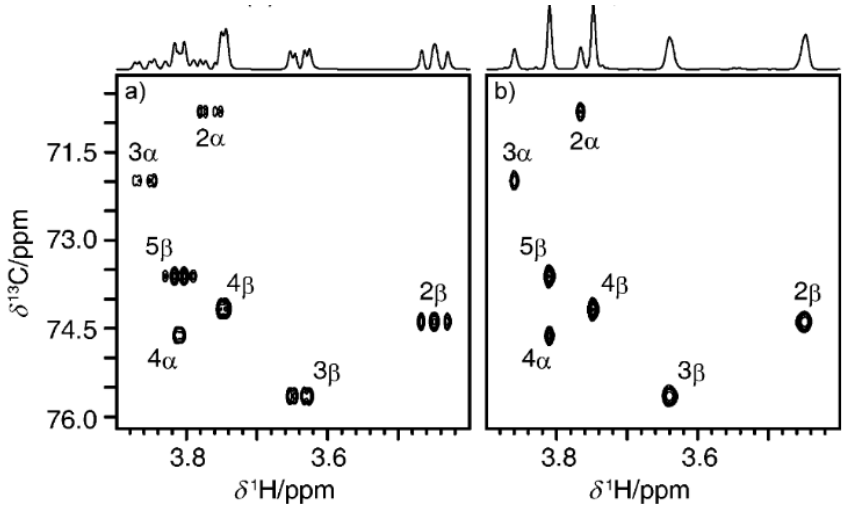
Heteronuclear 2D pure shift NMR experiments for structure analysis of small and medium sized molecules

