

On pulses, phases and gradients:
Phase cycling and Quadrature detection
Part II

Greater Bay Area Magnetic Resonance Workshop

15.05.2024



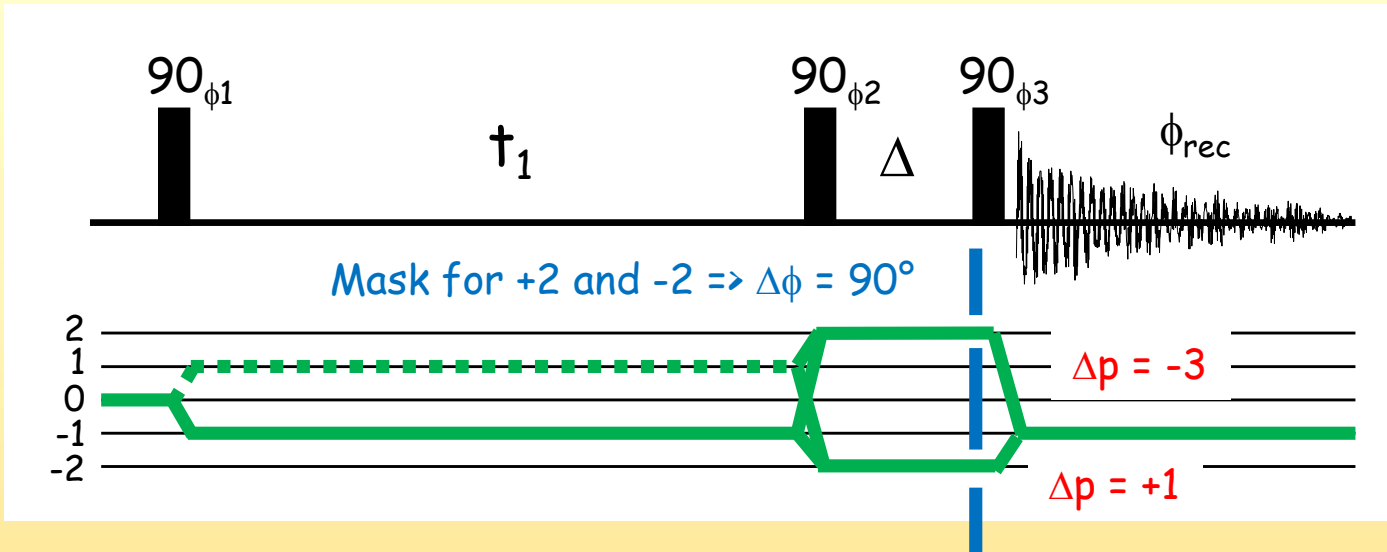
Phase Cycling

In part I we learned about coherence levels and that we can select certain coherence pathways by combining FIDs recorded with a variation in the phase settings.



The disadvantage of this kind of coherence level selection is that we take the difference of FIDs recorded one after the other and thus rely on the stability of the entire setup.

Phase Cycling



DQF-COSY

$$\phi_3 = 0, 1, 2, 3$$

$$\Delta p = -3 \text{ and } +1$$

	ϕ_1	ϕ_2	ϕ_3	$\sum \Delta p_i * \phi_i$ $\Delta p = +1$	$\sum \Delta p_i * \phi_i$ $\Delta p = -3$	„ ϕ_{rec} “ $\Delta p = +1$	„ ϕ_{rec} “ $\Delta p = -3$	ϕ_{rec}
1	0	0	0	0	0	0	0	0
2	0	0	1	1	-3	-1	3	3
3	0	0	2	2	-6	-2	6	2
4	0	0	3	3	-9	-3	9	1

Using „modulo 4“ we obtain identical phasecycles for both pathways



Phase Cycling

We will now use gradients to select the coherence pathways more directly.

The advantage of this kind of coherence level selection is that we do not have to rely on the stability of the spectrometer but can select a particular coherence pathway in a single scan.

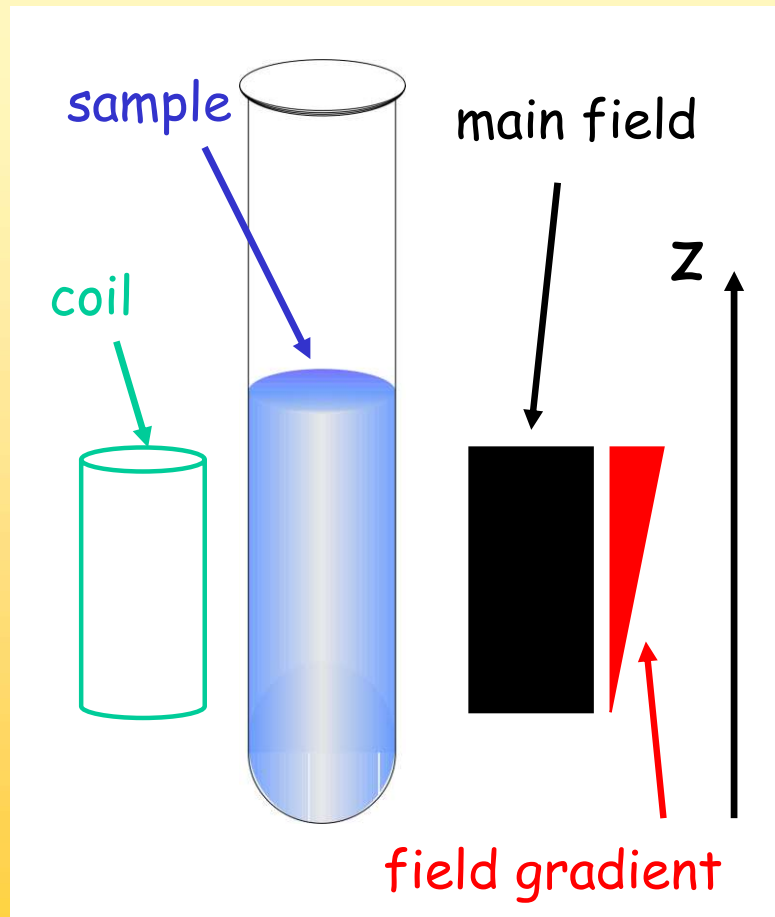
This often leads to much cleaner spectra, but we sometimes have to play tricks to get the same intensity and lineshape as with phase cycled spectra.



Gradients and coherence levels

Gradients and coherence levels

Another powerful tool for NMR experiments are field gradients



While usually the homogeneity is kept as good and constant as possible, gradients are a way to change the magnetic field in a geometrically controlled manner. The Larmor frequency is then not the same for all molecules in the sample but spatially dependent:

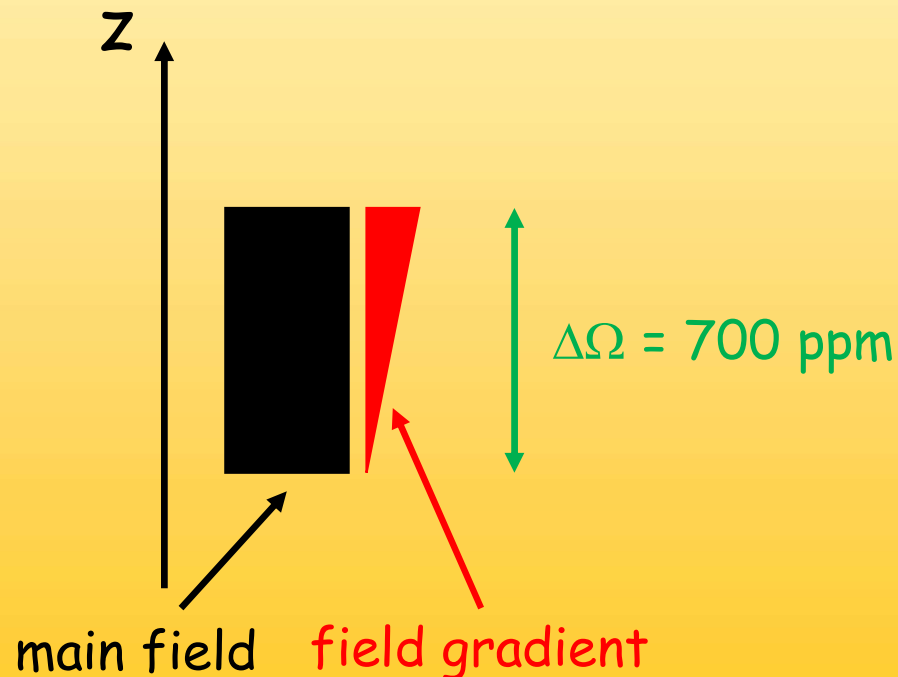
$$B = (1 + z) B_0$$

$$\omega = -\gamma B = -\gamma (1 + z) B_0$$

Gradients and coherence levels

Assuming a length of the coil of 2 cm and a typical gradient of 50 Gs/cm then we have a difference of $\Delta B = 10$ mT (1 Gs = 0.1 mT) between the upper and lower end of the sample.

The gyromagnetic ratio for the protons (^1H) is $\gamma = 26.75 \times 10^7$ rad/sT.



At a magnetic field of 14.1 T we thus obtain a frequency of

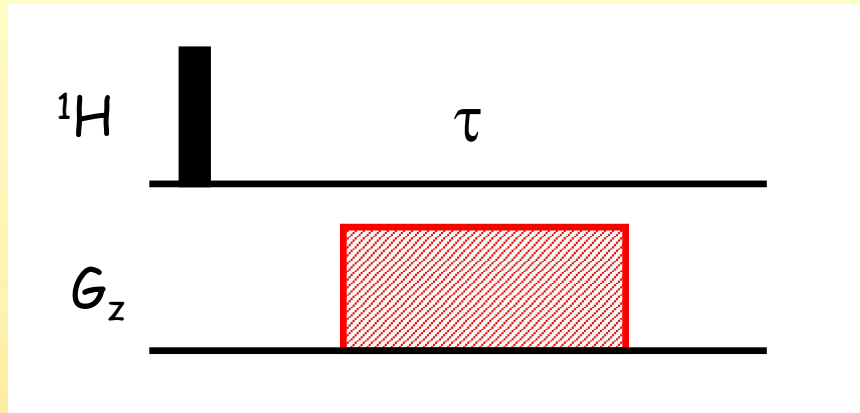
$$\nu = \omega/2\pi = \gamma B/2\pi = 600 \text{ MHz}$$

For a $\Delta B = 10$ mT we thus obtain a $\Delta\nu = 425$ kHz, which corresponds to ~ 700 ppm

(the minus is left out for clarity)

Gradients and coherence levels

Despite the spacial differences field gradients are in essence only delays



But the chemical shift is dependent on the z-coordinate

$$B_z = B_0 + G_z$$

(G_z is the gradient field)

And since $\Omega_z = \gamma B_z = \gamma(B_0 + G_z) = \gamma B_0 + \gamma G_z = \Omega_0 + \Omega(z)$

If we apply that to what we already know we obtain

$$\begin{aligned} I_x &= \frac{1}{2} (I^+ + I^-) \xrightarrow{I_z \Omega_z \tau} \frac{1}{2} [I^+ \exp(-i\Omega_z \tau) + I^- \exp(+i\Omega_z \tau)] \\ &= \frac{1}{2} [I^+ \exp(-i(\Omega_0 + \Omega(z))\tau) + I^- \exp(+i(\Omega_0 + \Omega(z))\tau)] \end{aligned}$$

Gradients and coherence levels

That can be separated in a spatially dependent and an independent part

$$= \frac{1}{2} I^+ \exp(-i\Omega_0\tau) \exp(-i\Omega(z)\tau) \\ + \frac{1}{2} I^- \exp(+i\Omega_0\tau) \exp(+i\Omega(z)\tau)$$

The additional phase created by the gradient has opposite sign for I^+ and I^- , and since $\Omega(z) = \gamma G_z$ it does not only depend on the gradient strength but also on the gyromagnetic ratio of the nuclei, the shift will depend on the type of nucleus.


