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Coherence order and coherence selection

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Outline

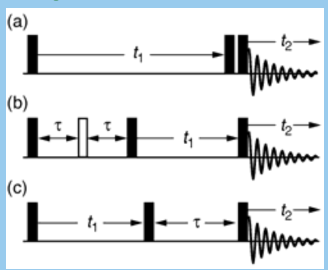
- Why we need coherence selection
- Concept of coherence order
- Coherence transfer pathways (CTPs)
- Selecting a CTP with phase cycling
- Selecting a CTP with gradients
- Suppression of zero-quantum coherence

Further information

- PDF of these slides available at http://www-keeler.ch.cam.ac.uk/
- See also:
  Understanding NMR Spectroscopy, James Keeler (Wiley) [Chapt. 11]

  Spin Dynamics. Basics of Nuclear Magnetic Resonance, Malcolm Levitt (Wiley)

Why we need coherence selection



DQF COSY

DQ spectrum

NOESY

The spins don't know what we want !
We want one out of many possibilities

Coherence order, *p*

Defined by phase acquired during rotation by   about z

$$\hat{\rho}^{(p)} \xrightarrow{\text{rotate by } \varphi \text{ about } z} \hat{\rho}^{(p)} \times \exp(-\mathrm{i}p\varphi)$$

$\boxed{\text{phase acquired is } -p\varphi}$

different p separated by using this property

Properties of coherence order

- takes values 0, ±1, ±2 …
  0 is z-magnetization,
  ±1 is single quantum,
  ±2 is double quantum etc.
- only $p = -1$ is observable
- maximum/minimum value is $\pm N$, where N is number of spins

Effect of pulses

$p \xrightarrow{\text{RF pulse}}$ all possible values of p

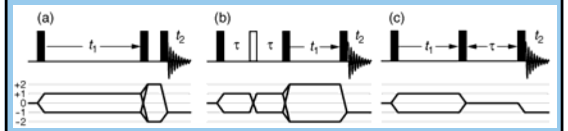
- which is why we need selection

special case:

$p \xrightarrow{180° \text{ pulse}} -p$

Coherence transfer pathway (CTP)

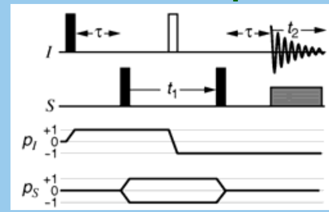
Indicates the *desired* coherence order at each point



DQF COSY   DQ spect.   NOESY

note: always starts at $p = 0$
always ends at $p = -1$

Heteronuclear experiments

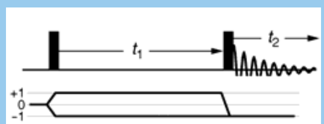


HMQC

separate p for each nucleus (p_I, p_S)
ends with $p = -1$ on *observed* nucleus
pulse to S only affects p_S

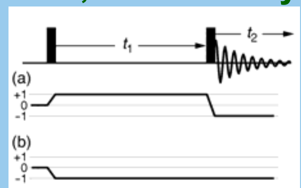
Frequency discrimination and lineshapes in 2D

for absorption mode spectra must retain $p = \pm 1$ during t_1: *symmetrical pathways*



combine this with frequency discrimination using ‘TPPI’ or ‘States’

- or, alternatively



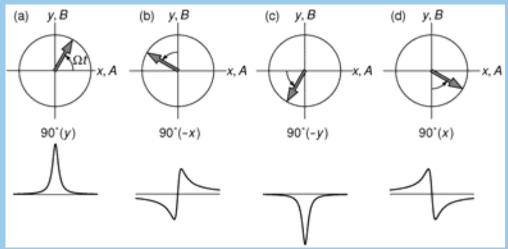
N-type

P-type

1. record two *separate* spectra:
   echo or N-type: $p = +1$ during t_1
   anti-echo or P-type: $p = -1$ during t_1
2. combine to give absorption spectrum