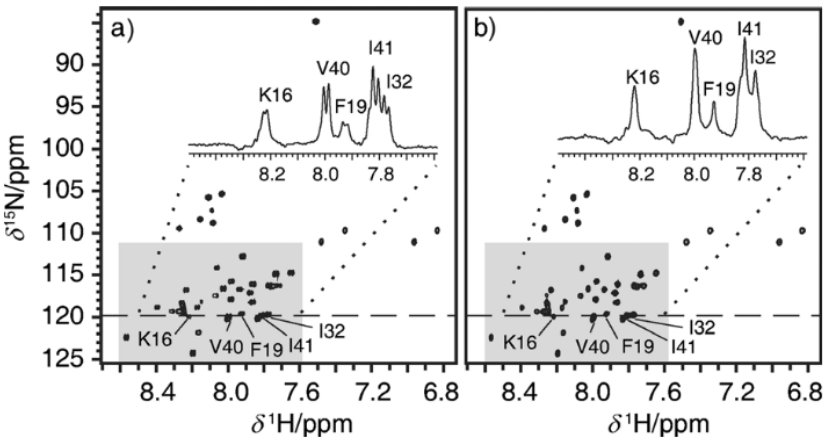
Conventional ^{1}H-^{13}C HSQC

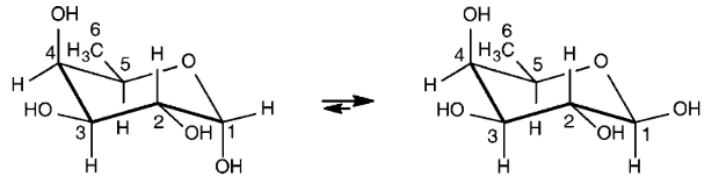
Pure shift real-time ^{1}H-^{13}C HSQC

Conventional ^{1}H-^{15}N HSQC

Pure shift real-time ^{1}H-^{15}N HSQC

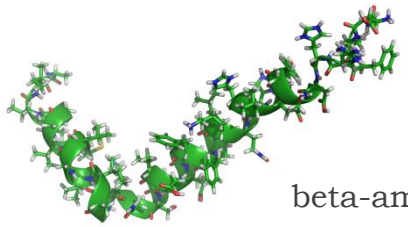






α-D(+)-fucose

β-D(+)-fucose



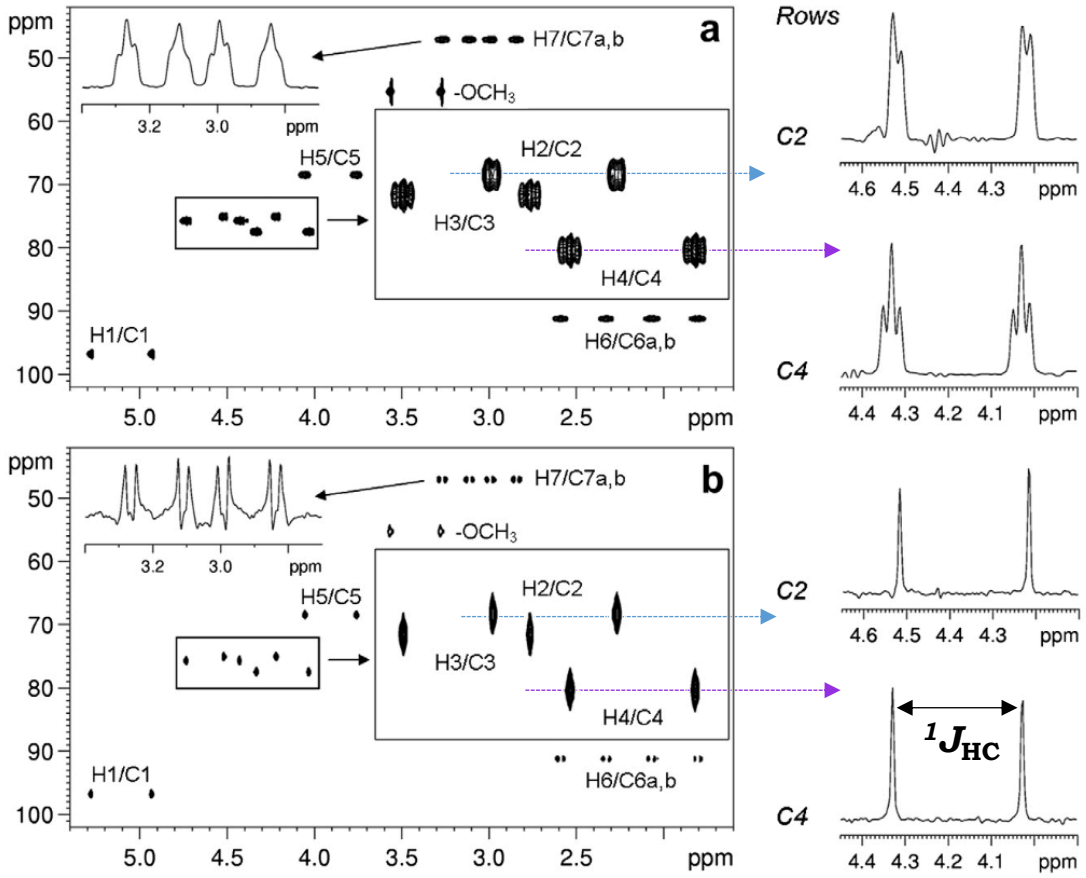
^{15}N-labeled
beta-amyloid peptide 1-42

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

2D Pure shift NMR experiments for accurate determination of one-bond heteronuclear coupling constants