We have seen that a gradient of 50 Gs/cm creates a difference of 425 kHz for ^1H spins, consequently the difference will be only 107 kHz for ^{13}C nuclei

Gradients and coherence levels

The additional shift will be twice as large for DQC than for SQC, ZQC will not be affected at all, they are insensitive to gradients.

$$I_{1+}I_{2+} \xrightarrow{I_z\Omega_z\tau}$$

$$\begin{aligned} I_{1+}\exp(-i\Omega_z\tau)I_{2+}\exp(-i\Omega_z\tau) &= I_{1+}I_{2+}\exp(-i(\Omega_1+\Omega(z))\tau)\exp(-i(\Omega_2+\Omega(z))\tau) \\ &= I_{1+}I_{2+}\exp(-i[\Omega_1+\Omega_2]\tau)\exp(-i2\Omega(z)\tau) \end{aligned}$$

 This is the coherence order p !!

$$I_{1+}I_{2-} \xrightarrow{I_z\Omega_z\tau}$$

$$\begin{aligned} I_{1+}\exp(-i\Omega_z\tau)I_{2-}\exp(+i\Omega_z\tau) &= I_{1+}I_{2-}\exp(-i(\Omega_1+\Omega(z))\tau)\exp(+i(\Omega_2+\Omega(z))\tau) \\ &= I_{1+}I_{2-}\exp(-i[\Omega_1-\Omega_2]\tau) \end{aligned}$$

$$\exp(-i[\Omega(z)-\Omega(z)]\tau) = 1$$

Here is the coherence order $p = 0$!

Gradients and coherence levels

The calculation is a bit more involved for mixed MQC:
heteronuclear ZQC are not insensitive to gradients !

$$H_+C_+ \xrightarrow{I_z \Omega_z \tau}$$

$$\begin{aligned} H_+ \exp(-i\Omega_{Hz}\tau) C_+ \exp(-i\Omega_{Cz}\tau) &= H_+C_+ \exp(-i(\Omega_H + \Omega_H(z)) \tau) \exp(-i(\Omega_C + \Omega_C(z)) \tau) \\ &= H_+C_+ \exp(-i[\Omega_H + \Omega_C]\tau) \exp(-i[\Omega_H(z) + \Omega_C(z)]\tau) \\ &= H_+C_+ \exp(-i[\Omega_H + \Omega_C]\tau) \exp(-i[\gamma_H G + \gamma_C G]\tau) \\ &= H_+C_+ \exp(-i[\Omega_H + \Omega_C]\tau) \exp(-i[\gamma_H + \gamma_C] G \tau) \end{aligned}$$

$$H_+C_- \xrightarrow{I_z \Omega_z \tau}$$

$$\begin{aligned} H_+ \exp(-i\Omega_z\tau) C_- \exp(+i\Omega_z\tau) &= H_+C_- \exp(-i(\Omega_H + \Omega_H(z)) \tau) \exp(+i(\Omega_C + \Omega_C(z)) \tau) \\ &= H_+C_- \exp(-i[\Omega_H - \Omega_C]\tau) \exp(-i[\Omega_H(z) - \Omega_C(z)]\tau) \\ &= H_+C_- \exp(-i[\Omega_H - \Omega_C]\tau) \exp(-i[\gamma_H - \gamma_C] G \tau) \end{aligned}$$

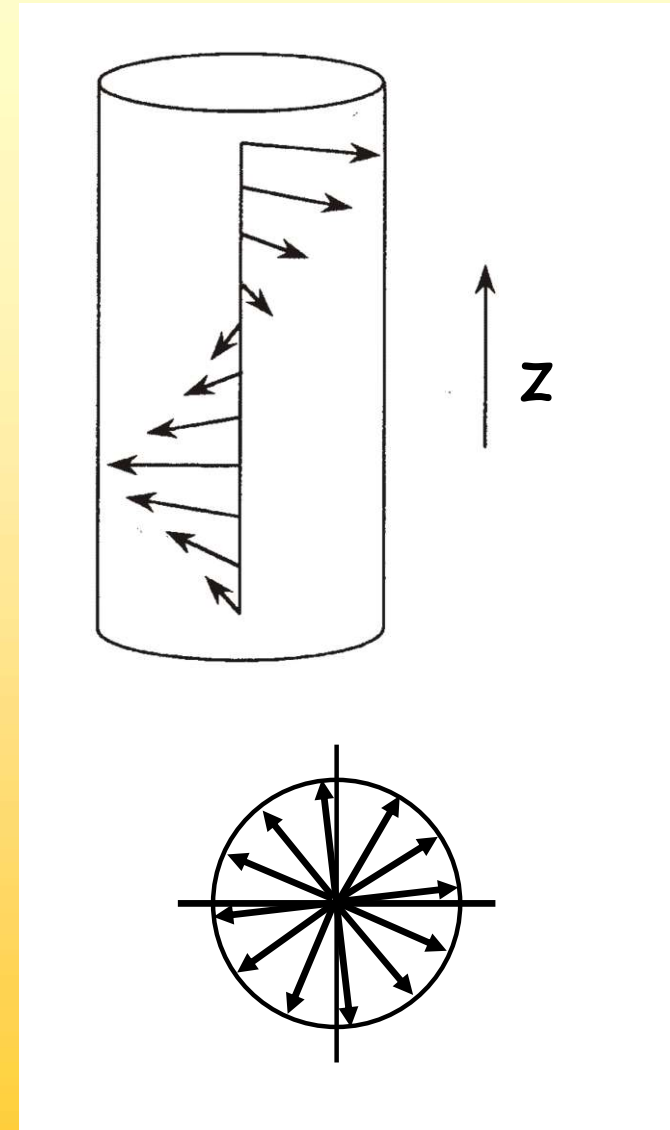
Gradients and coherence levels

Since the chemical shift evolution during the delay is spatially dependent, a single gradient will destroy magnetization.

However, the changes in the magnetic field are not random, the signal can thus be recovered by appropriate other gradients.

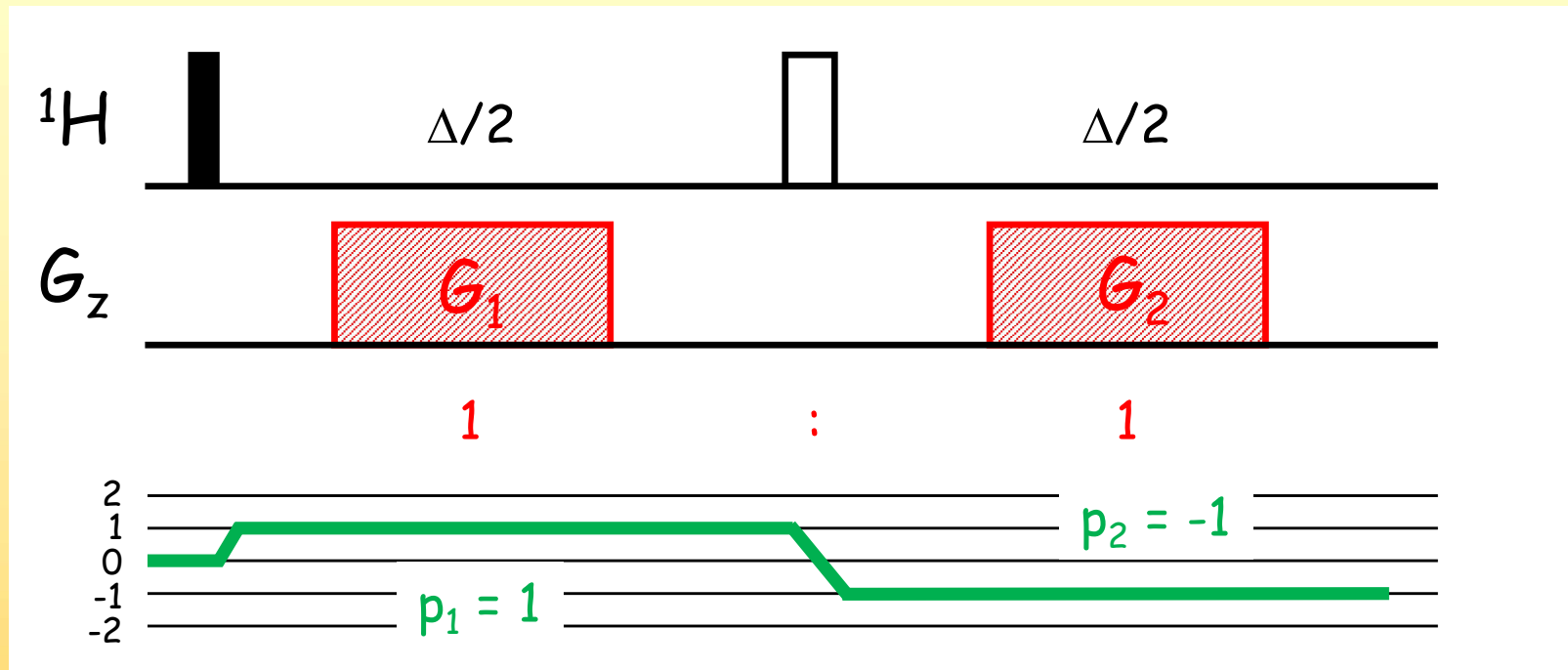
Gradients can be applied in both $+z$ and $-z$, i.e. in both directions of the magnetic field.

(Given the proper equipment one can also apply x and y gradients, but those are rarely used in high resolution NMR these days)



Gradients and coherence levels

To reverse the effect of a gradient there are several ways

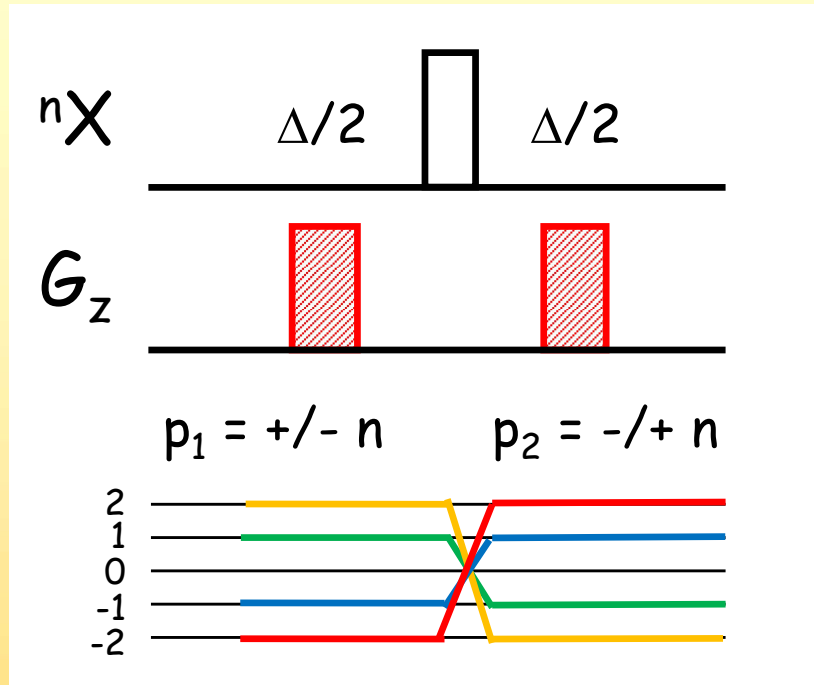


180° pulses reverse the effect of chemical shift and thus also that of gradients.