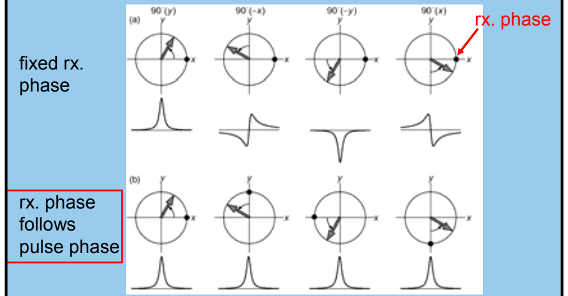
Phase cycling

Pulse phase



the phase of the spectrum depends on the phase of the pulse

Receiver (rx.) phase



Receiver phase

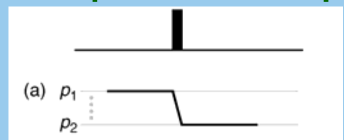
If the signal generated by the pulse sequence shifts in phase, then this can always be compensated for by shifting the receiver by the same amount.

Phase cycling

Selection of a pathway by repeating the sequence with a systematic variation of the pulse and rx. phases

How to design the sequence of phases,
- the *phase cycle*?

Effect of phase shift of pulse



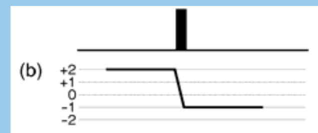
Pulse causes transfer from p_1 to p_2

Change in coherence order $\Delta p = p_2 - p_1$

If pulse phase shifted by $\Delta\varphi$ phase acquired by signal is

$$\boxed{-\Delta p \times \Delta\varphi}$$

Selection of a single pathway



+2 to −1, so $\Delta p = -1 - (+2) = -3$

phase acquired by signal when pulse shifted by $\Delta\varphi$ is

$$-\Delta p \times \Delta\varphi = 3\,\Delta\varphi$$

Four-step cycle

step	pulse Δφ	3 Δφ	equiv(3 Δφ)
1	0°		
2	90°		
3	180°		
4	270°		

Four-step cycle

step	pulse Δφ	3 Δφ	equiv(3 Δφ)
1	0°	0°	
2	90°	270°	
3	180°	540°	
4	270°	810°	

Four-step cycle

step	pulse Δφ	3 Δφ	equiv(3 Δφ)
1	0°	0°	0°
2	90°	270°	270°
3	180°	540°	180°
4	270°	810°	90°

Four-step cycle

Pulse goes
[0°, 90°, 180°, 270°]

Pathway with $\Delta p = -3$ acquires phase
[0°, 270°, 180°, 90°]

If receiver phase follows these phases, contribution from the pathway will add up

- but what about other pathways?

- other pathways

e.g. $\Delta p = -2$ so $-\Delta p \times \Delta\varphi = 2\,\Delta\varphi$

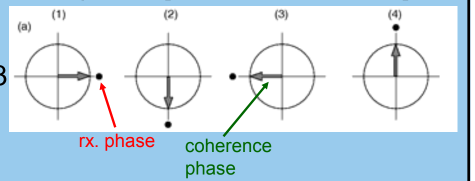
step	pulse Δφ	2 Δφ	equiv(2 Δφ)
1	0°	0°	0°
2	90°	180°	180°
3	180°	360°	0°
4	270°	540°	180°

Selected with rx. phases
[0°, 270°, 180°, 90°] ?

Selected pathways

rx. phase [0°, 270°, 180°, 90°]

$\Delta p = -3$

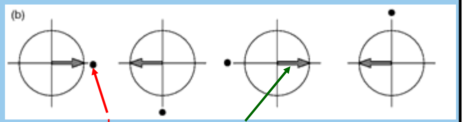


For $\Delta p = -3$, rx. phase follows coherence phase:
all four steps add up

Selected pathways

rx. phase [0°, 270°, 180°, 90°]

$\Delta p = -2$



For $\Delta p = -2$, signal cancels on four steps

Selectivity

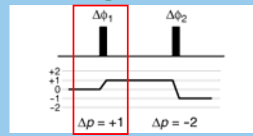
A four-step cycle designed to select a particular value of Δp will also select $\Delta p + 4$, $\Delta p + 8$ … and $\Delta p - 4$, $\Delta p - 8$…