Conventional ^{1}H-^{13}C CLIP-HSQC

Pure shift interferogram ^{1}H-^{13}C CLIP-HSQC

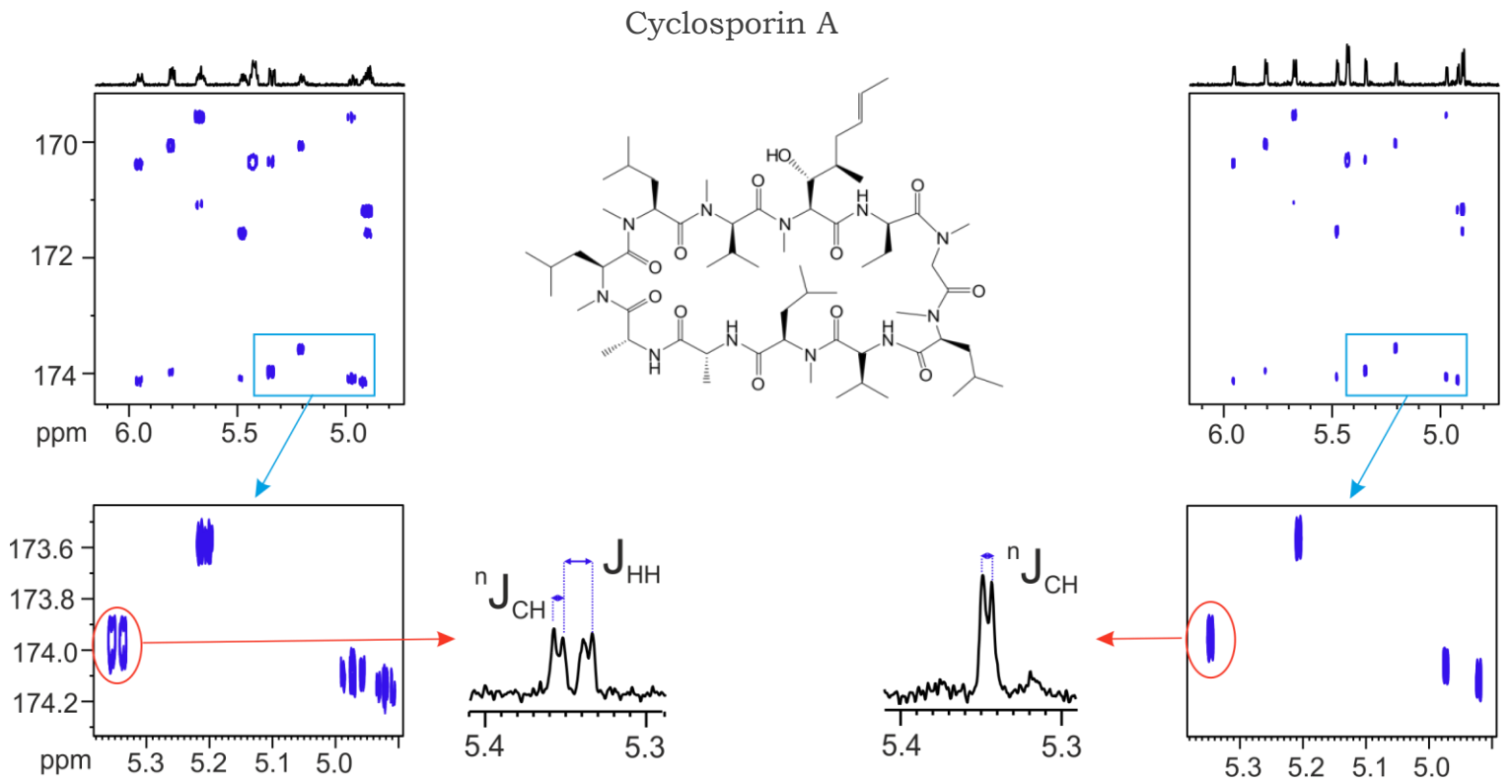


J. Magn. Reson. **239**, 110 (2014); *J. Magn. Reson.* **239**, 130 (2014)

2D Pure shift NMR experiments for accurate determination of long-range heteronuclear coupling constants

Conventional
^{1}H-^{13}C HSQMBC

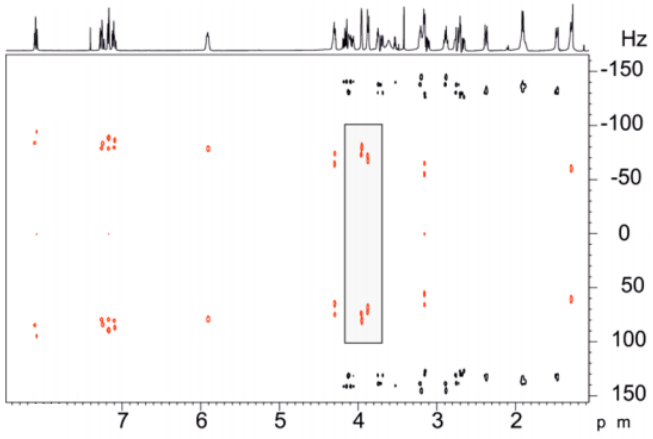
Pure shift real-time BS
^{1}H-^{13}C HSQMBC