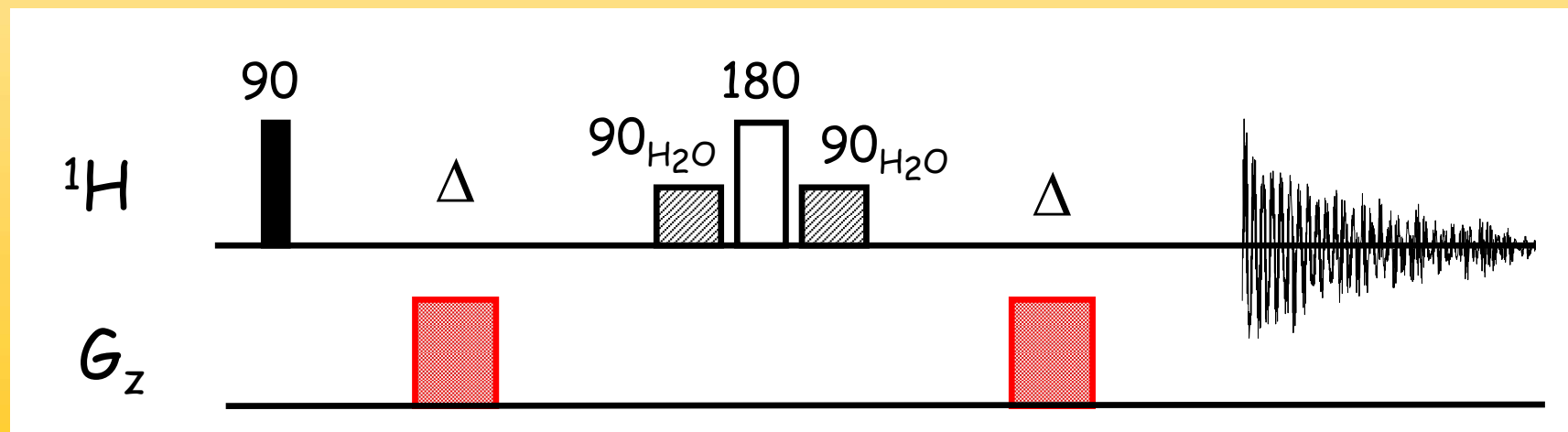
Another way of looking at it: the products of coherence order and gradient strength for all gradients have to add up to 0!

$$p_1 * G_1 + p_2 * G_2 = 1 * 1 + -1 * 1 = 0 \text{ (if } G_1 = G_2 \text{)}$$

Gradients and coherence levels

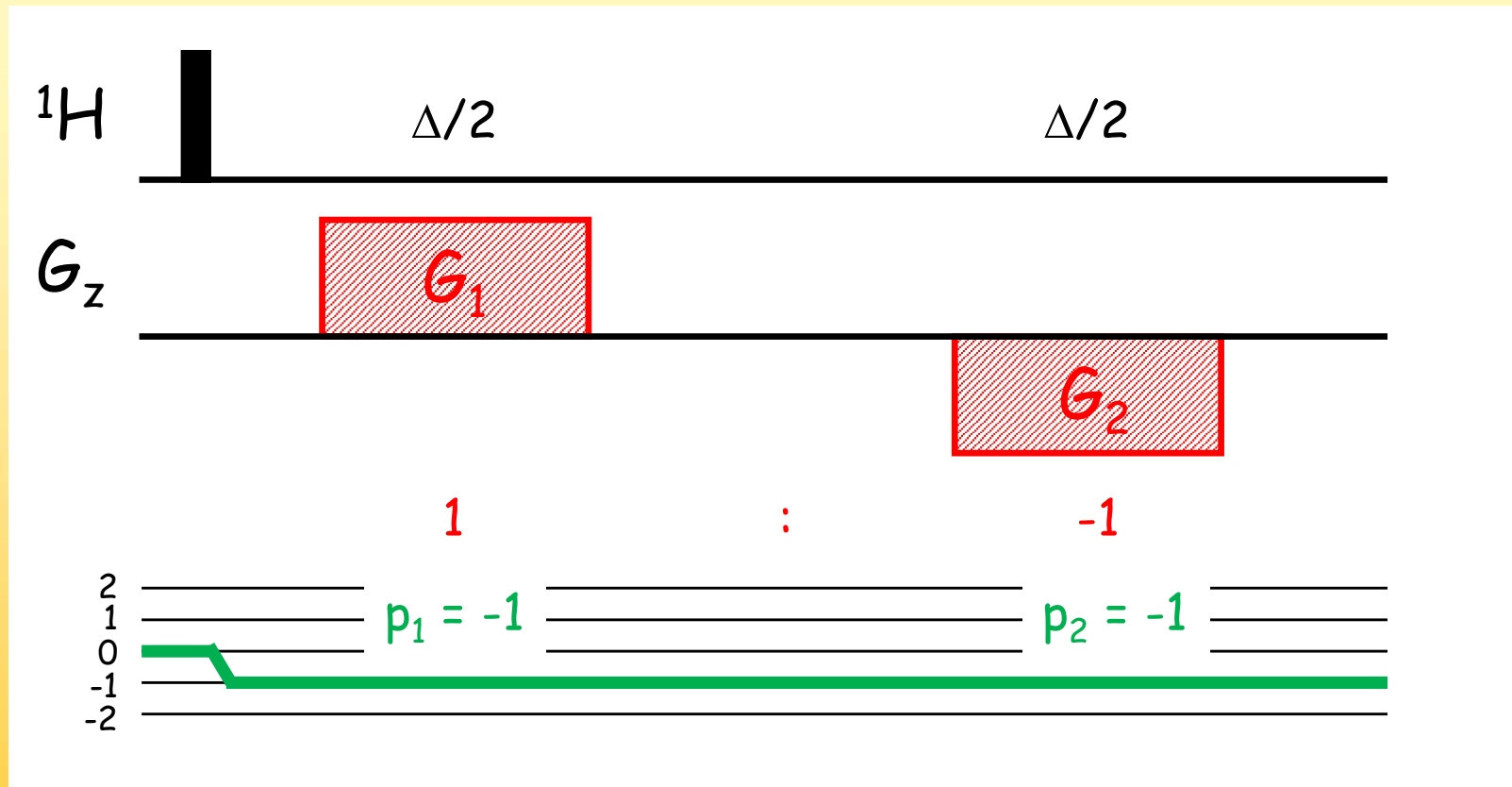


That is why two gradients
"clean up" a 180° pulse and why
WATERGATE works so well
for suppression of water signals



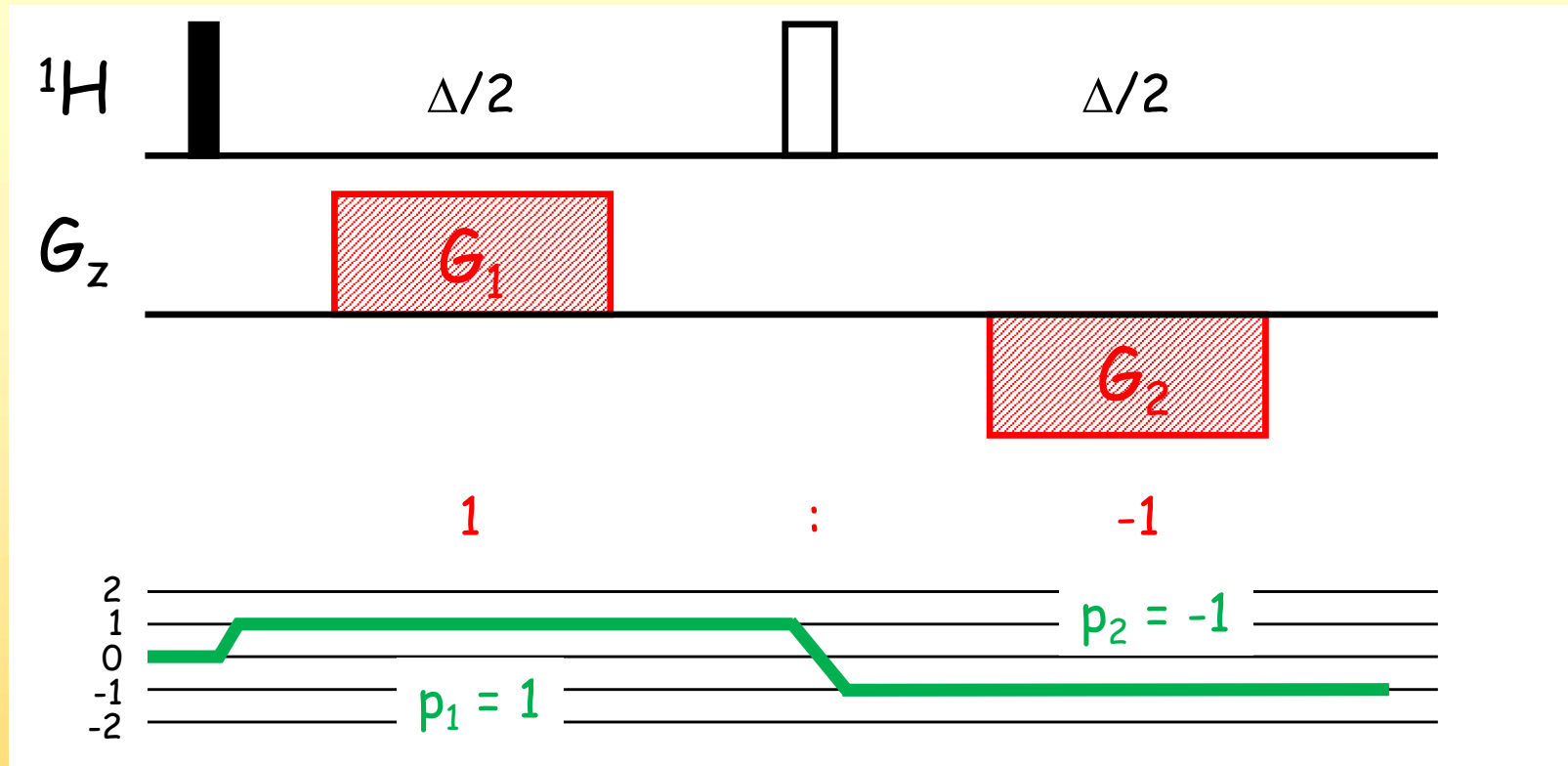
Gradients and coherence levels

Instead of changing the sign of the coherence order we can change that of the gradient