- all other pathways are suppressed

(−4) **−3** (−2) (−1) (0) **1** (2) (3) (4) **5**

selected in **bold**, suppressed in ()

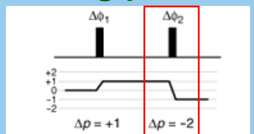
Combining phase cycles



four-step cycle to select $\Delta p = +1$

step	pulse $\Delta\varphi_1$	$-\Delta\varphi_1$	equiv($-\Delta\varphi_1$)
1	0°	0°	0°
2	90°	−90°	270°
3	180°	−180°	180°
4	270°	−270°	90°

Combining phase cycles



four-step cycle to select $\Delta p = -2$

step	pulse $\Delta\varphi_2$	$2\,\Delta\varphi_2$	equiv($-\Delta\varphi_2$)
1	0°	0°	0°
2	90°	180°	180°
3	180°	360°	0°
4	270°	540°	180°

Complete both cycles independently

step	$\Delta\varphi_1$	$-\Delta\varphi_1$	equiv($-\Delta\varphi_1$)	$\Delta\varphi_2$	$2\,\Delta\varphi_2$	equiv($2\Delta\varphi_2$)	total
1	0°	0°	**0°**	0°	0°	**0°**	**0°**
2	90°	−90°	**270°**	0°	0°	**0°**	**270°**
3	180°	−180°	**180°**	0°	0°	**0°**	**180°**
4	270°	−270°	**90°**	0°	0°	**0°**	**90°**
5	0°	0°	**0°**	90°	180°	**180°**	**180°**
6	90°	−90°	**270°**	90°	180°	**180°**	**90°**
7	180°	−180°	**180°**	90°	180°	**180°**	**0°**
8	270°	−270°	**90°**	90°	180°	**180°**	**270°**
9	0°	0°	**0°**	180°	360°	**0°**	**0°**
10	90°	−90°	**270°**	180°	360°	**0°**	**270°**
11	180°	−180°	**180°**	180°	360°	**0°**	**180°**
12	270°	−270°	**90°**	180°	360°	**0°**	**90°**
13	0°	0°	**0°**	270°	540°	**180°**	**180°**
14	90°	−90°	**270°**	270°	540°	**180°**	**90°**
15	180°	−180°	**180°**	270°	540°	**180°**	**0°**
16	270°	−270°	**90°**	270°	540°	**180°**	**270°**

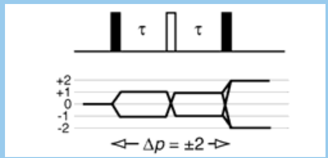
Tricks: 1

1. The first pulse can *only* generate $p = \pm 1$ from equilibrium magnetization

- no need to phase cycle this pulse

Tricks: 2

2. Group pulses together and cycle as a unit



All pulses:	[0°, 90°, 180°, 270°]
Rx. for Δ*p* = ±2:	[0°, 180°, 0°, 180°]

Tricks: 3

3. Only *p* = −1 is observable, so it does not matter if other values of *p* are generated by the *last pulse*

- no need to phase cycle the *last pulse,* if a coherence order has been selected unambiguously *before* this pulse

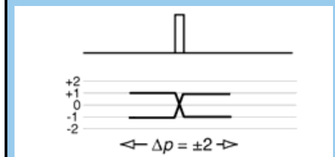
Tricks: 4

4. Don’t worry about high orders of multiple quantum coherence e.g ≥ 4.

- they are hard to generate and likely to give weak signals, especially if the lines are broad

Refocusing pulses: EXORCYCLE

Refocusing pulses cause $p \rightarrow -p$



e.g. Δ*p* = ±2 (single quantum)

Pulse:	[0°, 90°, 180°, 270°]
Rx. for Δ*p* = ±2:	[0°, 180°, 0°, 180°]