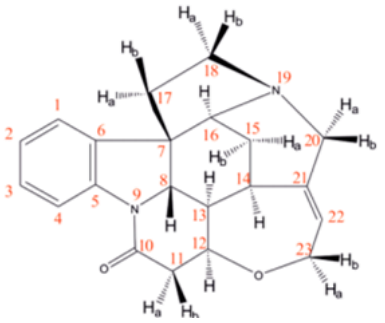


J. Magn. Reson. **238**, 63 (2014)

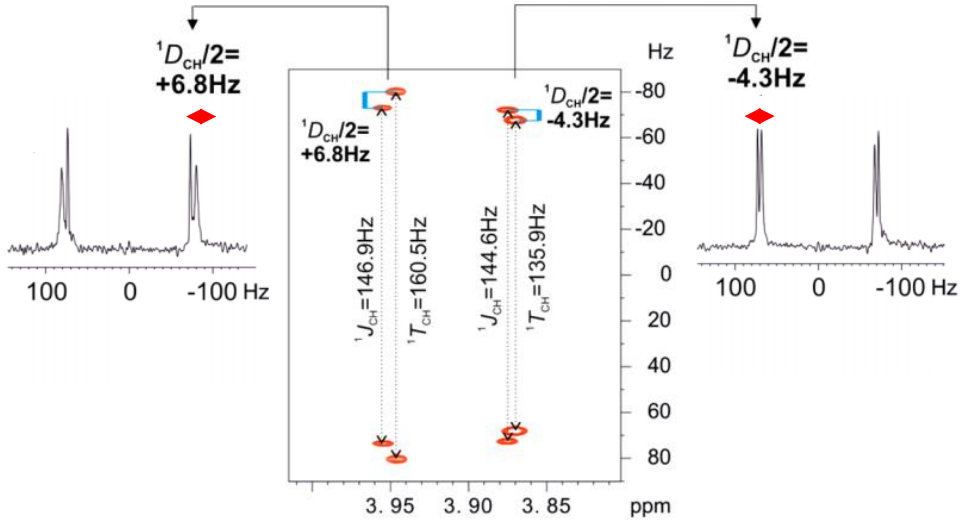
One-shot determination of residual dipolar coupling (RDCs) using pure shift NMR experiments