$$p_1 * G_1 + p_2 * G_2 = -1 * 1 + -1 * -1 = 0$$

Gradients and coherence levels



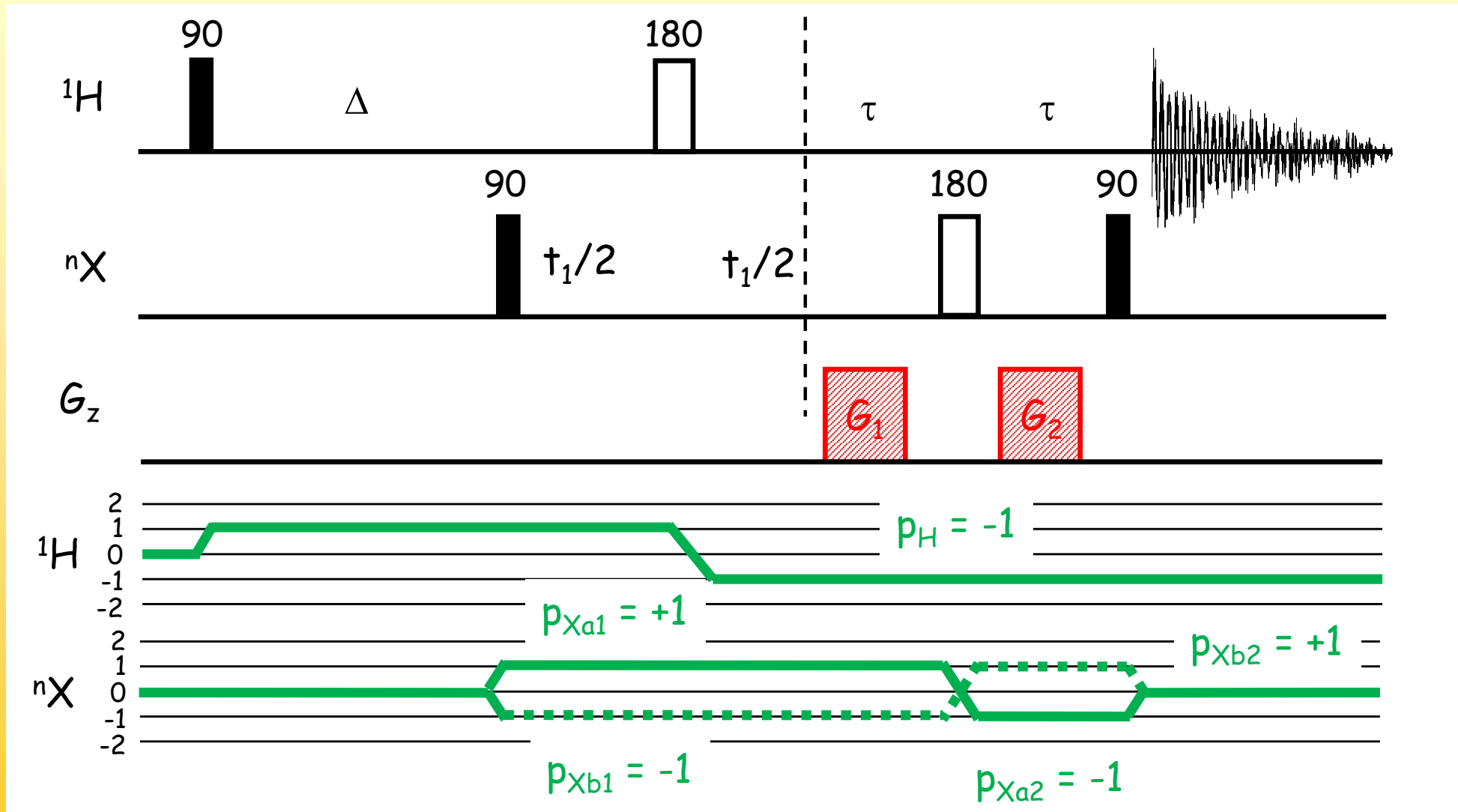
Here we use two opposite gradients to reduce the effect on the overall stability of the setup, but use the 180° pulse to still create a strong gradient

$$p_1 * G_1 + p_2 * G_2 = 1 * 1 + -1 * -1 = 2 \text{ (if } G_1 = -G_2\text{)}$$

These bipolar gradients are used e.g. in DOSY experiments

Gradients and coherence levels

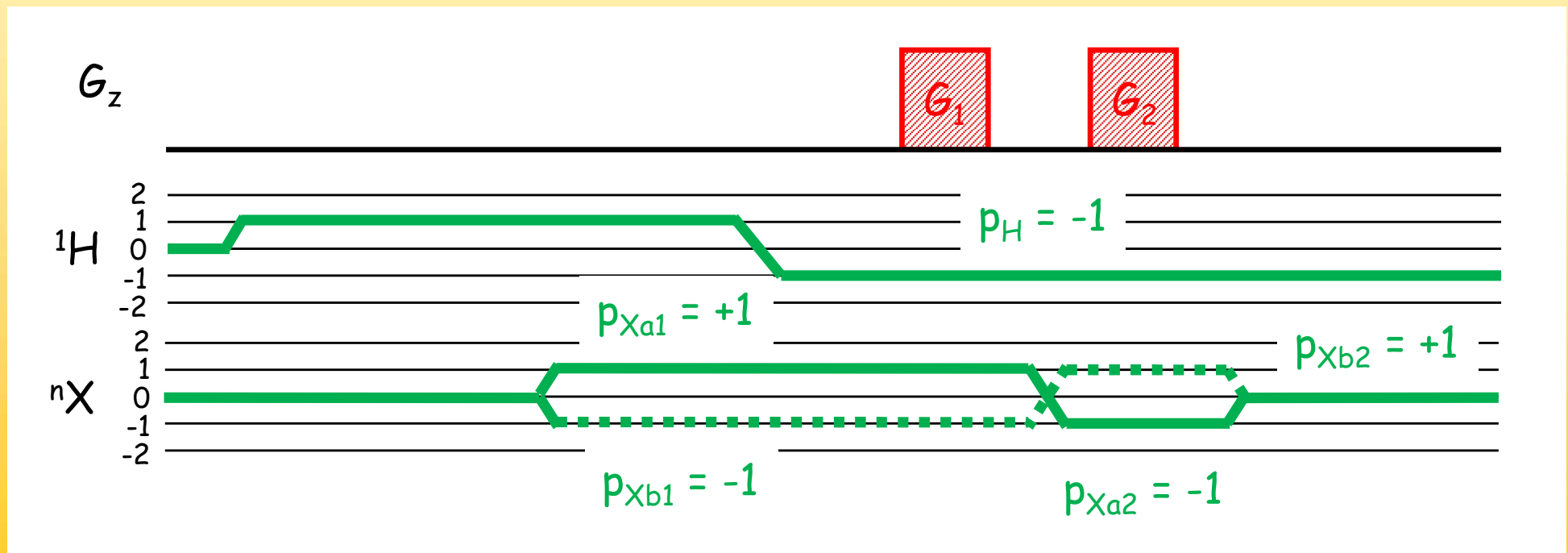
Now let's look at a "real" experiment: an HMBC with gradient selection



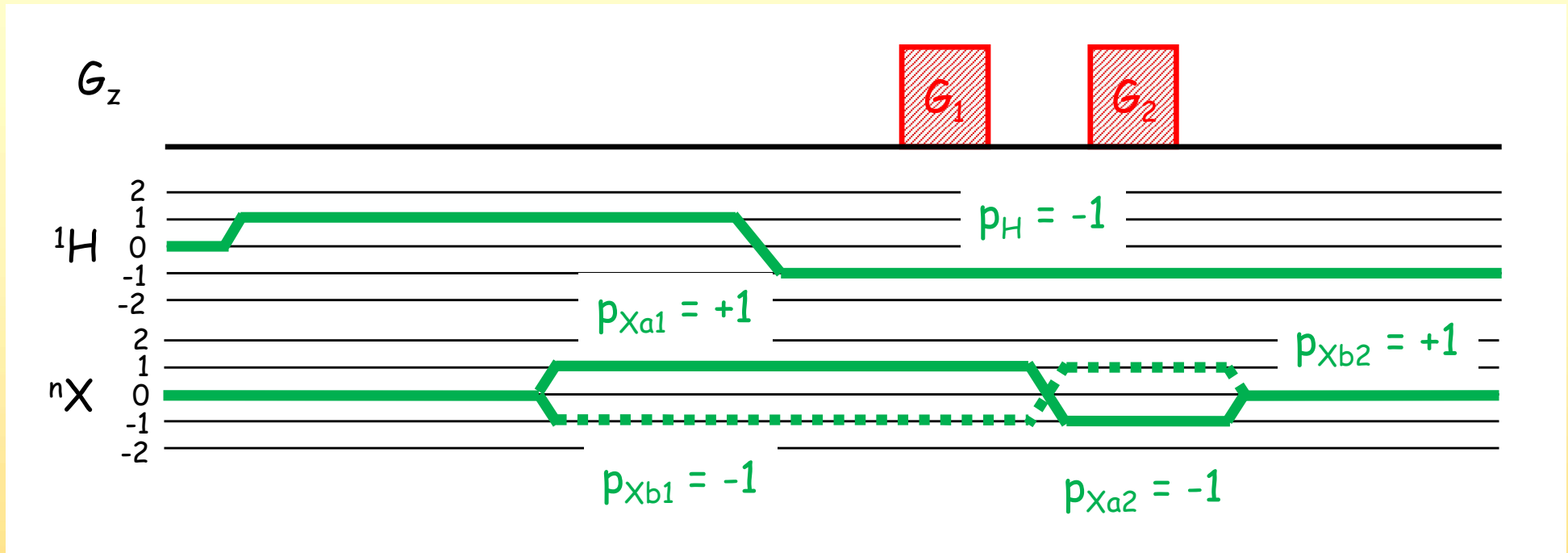
Gradients and coherence levels

Gradients, coherence levels and gyromagnetic ratio still have to add up to 0.

There are two pathways for the X-nucleus (we will learn later why), since gradients are sensitive to the sign of the coherence level we will not be able to select them simultaneously.



Gradients and coherence levels



Pathway a:

$$(p_H * \gamma_H + p_{Xa1} * \gamma_X) * G_1 + (p_H * \gamma_H + p_{Xa2} * \gamma_X) * G_2 = 0$$

$$(-\gamma_H + \gamma_X) * G_1 + (-\gamma_H - \gamma_X) * G_2 = 0$$

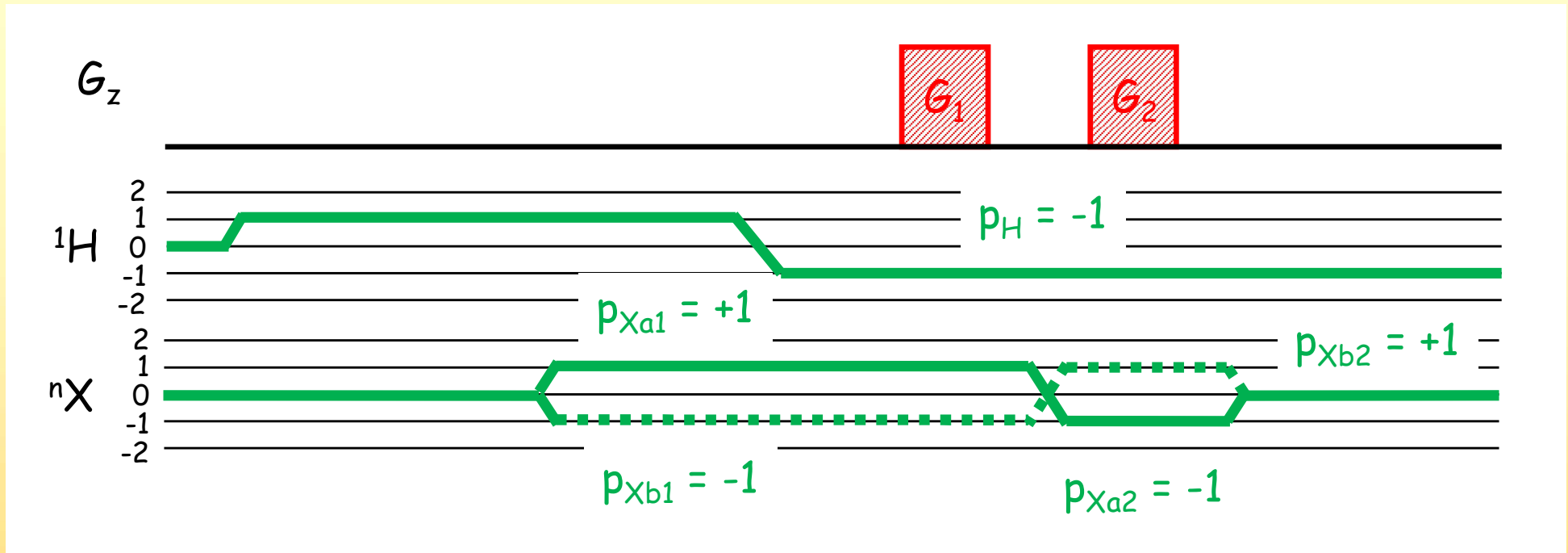
$$(-\gamma_H + \gamma_X) * G_1 = (\gamma_H + \gamma_X) * G_2$$