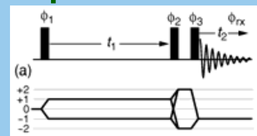
Axial peak suppression

z-magnetization which recovers by relaxation during a pulse sequence is made observable by last pulse

- leads to peaks at ω_1=0: **axial peaks**
- easily suppressed using a two-step cycle

1st pulse:	[0°, 180°]
Rx. for Δ*p* = ±1:	[0°, 180°]

Examples: DQF COSY



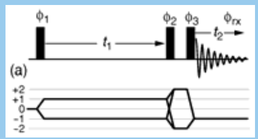
symmetrical pathways in t_1

final pulse has Δ*p* = −3 and +1
- select using four-step cycle:

φ_3 = [0°, 90°, 180°, 270°]
φ_{rx} = [0°, 270°, 180°, 90°]

this is sufficient, as *p* can only be ±1 in t_1

DQF COSY (alternative)



symmetrical pathways in t_1

group first two pulses and select $\Delta p = \pm 2$

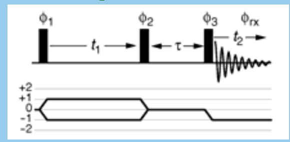
- select using four-step cycle:

φ_1 and φ_2 = [0°, 90°, 180°, 270°]

φ_{rx} = [0°, 180°, 0°, 180°]

this is sufficient, as p can only be −1 in t_2

Examples: NOESY



symmetrical pathways in t_1

final pulse has $\Delta p = -1$

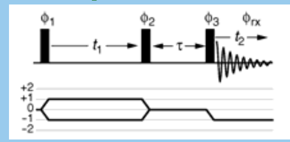
- select using four-step cycle:

φ_3 = [0°, 90°, 180°, 270°]

φ_{rx} = [0 °, 90°, 180°, 270°]

this is sufficient, as p can only be ±1 in t_1

Examples: NOESY



axial peak suppression also required

φ_1 = [0°, 180°] φ_{rx} = [0°, 180°]

Step	1	2	3	4	5	6	7	8
Φ_1	0°	0°	0°	0°	180°	180°	180°	180°
Φ_3	0°	90°	180°	270°	0°	90°	180°	270°
Φ_{rx}	0°	90°	180°	270°	180°	270°	0°	90°

Problems with phase cycling

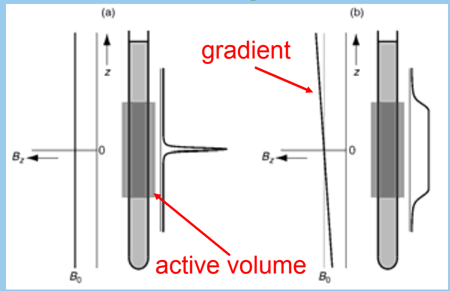
- phase cycle must be completed:
  - unacceptably long experiment, especially for 2D/3D
- cancellation of unwanted signals may be imperfect (especially for proton detected experiments)

Gradient pulses

Field gradient pulses

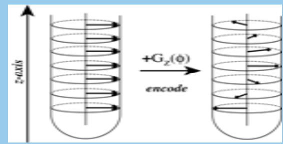
- the B_0 field is made inhomogeneous for a short period (few ms)
- coherences dephase, all signal lost
- a subsequent gradient may rephase some of the coherences

Effect of a gradient

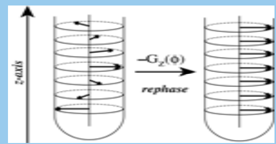


off: sharp line **on**: v. broad line

Dephasing and rephasing



dephase



rephase

Spatially dependent phase

phase acquired by coherence p at position z in sample, after time t

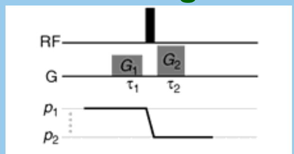
$$\boxed{\varphi(z) = -p \times \gamma\, G\, z\, t}$$