Pure shift real-time *J*-resolved ^{1}H-^{13}C HSQC



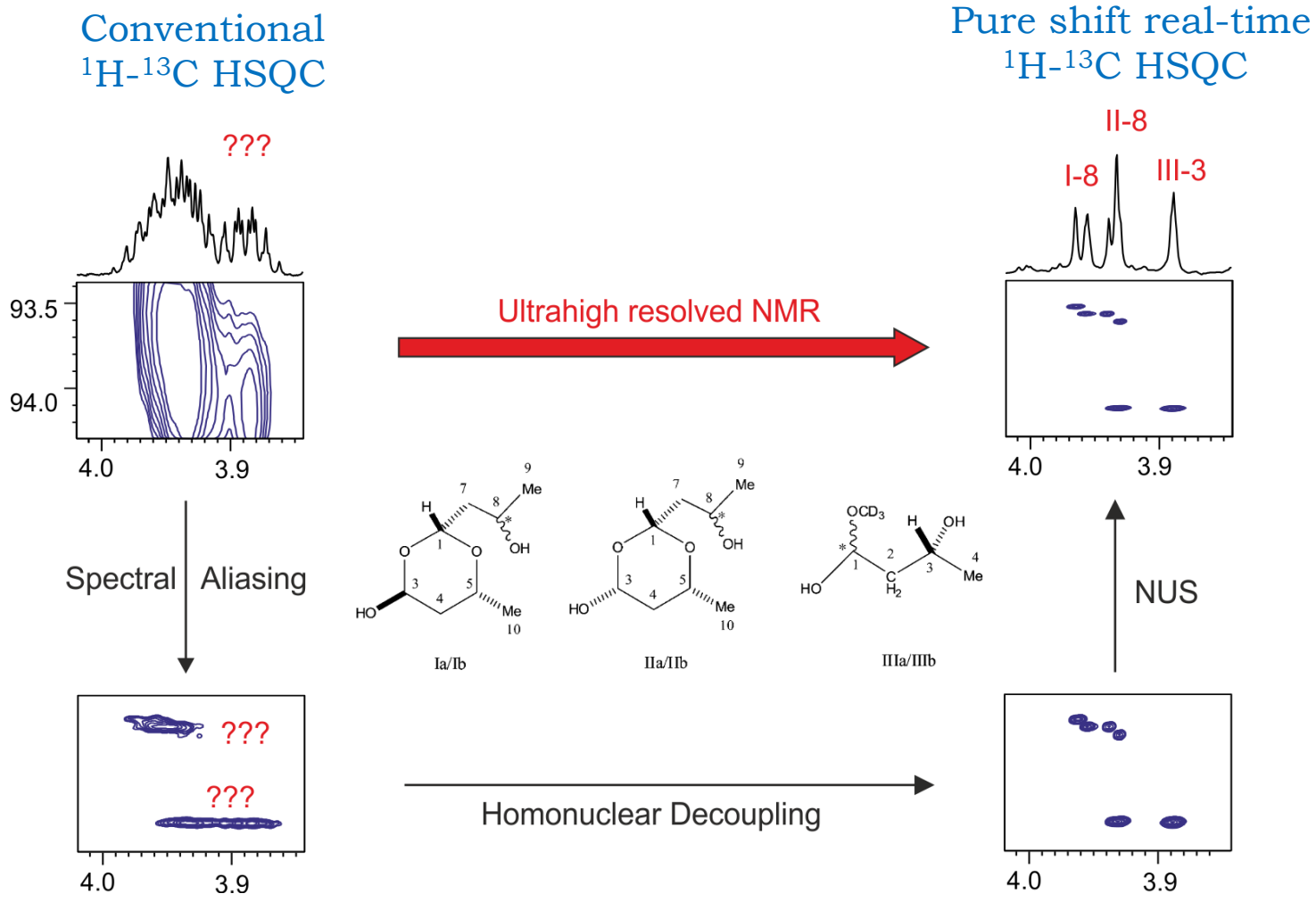


Strychnine



J. Org. Chem. **81**, 11126 (2016)

2D pure shift NMR experiments for the study of complex mixtures

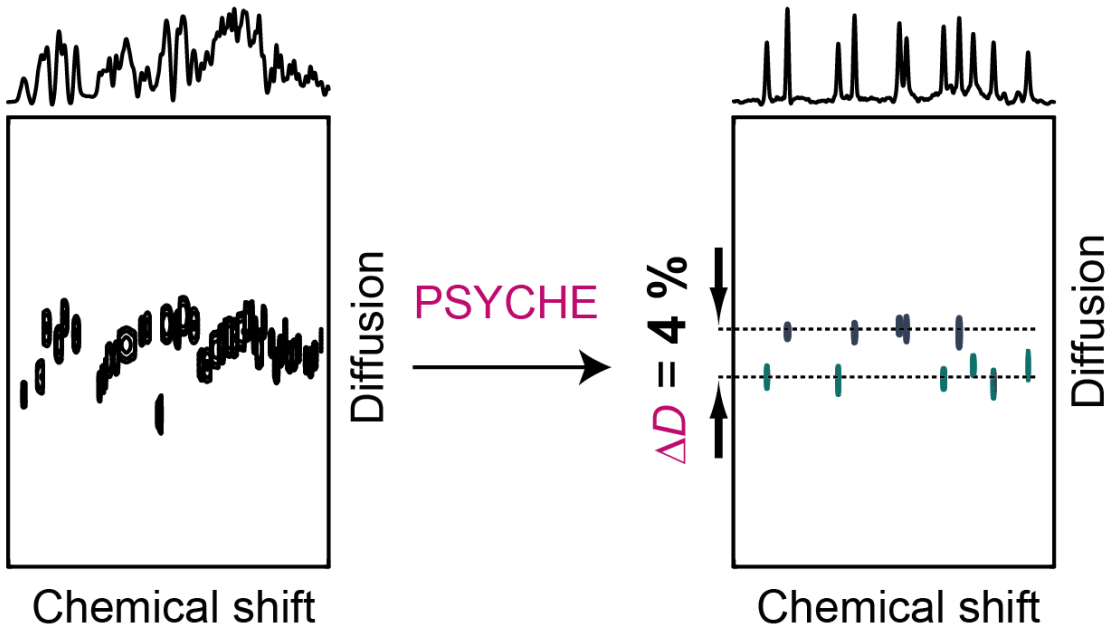


Chem. Eur. J. **21**, 7682 (2015)