$$G_2 = \frac{(-\gamma_H + \gamma_X)}{(\gamma_H + \gamma_X)} * G_1 = \frac{(-\gamma_H + n * \gamma_H)}{(\gamma_H + n * \gamma_H)} * G_1 = -\frac{(1 - n)}{(1 + n)} * G_1$$

$$n = \gamma_X / \gamma_H$$



Gradients and coherence levels



Pathway b:

$$(p_H * \gamma_H + p_{Xb1} * \gamma_X) * G_1 + (p_H * \gamma_H + p_{Xb2} * \gamma_X) * G_2 = 0$$

$$(-\gamma_H - \gamma_X) * G_1 + (-\gamma_H + \gamma_X) * G_2 = 0$$

$$(-\gamma_H - \gamma_X) * G_1 = (\gamma_H - \gamma_X) * G_2$$

$$G_2 = \frac{(-\gamma_H - \gamma_X)}{(\gamma_H - \gamma_X)} * G_1 = \frac{(-\gamma_H - n * \gamma_H)}{(\gamma_H - n * \gamma_H)} * G_1 = -\frac{(1+n)}{(1-n)} * G_1$$

$$n = \gamma_X / \gamma_H$$

a vs. b

$$-\frac{(1-n)}{(1+n)} * G_1$$

Gradients and coherence levels

This is exactly what you will find in pulse programs, only written a little different.

```
"cnst30=(1-sfo2/sfo1)/(1+sfo2/sfo1)"

define list<gradient> EA1 = { 1.000 -cnst30}
define list<gradient> EA2 = { -cnst30 1.000}

(p3 ph4):f2
  d0
  (p2 ph2)
  d0
  p16:gp1*EA1
  d16
  (p24:sp7 ph5):f2
  DELTA4
  p16:gp1*EA2
  d16 p12:f2
  (p3 ph5):f2
  d20
  (p14:sp3 ph1):f2
  d20
  4u BLKGRAD
  go=2 ph31
```

$$n = \gamma_X / \gamma_H = \text{sfo2/sfo1}$$

$$\text{a: } G_2 = -G_1 \frac{(1 - n)}{(1 + n)}$$

$$\text{b: } G_2 = -G_1 \frac{(1 + n)}{(1 - n)}$$

$$G_1 = -G_2 \frac{(1 - n)}{(1 + n)}$$

Gradients and coherence levels

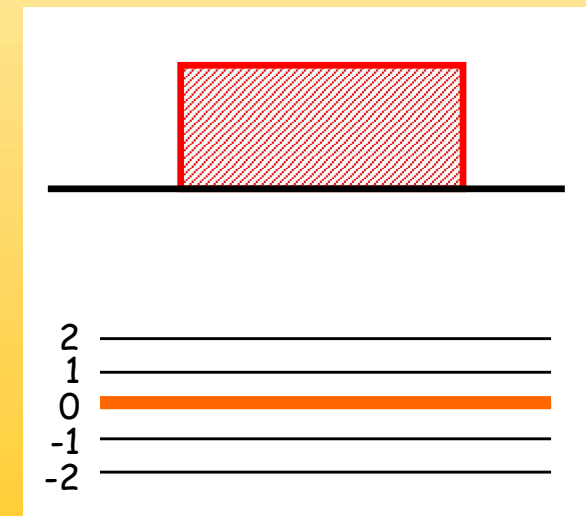
Two more things:

An advantage of gradients compared to phase cycling is that the selection is accomplished with a single scan, no addition or subtraction of signals is necessary. So there are no subtraction artefacts and the receiver gain can be adjusted to the desired signal and does not have to accommodate signals that disappear later.

We have seen already that gradients do NOT affect coherence order 0:

$p * G = 0$ for $p = 0$ independent of G !!

Since ZQC and z-magnetization both have coherence order 0, they can not be separated or suppressed by gradients (nor separated by phase cycling).



Quadrature detection in 2D

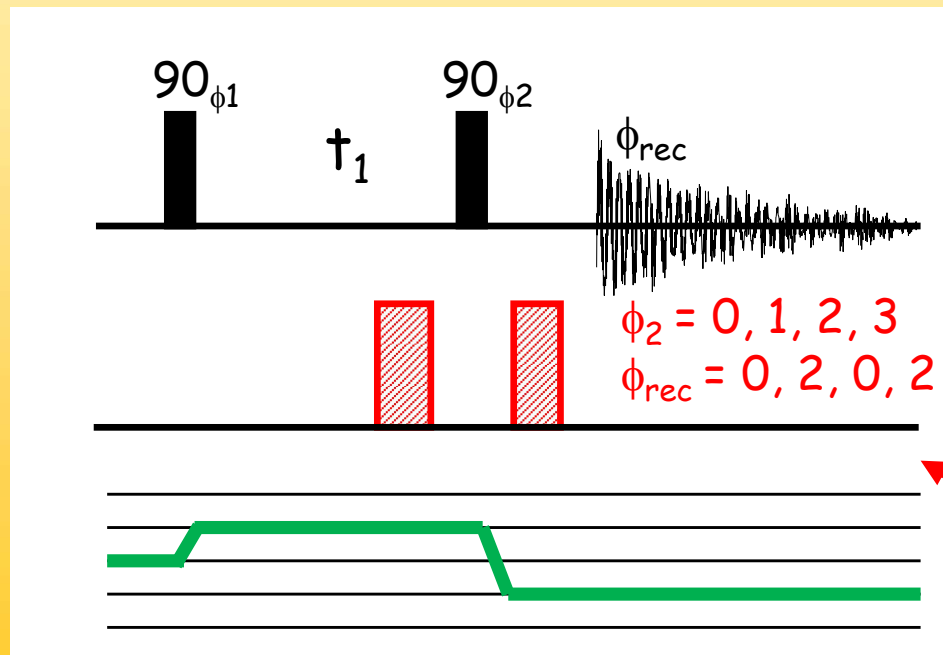
Quadrature Detection in 2D

The problem of sign discrimination when putting the carrier in the center of the spectrum occurs in every dimension of an nD-spectrum.

In case of 1D-NMR we have seen that we can solve the problem by obtaining a complex signal i.e. by selecting only one coherence level.

$$s(t) = \exp(i\Omega_0 t) \exp(-t/T_2)$$

$$S(\Omega) = A(\Omega) + i D(\Omega)$$



We have seen now that we can select one coherence level in the indirect dimension of an nD using either gradients or a phase cycle, so it should be easy to obtain a complex signal.

"Service-COSY"

Quadrature Detection in 2D

The signal we obtain is then:

$$s(t_1, t_2) = \exp(i\Omega_1 t_1) \exp(-t_1/T_2) \exp(i\Omega_2 t_2) \exp(-t_2/T_2)$$

After the first FT we get:

$$S(t_1, \Omega_2) = \exp(i\Omega_1 t_1) \exp(-t_1/T_2) [A(\Omega_2) + i D(\Omega_2)]$$

And the second FT yields:

$$S(\Omega_1, \Omega_2) = [A(\Omega_1) + i D(\Omega_1)] [A(\Omega_2) + i D(\Omega_2)]$$

$$S(\Omega_1, \Omega_2) = [A(\Omega_1) A(\Omega_2) - D(\Omega_1) D(\Omega_2)] + i [A(\Omega_1) D(\Omega_2) + D(\Omega_1) A(\Omega_2)]$$

We will only look at the real part of the spectrum and as it turns out the frequency discrimination worked but we have dispersive components in the signal ! We need a magnitude calculation and loose resolution.

Quadrature Detection in 2D

The solution is to record and store the real and imaginary part in the indirect dimension separately as cosine and sine component. After the first FT we get:

$$S_C(t_1, \Omega_2) = \cos(\Omega_A t_1) \exp(-t_1/T_2) [A(\Omega_2) + i D(\Omega_2)]$$

$$S_S(t_1, \Omega_2) = \sin(\Omega_A t_1) \exp(-t_1/T_2) [A(\Omega_2) + i D(\Omega_2)]$$

If we now take only the real part and combine both to yield a complex dataset we get what we want:

$$S(t_1, \Omega_2) = [\cos(\Omega_A t_1) + i \sin(\Omega_A t_1)] \exp(-t_1/T_2) A(\Omega_2)$$

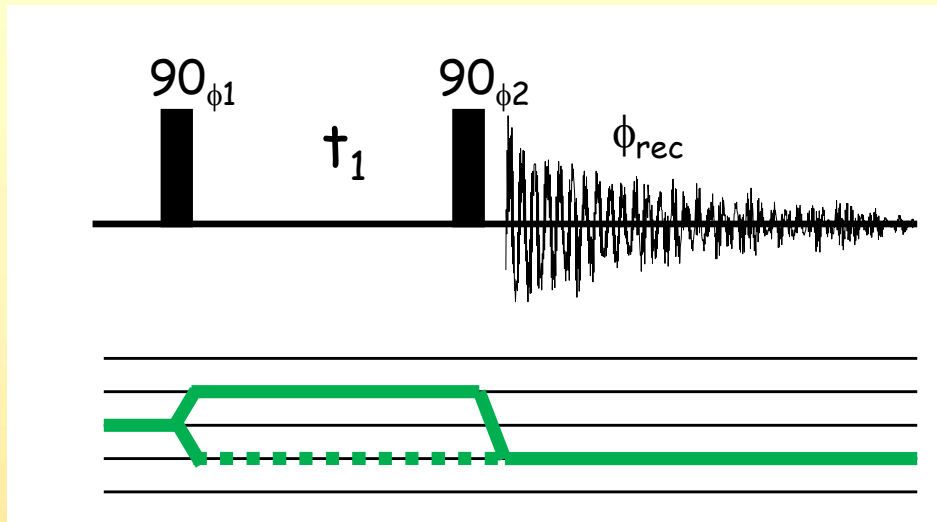
$$S(t_1, \Omega_2) = \exp(i\Omega_A t_1) \exp(-t_1/T_2) A(\Omega_2)$$

$$S(\Omega_1, \Omega_2) = [A(\Omega_1) + i D(\Omega_1)] A(\Omega_2)$$

$$S(\Omega_1, \Omega_2) = A(\Omega_1) A(\Omega_2) + i D(\Omega_1) A(\Omega_2)$$

Now the real part has pure absorption phase, this is Ruben-States-Haberhorn

Quadrature Detection in 2D



This means that we allow two coherence levels (ϕ_2 needs to be set properly).

In addition, we have to manipulate ϕ_1 , to obtain a cosine and a sine signal:

$$\phi_1 = x, \phi_2 = x$$

$$I_z \xrightarrow{90^\circ I_x} -I_y \xrightarrow{I_z \Omega \tau} -I_y \cos \Omega t + I_x \sin \Omega t \xrightarrow{90^\circ I_x} -I_z \cos \Omega t + I_x \sin \Omega t$$

$$\phi_1 = y, \phi_2 = x$$

$$I_z \xrightarrow{90^\circ I_y} I_x \xrightarrow{I_z \Omega \tau} I_x \cos \Omega t + I_y \sin \Omega t \xrightarrow{90^\circ I_x} I_x \cos \Omega t + I_z \sin \Omega t$$

Quadrature Detection in 2D

There are several established ways to do it, TPPI is the 2D-variant of the Redfield-trick.

They all achieve the same goal but they differ in the way they affect axial peaks and the position of peaks outside the frequency range given by the Nyquist theorem.