gyromagnetic ratio

gradient strength, G cm^{-1}

phase depends on position and p

Selection with a gradient pair

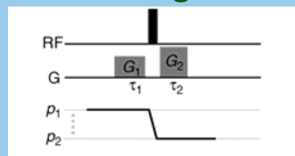


phase due to G_1: $\varphi_1(z) = -p_1 \times \gamma\, G_1\, z\, \tau_1$

phase due to G_2: $\varphi_2(z) = -p_2 \times \gamma\, G_2\, z\, \tau_2$

$\boxed{\text{refocusing condition: } \varphi_1(z) + \varphi_2(z) = 0}$

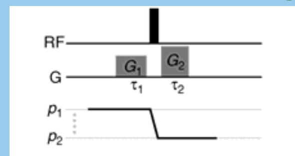
Selection with a gradient pair



$\varphi_1(z) + \varphi_2(z) = -p_1\, \gamma\, G_1\, z\, \tau_1 - p_2\, \gamma\, G_2\, z\, \tau_2 = 0$

$$\boxed{\frac{G_1 \tau_1}{G_2 \tau_2} = -\frac{p_2}{p_1}}$$

Selection with a gradient pair

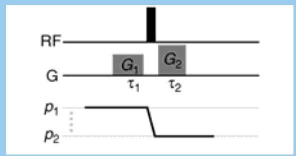


$$\boxed{\frac{G_1 \tau_1}{G_2 \tau_2} = -\frac{p_2}{p_1}}$$

e.g. $p_1 = +2$, $p_2 = -1 \longrightarrow \dfrac{G_1 \tau_1}{G_2 \tau_2} = -\dfrac{-1}{+2} = \dfrac{1}{2}$

alternatives $\begin{cases} \text{if } G_1 = G_2,\ \tau_2 = 2\,\tau_1 \\ \text{if } \tau_1 = \tau_2,\ G_2 = 2\,G_1 \end{cases}$

Selection with a gradient pair



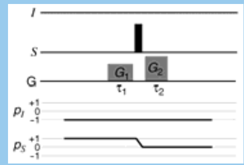
$$\boxed{\frac{G_1\tau_1}{G_2\tau_2} = -\frac{p_2}{p_1}}$$

e.g. $p_1 = -2$, $p_2 = -1 \longrightarrow \frac{G_1\tau_1}{G_2\tau_2} = -\frac{-1}{-2} = -\frac{1}{2}$

refocusing: $\tau_1 = \tau_2$, $G_2 = -2\ G_1$

'$-G$' means opposite sense of gradient

Heteronuclear case



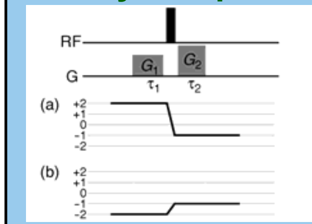
only p_S changes

$\varphi_1(z) = -(p_I\,\gamma_I + p_S\,\gamma_S)G_1 z\tau_1 = -(-\gamma_I + \gamma_S)G_1 z\tau_1$

$\varphi_2(z) = -(p_I\,g_I + p_S\,\gamma_S)G_2 z\tau_2 = -(-\gamma_I - 0)G_2 z\tau_2$

$$\boxed{\frac{G_1\tau_1}{G_2\tau_2} = \frac{1}{(\gamma_S/\gamma_I)-1}}$$

Only one pathway selected

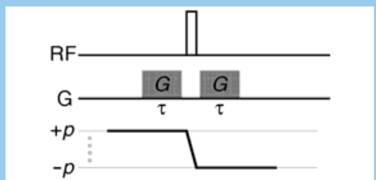


$\longleftarrow \frac{G_1\tau_1}{G_2\tau_2} = \frac{1}{2}$

$\longleftarrow \frac{G_1\tau_1}{G_2\tau_2} = -\frac{1}{2}$

can only select *one* of these pathways
- potential loss of sensitivity
- problems in two-dimensional NMR