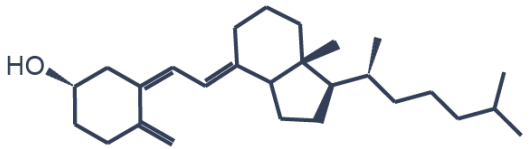
Ultrahigh-resolution diffusion-ordered spectroscopy

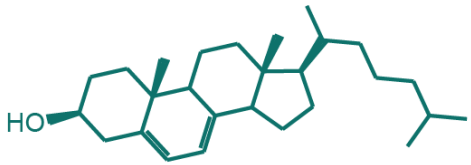
Conventional DOSY

Pure shift interferogram PSYCHE-iDOSY



Vitamin D_3
(secosteroids)





Provitamin D_3
(zoosterol)

Angew. Chem. Int. Ed. **55**, 15579 (2016)

Review articles

Pure shift NMR spectroscopy
R. W. Adams, *EMagRes*, **2014**, 3, 295-310

Broadband ^{1}H homodecoupled NMR experiments: recent developments, methods and applications
L. Castañar and T. Parella, *Magn. Reson. Chem.*, **2015**, 53, 399-426

Pure shift NMR
K. Zangger, *Prog. Nucl. Magn. Reson. Spectrosc.*, **2015**, 86-87, 1-20

Pure shift ^{1}H NMR: what is next?
L. Castañar, *Magn. Reson. Chem.*, **2017**, 55, 47-53

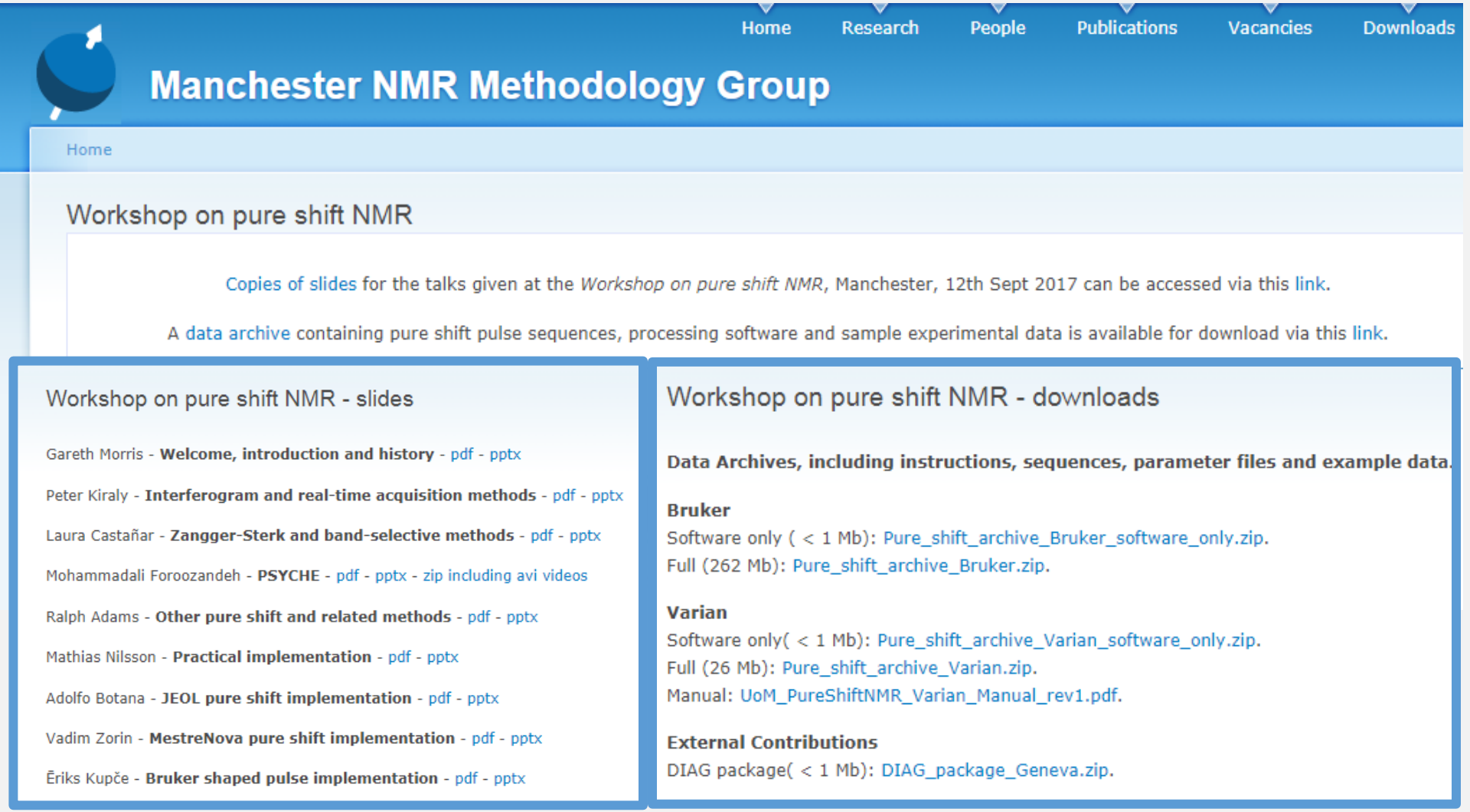
PSYCHE pure shift NMR spectroscopy
M. Foroozandeh, G. A. Morris, M. Nilsson, *Chem. Eur. J.* **2018**, *24*, 13988-14000