"States"			"States-TPPI"			"TPPI"		
ϕ_1	t_1	ϕ_{rec}	ϕ_1	t_1	ϕ_{rec}	ϕ_1	t_1	ϕ_{rec}
x	0	x	x	0	x	x	0	x
y	0	x	y	0	x	y	$\Delta t/2$	x
x	Δt	x	-x	Δt	-x	-x	Δt	x
y	Δt	x	-y	Δt	-x	-y	$3\Delta t/2$	x

Quadrature Detection in 2D

By collecting a sine in first FID and cosine in the second, the other part does not contribute to the signal and is "wasted".

$$\phi_1 = x, \phi_2 = x$$

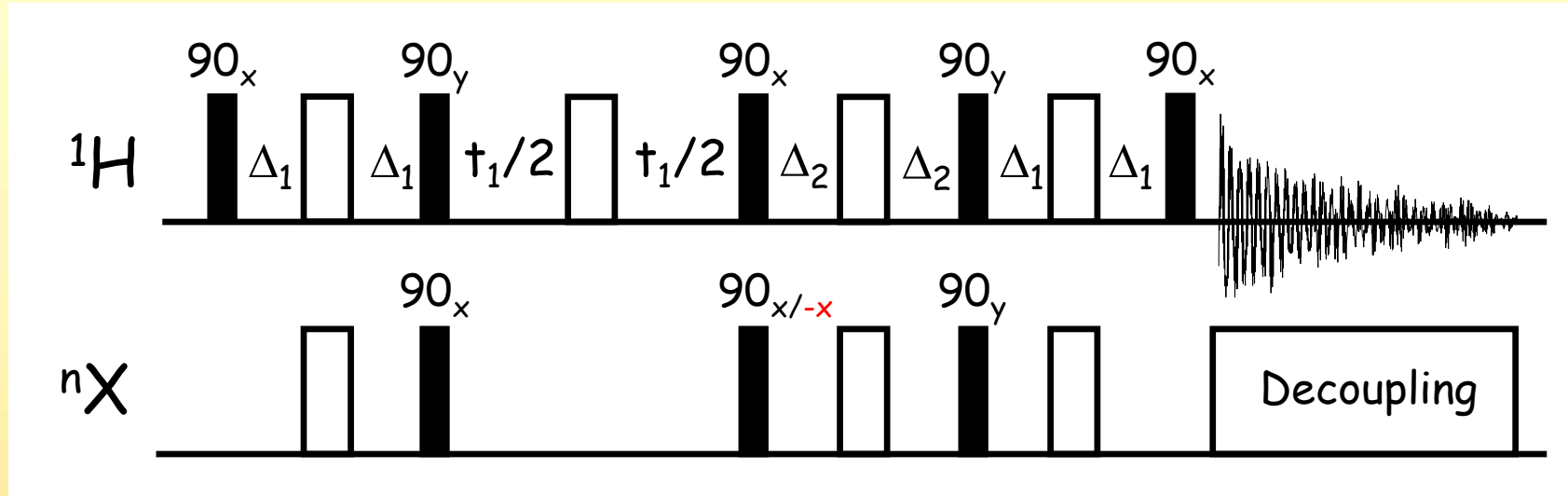
$$I_z \xrightarrow{90^\circ I_x} -I_y \xrightarrow{I_z \Omega \tau} -I_y \cos \Omega t + I_x \sin \Omega t \xrightarrow{90^\circ I_x} \cancel{-I_z \cos \Omega t} + I_x \sin \Omega t$$

$$\phi_1 = y, \phi_2 = x$$

$$I_z \xrightarrow{90^\circ I_y} I_x \xrightarrow{I_z \Omega \tau} I_x \cos \Omega t + I_y \sin \Omega t \xrightarrow{90^\circ I_x} I_x \cos \Omega t + \cancel{I_z \sin \Omega t}$$

To recover that loss a scheme was designed that obtained the name "sensitivity enhancement", even so the length of the sequence prevents an actual enhancement in case of faster relaxing molecules. One part of the signal is stored and the other recovered during the sequence.

Quadrature Detection in 2D



The idea is to collect two FIDs with a slightly modified phase cycle that will allow both components to reach the receiver, albeit with different sign, and store them separately for further manipulation

$$- N_y H_z \cos \Omega t_1 + N_x H_z \sin \Omega t_1 \longrightarrow + N_z H_y \cos \Omega t_1 + N_x H_y \sin \Omega t_1 \longrightarrow$$

$$+ H_x \cos \Omega t_1 + N_x H_y \sin \Omega t_1 \longrightarrow + H_z \cos \Omega t_1 - N_z H_y \sin \Omega t_1 \longrightarrow$$

$$+ H_z \cos \Omega t_1 + H_x \sin \Omega t_1 \longrightarrow + H_y \cos \Omega t_1 + H_x \sin \Omega t_1$$

Quadrature Detection in 2D

Now we take the sum and the difference of the both FIDs we have collected

$$\begin{array}{lcl}
 & \text{sum} & \rightarrow 2 H_x \sin\Omega t_1 \\
 + H_y \cos\Omega t_1 + H_x \sin\Omega t_1 & & \\
 & \text{difference} & \rightarrow 2 H_y \cos\Omega t_1
 \end{array}$$

We have calculated before that we can convert H_y into H_x by taking the FID resulting from that magnetization and switching real and imaginary part and changing the sign of the real part.

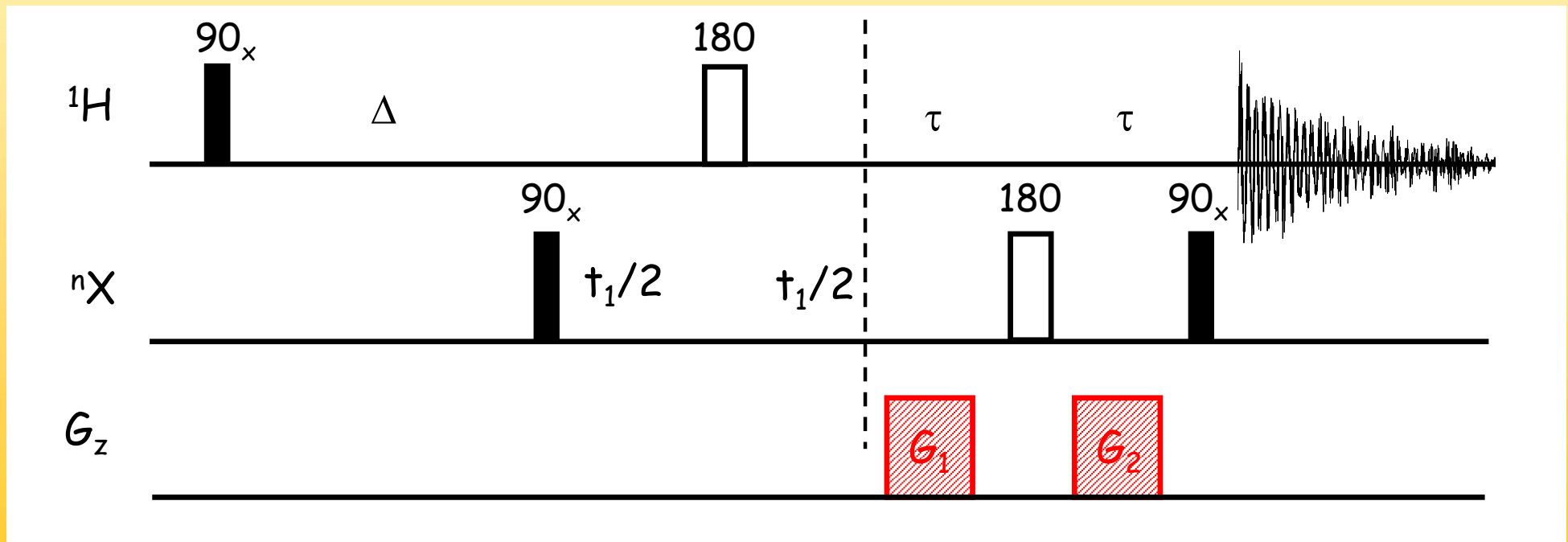
We thus obtain the two signals:

$$2 H_x \cos\Omega t_1 \quad 2 H_x \sin\Omega t_1$$

Which is exactly the same as if we would have done States, except we have a factor of 2 in there, which will lead to the enhancement.

Quadrature Detection in 2D

A related situation occurs when using gradients for coherence selection. We have seen that we can only select one pathway but that we need two. The solution has already been presented in the previous section we can use different signs for the gradients and collect both pathways. Since they are called echo and anti-echo so is the quadrature procedure.

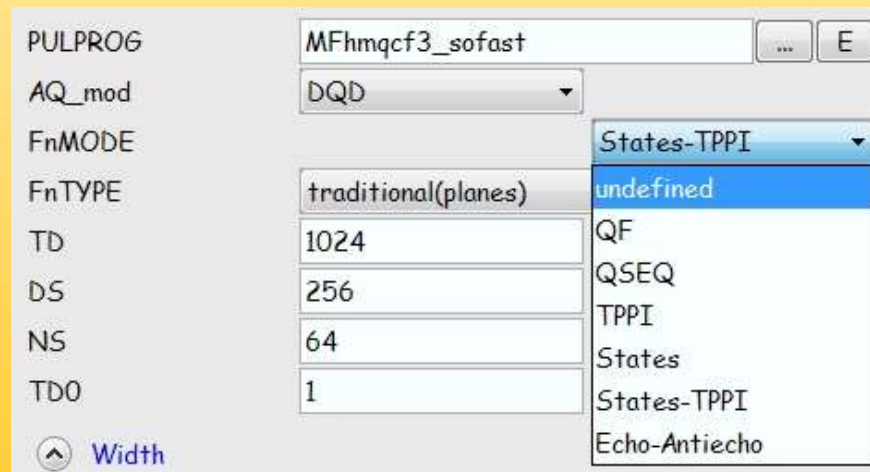


Quadrature Detection in 2D

In echo/anti-echo we collect both X_+ and X_- . Since these contain $[X_x + X_y]$ as well as $[X_x - X_y]$ and since $\exp(\pm \Omega_x t)$ contains a sine and a cosine, manipulation of the magnetization is possible to yield the same situation as with sensitivity enhancement:

$$H_x \cos(\Omega_x t_1) \pm H_y \sin(\Omega_x t_1)$$

Again forming the sum and the difference and manipulating the real and imaginary part somewhat yields data to be processed like States.



On Bruker spectrometers you actually choose the type of quadrature detection and the software will do it for you

Quadrature Detection in 2D

We heard already that the different schemes for quadrature detection differ in the way they handle axial peaks.

Axial peaks arise from magnetization that does not experience the phase shifts prior to the evolution time. These signals are treated differently by the various quadrature detection schemes. They do not "feel" changes in ϕ_1 and thus only experience the receiver phase.

ϕ_1	τ_1	ϕ_{rec}
x	0	x
y	0	x
x	Δt	x
y	Δt	x

If we use States the axial peaks will be detected as what they are: peaks at zero frequency which is the center of the spectrum

Quadrature Detection in 2D

ϕ_1	τ_1	ϕ_{rec}
x	0	x
y	0	x
-x	Δt	-x
-y	Δt	-x

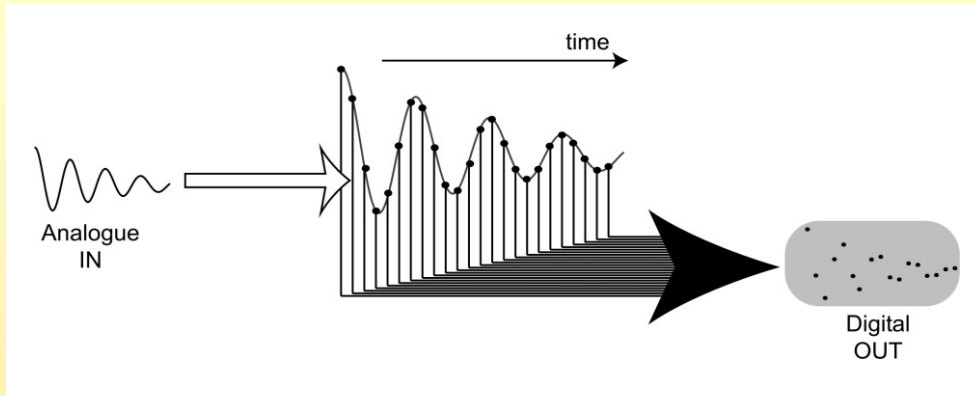
ϕ_1	τ_1	ϕ_{rec}
x	0	x
y	$\Delta t/2$	x
-x	Δt	x
-y	$3\Delta t/2$	x

In case of **States-TPPI**, the sign of the receiver is changed from point to point.