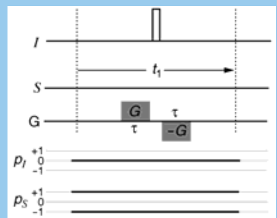
Refocusing pulses



Ideal 180° causes $p \rightarrow -p$

Selected *for all p* by equal gradients
- 'cleans up' imperfect 180°

180° in heteronuclear case

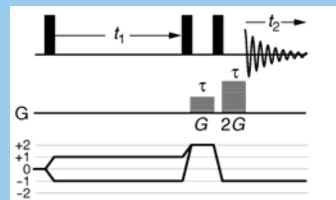


⟵ no coherence on *I* spin

180° to *I* is acting as *inversion pulse*

Gradient pair 'cleans up' imperfect 180°
- leaves *S* spin coherences unaffected

Phase errors



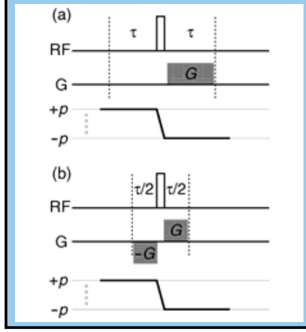
DQF COSY

Offsets continue to evolve during gradients

- results in severe frequency-dependent phase errors

Avoiding phase errors

add refocusing pulse / use an existing one



offset evolution refocused by 180° pulse

more time efficient alternative

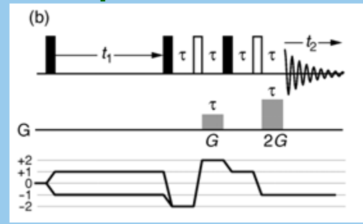
Selection of *z*-magnetization

A gradient dephases all* coherences:
- leaves behind only *z*-magnetization
- simple and convenient

called a *purge gradient* or *homospoil*

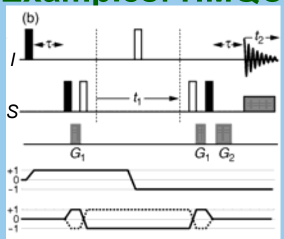
*except homonuclear zero-quantum

Examples: DQF COSY



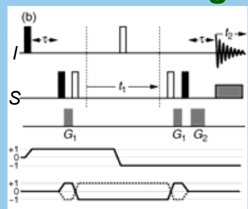
- symmetrical pathways in t_1 (no gradient)
- extra 180° pulses to avoid phase errors
- loss of sensitivity

Examples: HMQC



- separate expts. for P- and N-type
- additional 180° associated with both G_1
- G_2 in existing delay, so no phase error

HMQC: refocusing condition



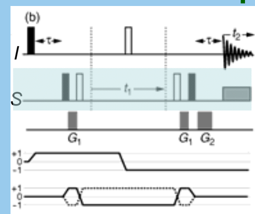
P-type (solid line)

$$(-\gamma_I G_1 z\tau_1 - \gamma_S G_1 z\tau_1) + (\gamma_I G_1 z\tau_1 - \gamma_S G_1 z\tau_1) + (\gamma_I G_2 z\tau_2) = 0$$

$$-2\gamma_S G_1 z\tau_1 + \gamma_I G_2 z\tau_2 = 0$$

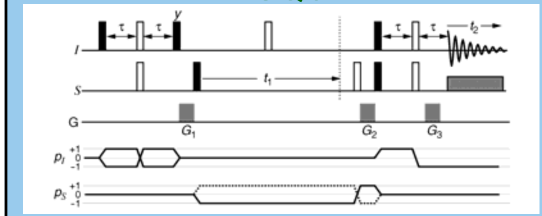
$$\frac{G_1\tau_1}{G_2\tau_2} = \frac{\gamma_I}{2\gamma_S}$$

HMQC: suppression of *I* spin magnetization not coupled to *S*



- *I* magnetization dephased by 1st G_1, but rephased by second G_1, and then dephased by G_2

HSQC



- G_1 is purge gradient
- extra 180° associated with G_2
- G_3 in existing spin echo
- can omit G_2 and G_3 (labelled samples)

Advantages and disadvantages

\+ minimizes experiment time
\+ excellent suppression, especially in heteronuclear experiments with ^{1}H obs.