Book chapter

High-resolution NMR techniques in organic chemistry
T. D. W. Claridge, Elsevier Science, 3rd Edition, **2016**, chapter 8.

Example data: download from our website

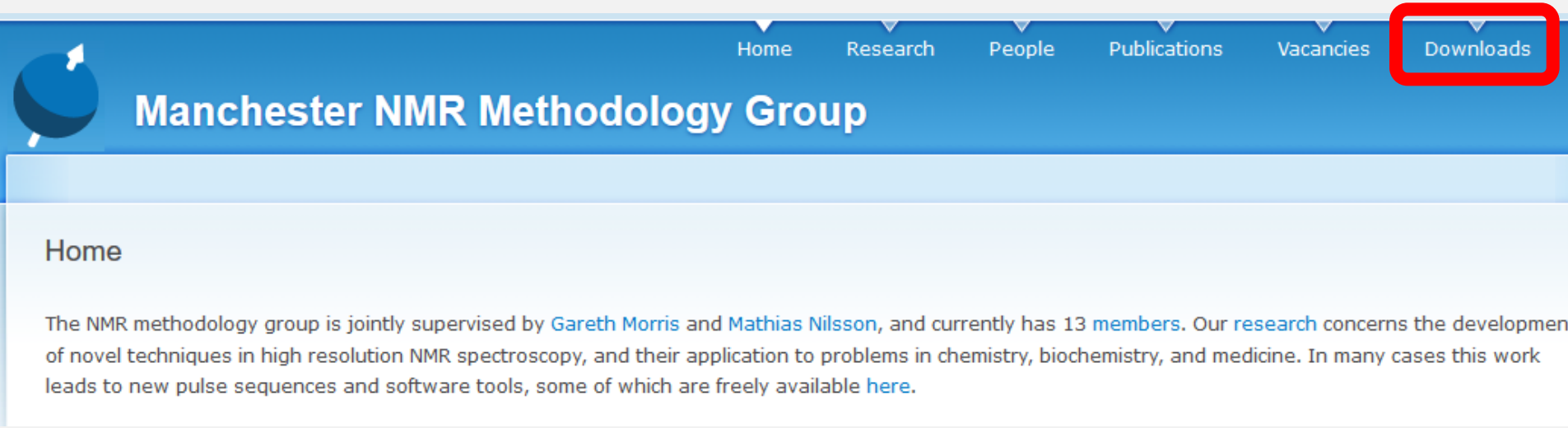
http://nmr.chemistry.manchester.ac.uk/pureshift



The Bruker and Varian/Agilent pure shift data and software archives can also be downloaded from DOI:10.17632/w9nz44cyft.1 and DOI:10.17632/rgj4jwcsnz.1 respectively

Example data: download from our website

http://nmr.chemistry.manchester.ac.uk/pureshift



Download from our website:

http://nmr.chemistry.manchester.ac.uk

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Manchester NMR Methodology Group

Downloads

Pulse Sequences

We are currently preparing many of our pulse sequences, parameter sets, example datasets and processing macros for the website. Some are available here but if you would like to use any of the other the sequences, as described in the publications section, please email us. The majority of sequences are available for Varian systems and we are gradually writing the Bruker variants.