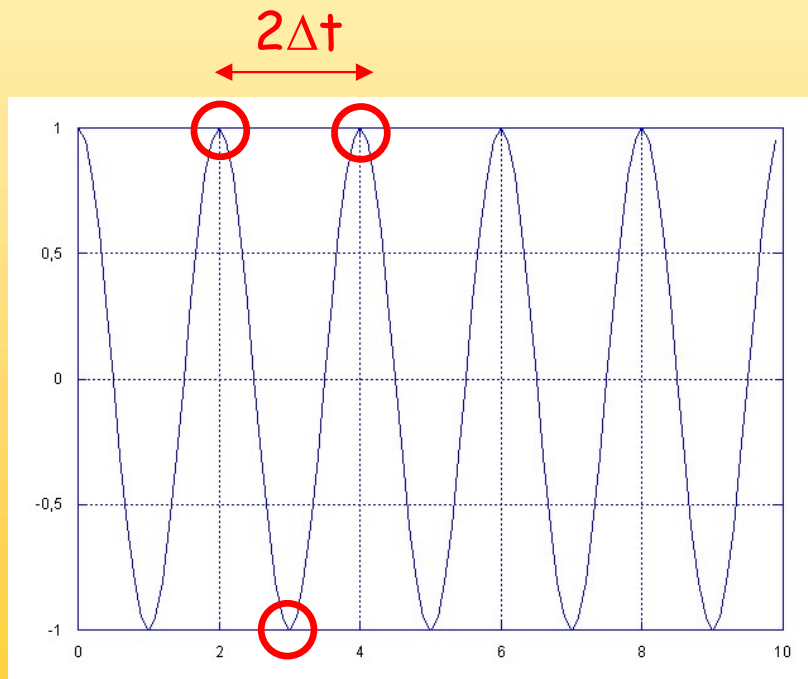
Since the same is done for ϕ_1 , the real signals do not differ from States. But the axial peaks are shifted by half the sweep width to the edge of the spectrum.

In case of **TPPI**, the sign of the receiver is not changed so the axial peaks stay in the center. But the real peaks are shifted and the processing moves the spectrum by half the sweep width so the axial peaks are again at the edge.

Quadrature Detection in 2D



The effects that are observed regarding peaks outside the chosen spectral range result from the digitization of the signal prior to processing.



The Nyquist-theorem states that the highest frequency detectable with a sampling rate of Δt is

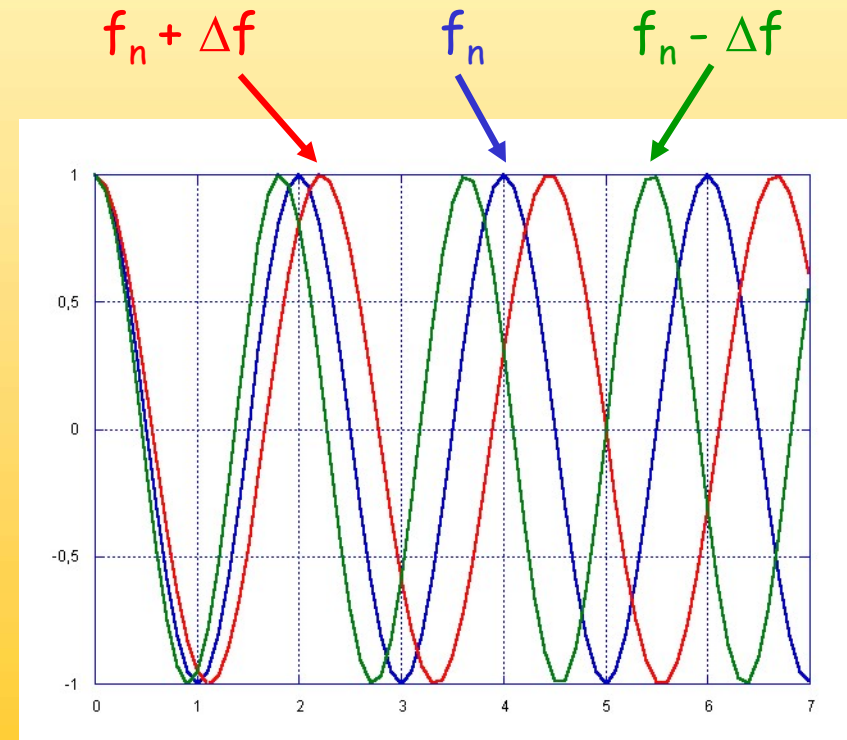
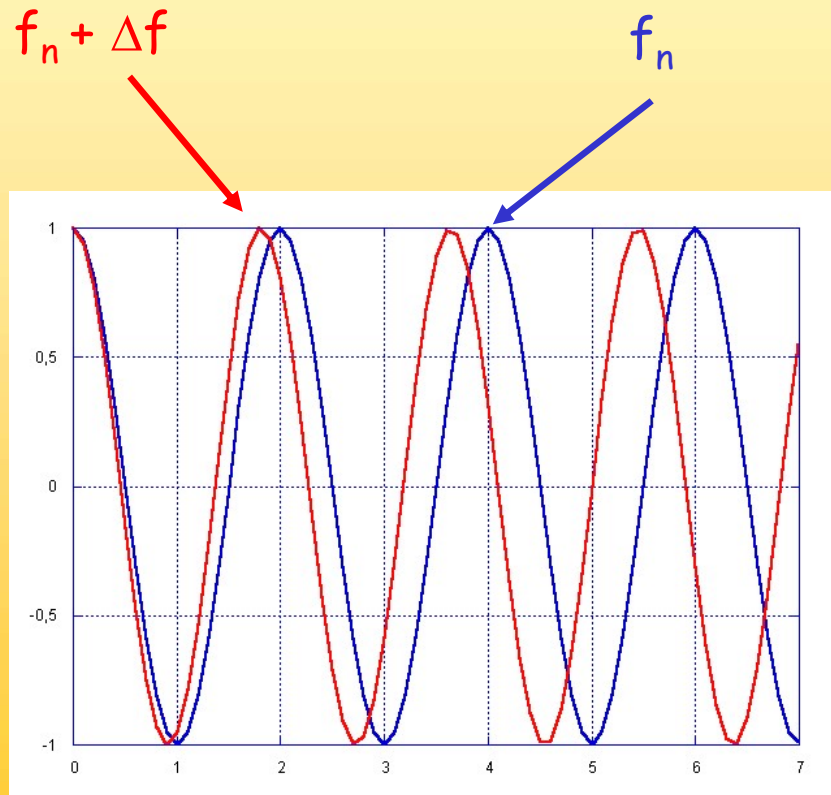
$$f_n = 1/(2\Delta t)$$

which means that we have to have three datapoints per period. Since we can distinguish the sign we have a spectral width

$$SW = 2 * f_n = 1/\Delta t$$

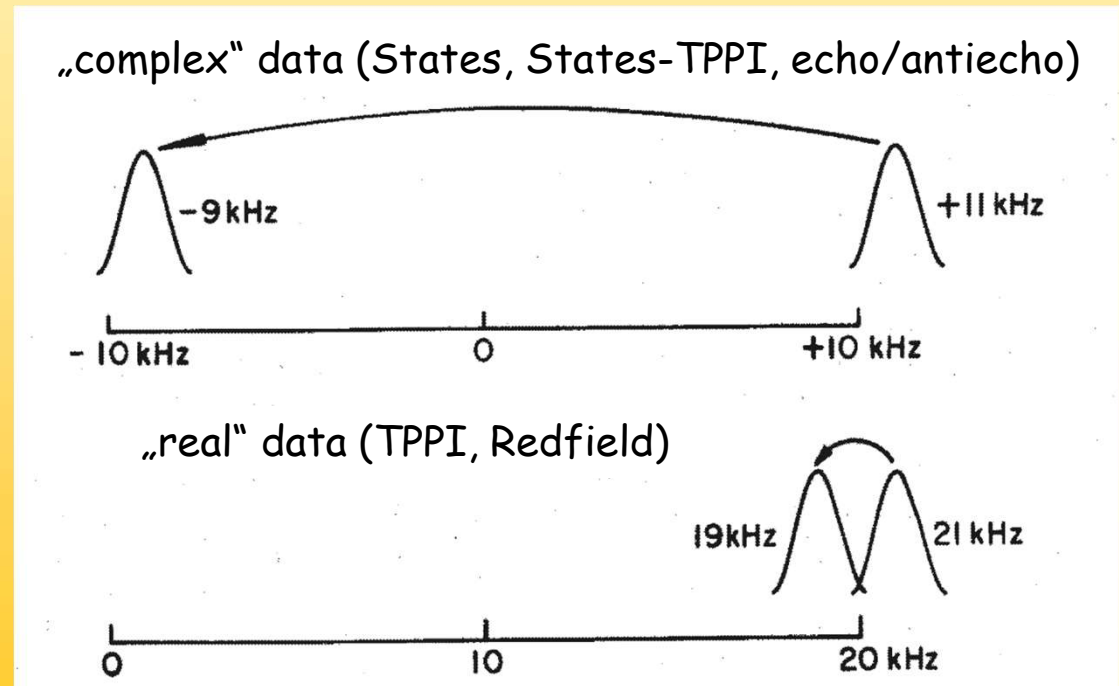
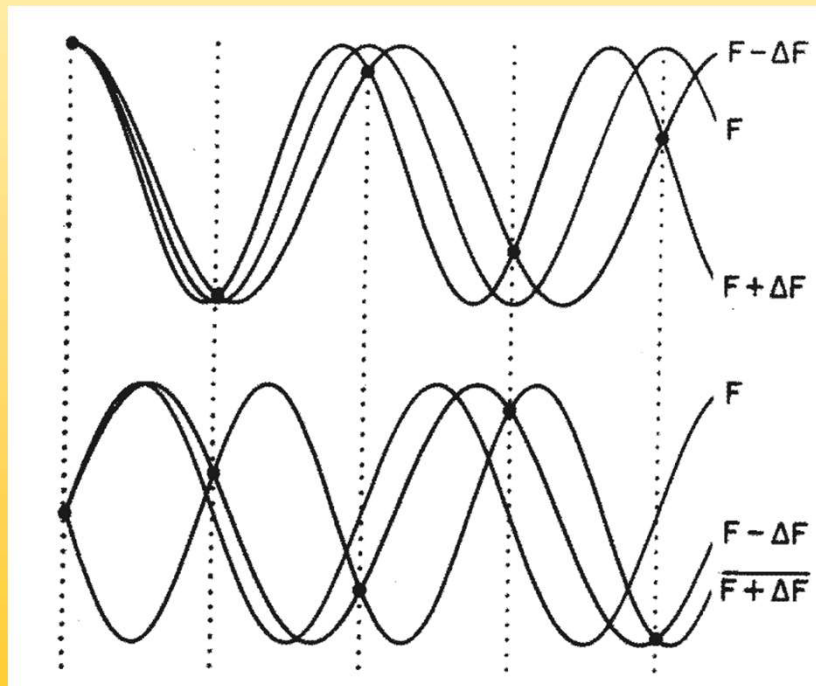
Quadrature Detection in 2D

If a frequency is **higher** than the **Nyquist-Frequency** it simply appears as if the frequency were **lower** since the digitizer can simply not distinguish the higher frequency from a lower one within the "Nyquist range".