\- cannot select more than one pathway
→ possible loss of SNR
→ obtaining pure phase more complex
\- phase errors
→ requires elaboration of sequence
\- loss due to diffusion

Zero-quantum dephasing

An old, old problem in NMR

z-magnetisation and zero-quantum coherence cannot be separated using phase cycling or gradients

because
neither respond to *z*-rotations

i.e. both have coherence order, *p*, of zero

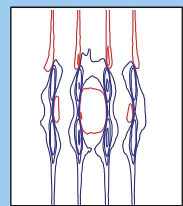
Why is it a problem?

a 90° pulse converts *z*-magnetization into **in-phase** magnetization along *y*

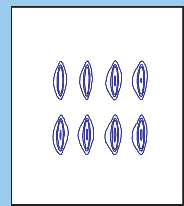
but converts ZQ into **anti-phase** along *x*

the result is **phase distortion** and **unwanted peaks**

Result: distorted multiplets in 2D

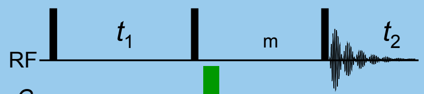


z-magn. + ZQ



z-magn. only

Example: NOESY

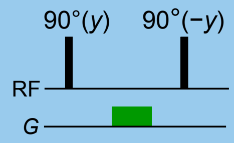


wanted: z-magn. during $_\mathrm{m}$
→ in-phase, absorption multiplets

unwanted: ZQ during $_\mathrm{m}$
→ anti-phase, dispersion multiplets
'J-peaks'

The z-filter

Sørensen, Rance, Ernst 1984

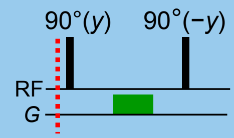


$I_{1x} \longrightarrow -I_{1z} \longrightarrow I_{1x}$

everything else ⟶ | dephased

only in-phase magnetization survives

but …



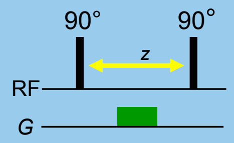
$2I_{1y}I_{2z} \longrightarrow 2I_{1y}I_{2x}$ mixture of DQ and ZQ

$\longrightarrow \tfrac{1}{2}(2I_{1y}I_{2x} - 2I_{1x}I_{2y}) \longrightarrow \tfrac{1}{2}(2I_{1y}I_{2z} - 2I_{1z}I_{2y})$

ZQ

Anti-phase component passes through

Zero-quantum evolution

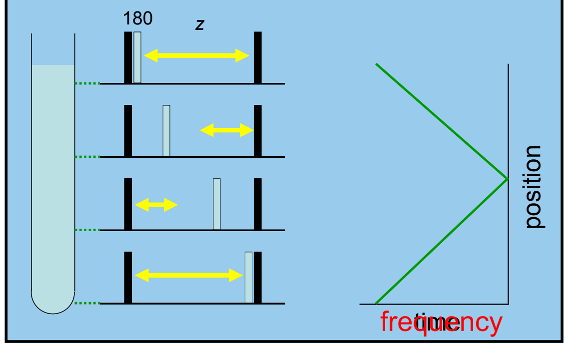


The zero quantum evolves during τ_z at $(\Omega_1 - \Omega_2)$, the difference of the shifts

Macura et al 1981

this is the key …

Make evolution dependent on position



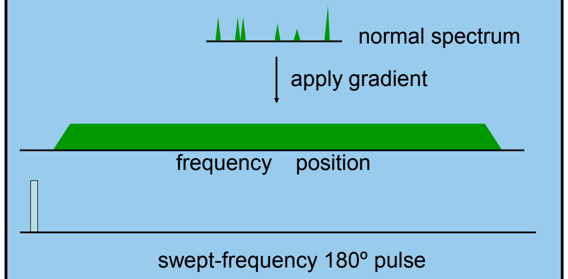
Zero-quantum dephasing

As frequency is a function of position, the zero-quantum coherence will dephase

Identical to dephasing in a conventional gradient

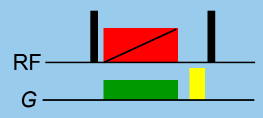
how to make 180° position dependent?