The pulse sequences and any macros required for data conversion can be accessed from this part of the website.

Workshops and presentations

The slides from some of the workshops and presentations given by group members are available from this part of the website. There is a pure shift NMR package available for download as part of our 2017 workshop on pure shift NMR.

Download from our website:

http://nmr.chemistry.manchester.ac.uk

Acknowledgments

Jaca 2011

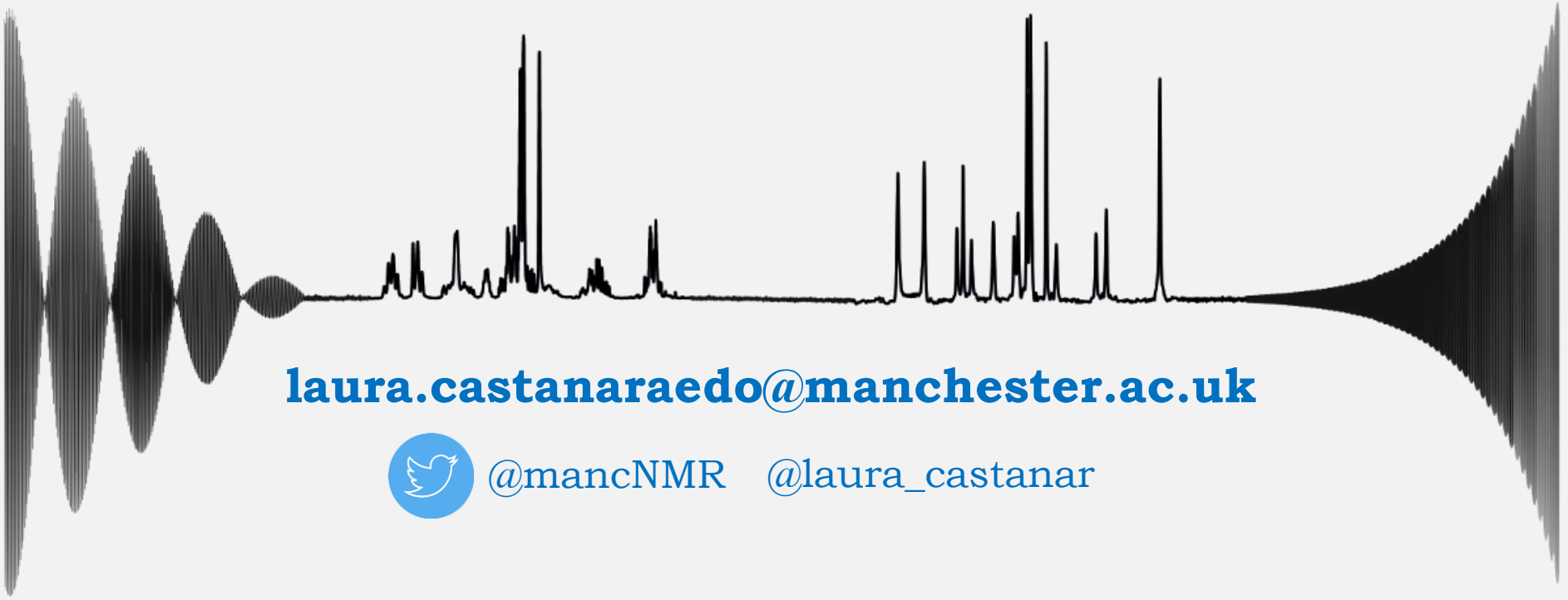
Jaca 2019

SeRMN group – UAB

CEISAM group – Nantes

mancNMR group – UoM

Thank you very much for your attention



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grupo especializado de
resonancia magnética nuclear