Swept-frequency 180º



different parts experience pulse at different times

z-filter with zero-quantum suppression



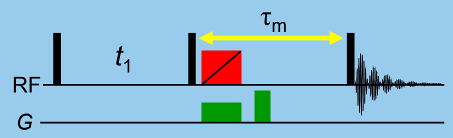
swept 180º with gradient

additional dephasing gradient
(to make sure everything is dephased)

Typical parameters

- swept pulse of duration 15 to 30 ms
- gradient 1 to 2 G cm^{-1}
- dephasing rate depends on ZQ frequency
- suppression of ZQ by factor of 100

NOESY with zero-quantum suppression

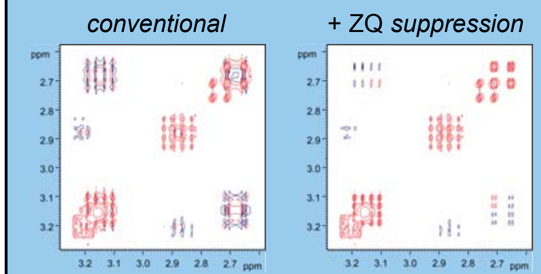


swept 180º with gradient

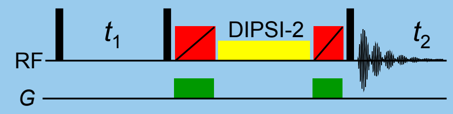
additional dephasing gradient

NOE continues to build up throughout

NOESY results (strychnine)



TOCSY

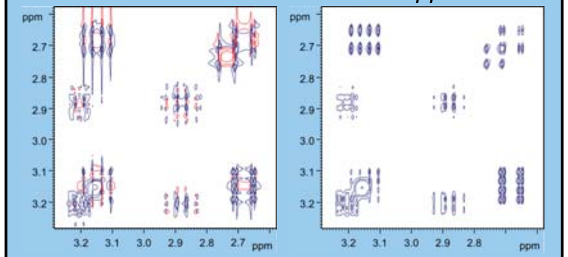


isotropic mixing within *z*-filter

ZQ dephasing needed before and after mixing; unequal durations

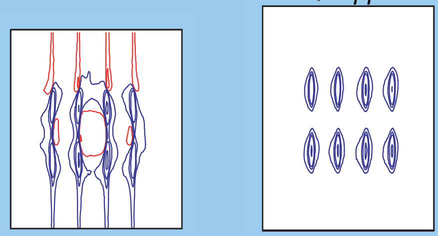
TOCSY results (strychnine)

conventional *+ ZQ suppression*



TOCSY results (strychnine)

conventional *+ ZQ suppress.*



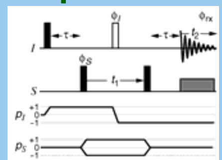
Advantages of the *z*-filter

- excellent suppression
- no increase in experiment time
- simple to implement
- widely applicable
- negligible reduction in signal

THE END

Phew!

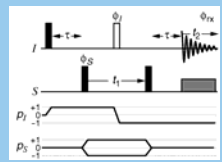
Examples: HMQC



select $\Delta p_S = \pm 1$ at first *S* pulse
and $\Delta p_I = \pm 2$ at 180° *I* pulse

step	1	2	3	4	5	6	7	8
φ_S	0°	180°	0°	180°	0°	180°	0°	180°
φ_I	0°	0°	90°	90°	180°	180°	270°	270°
φ_{rx}	0°	180°	180°	0°	0°	180°	180°	0°

Difference spectroscopy: HMQC



The cycle [0°, 180°] on first *S* pulse and rx. is just **difference spectroscopy**:
selects that part of the signal which goes via the *S* spin

Difference spectroscopy

In heteronuclear experiments, a simple two-step phase cycle ($+x/-x$) on the pulse causing the transfer often suffices

- this is simply difference spectroscopy