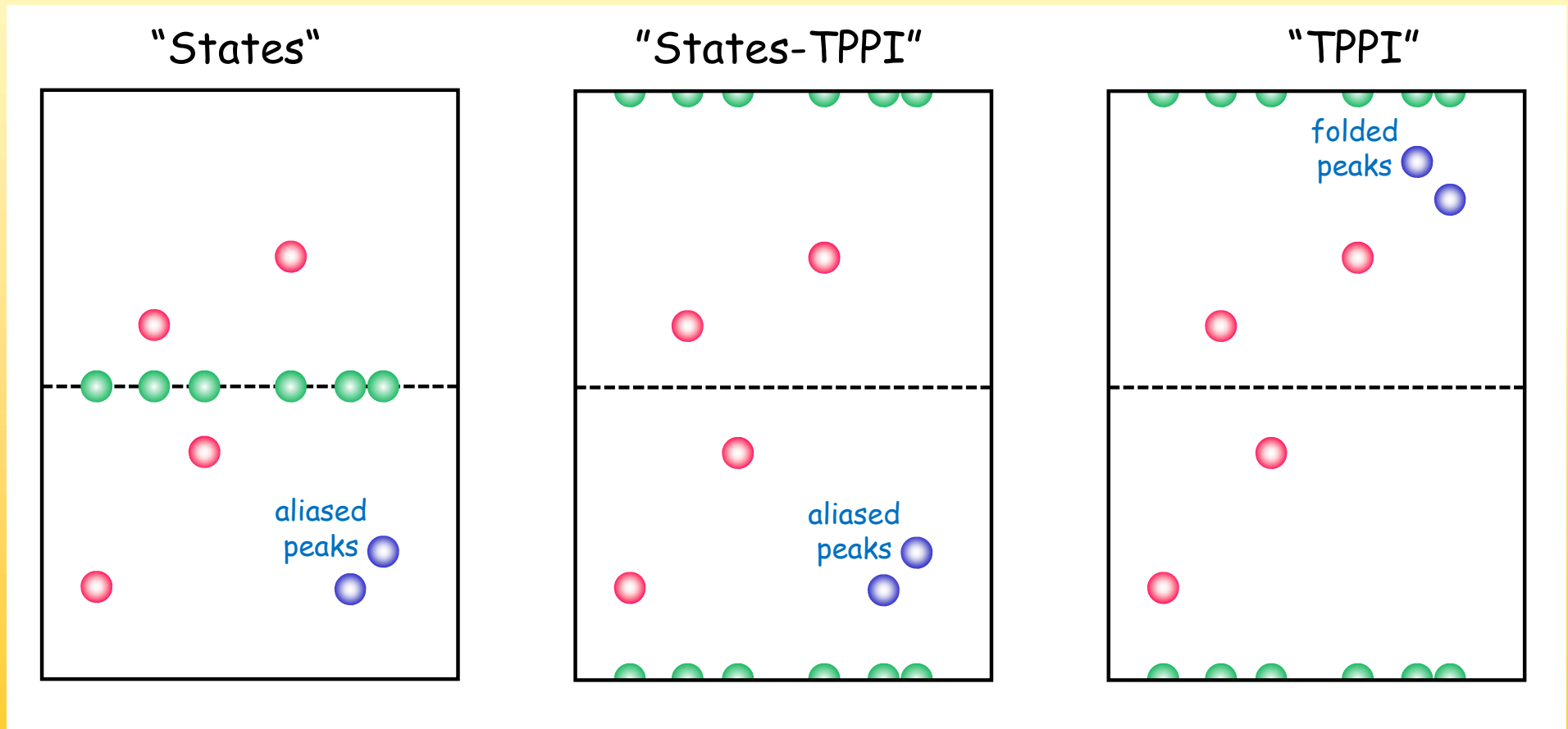
Quadrature Detection in 2D

The sign of a frequency outside the Nyquist range is dependent on the type of sampling. If only a cosine signal is collected (TPPI, Redfield) then a signal is "folded", i.e. $F+\Delta F$ is replaced by $F-\Delta F$. If a complex signal is collected (States, States-TPPI, echo/antiecho), then the signal is "aliased", i.e. $F+\Delta F$ is replaced by $-(F-\Delta F)$



Quadrature Detection in 2D

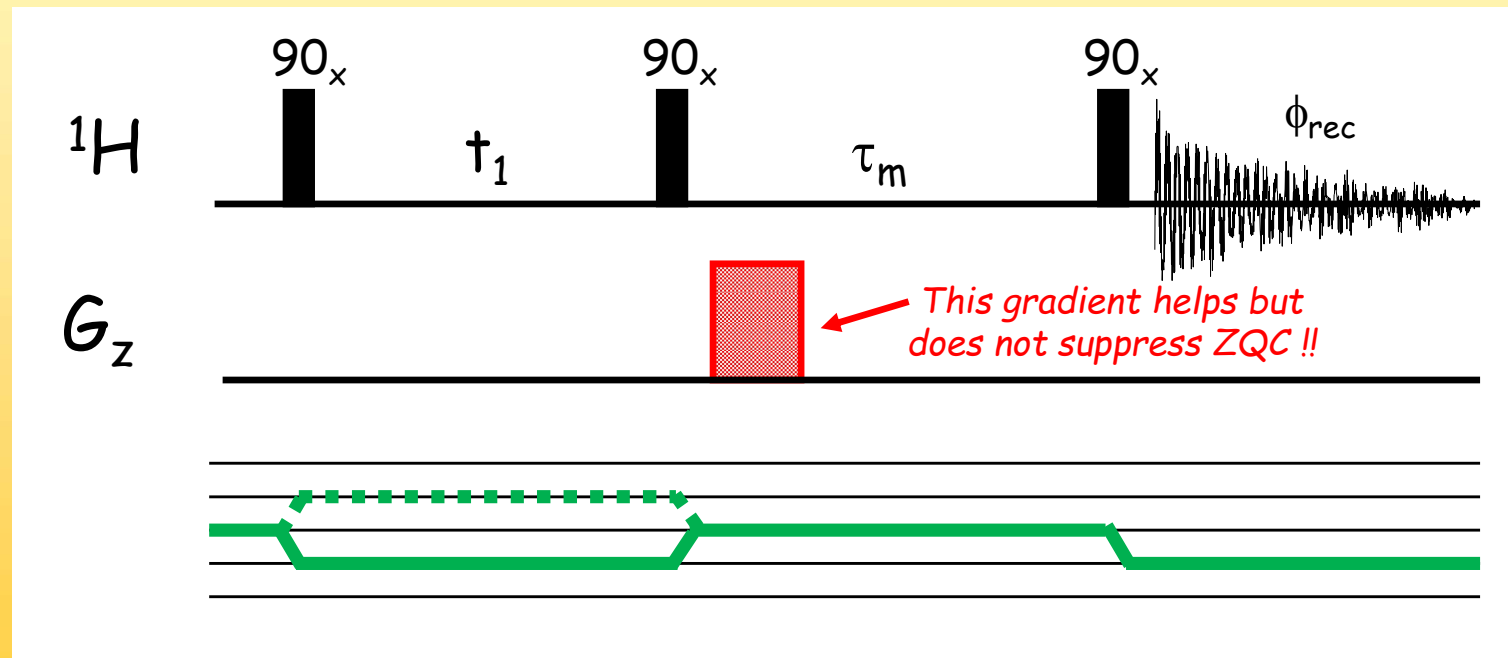
In summary all schemes yield in principle identical results, they differ, however, with respect to axial peak suppression and in the way peaks outside the spectral range are folded or aliased.



Z-Filter (ZQ-Suppression)

Z-Filter (ZQ-Suppression)

We have already discussed that neither a gradient nor phase-cycling is capable of separating z-magnetization from ZQC and thus suppressing one of them. This is a problem in several types of spectra the most prominent one is the NOESY of small molecules.



For larger molecules ZQC relax quite fast and vanish on their own

Z-Filter (ZQ-Suppression)

Why is that a problem ?

$$\begin{aligned}
 & H_{1z} \xrightarrow{90^\circ H_x} -H_{1y} \xrightarrow{2\pi\delta_{H1}t_1} -H_{1y} \cos 2\pi\delta_{H1}t_1 + H_{1x} \sin 2\pi\delta_{H1}t_1 \\
 & \xrightarrow{\pi J_{HH}t_1} -H_{1y} \cos 2\pi\delta_{H1}t_1 \cos \pi J_{HH}t_1 + 2H_{1x} H_{2z} \cos 2\pi\delta_{H1}t_1 \sin \pi J_{HH}t_1 \\
 & \quad + H_{1x} \sin 2\pi\delta_{H1}t_1 \cos \pi J_{HH}t_1 + 2H_{1y} H_{2z} \sin 2\pi\delta_{H1}t_1 \sin \pi J_{HH}t_1 \\
 & \xrightarrow{90^\circ H_x} \boxed{-H_{1z} \cos 2\pi\delta_{H1}t_1 \cos \pi J_{HH}t_1} - \boxed{2H_{1x} H_{2y} \cos 2\pi\delta_{H1}t_1 \sin \pi J_{HH}t_1} \\
 & \quad + H_{1x} \sin 2\pi\delta_{H1}t_1 \cos \pi J_{HH}t_1 - 2H_{1z} H_{2y} \sin 2\pi\delta_{H1}t_1 \sin \pi J_{HH}t_1
 \end{aligned}$$

This will yield the NOESY peaks

But this contains ZQCs !!

$$\begin{aligned}
 & \xrightarrow{\tau_m, 90^\circ H_x} H_{1y} \cos 2\pi\delta_{H1}t_1 \cos \pi J_{HH}t_1 + H_{2y} \cos 2\pi\delta_{H1}t_1 \cos \pi J_{HH}t_1 \\
 & \xrightarrow{t_2} H_{1y} \cos 2\pi\delta_{H1}t_1 \cos \pi J_{HH}t_1 \cos 2\pi\delta_{H1}t_2 \cos \pi J_{HH}t_2 \quad \text{diagonal peak} \\
 & \quad H_{2y} \cos 2\pi\delta_{H1}t_1 \cos \pi J_{HH}t_1 \cos 2\pi\delta_{H2}t_2 \cos \pi J_{HH}t_2 \quad \text{cross peak}
 \end{aligned}$$

Z-Filter (ZQ-Suppression)

$$\begin{aligned}
 2H_{1x} H_{2y} &= 2 \left(\frac{1}{2}(H_{1+} + H_{1-}) \right) \frac{1}{2}i (H_{2+} - H_{2-}) = \frac{1}{2}i [H_{1+}H_{2+} + H_{1-}H_{2+} - H_{1+}H_{2-} - H_{1-}H_{2-}] \\
 &\qquad\qquad\qquad \text{ZQC} \\
 &= \frac{1}{2}i [H_{1-}H_{2+} - H_{1+}H_{2-}] = \frac{1}{2}i [(H_{1x} - i H_{1y})(H_{2x} + i H_{2y}) - (H_{1x} + i H_{1y})(H_{2x} - i H_{2y})] \\
 &= \frac{1}{2}i [H_{1x}H_{2x} - i H_{1y}H_{2x} + i H_{1x}H_{2y} + H_{1y}H_{2y} - H_{1x}H_{2x} - i H_{1y}H_{2x} + i H_{1x}H_{2y} - H_{1y}H_{2y}] \\
 &= H_{1x}H_{2y} - H_{1y}H_{2x}
 \end{aligned}$$

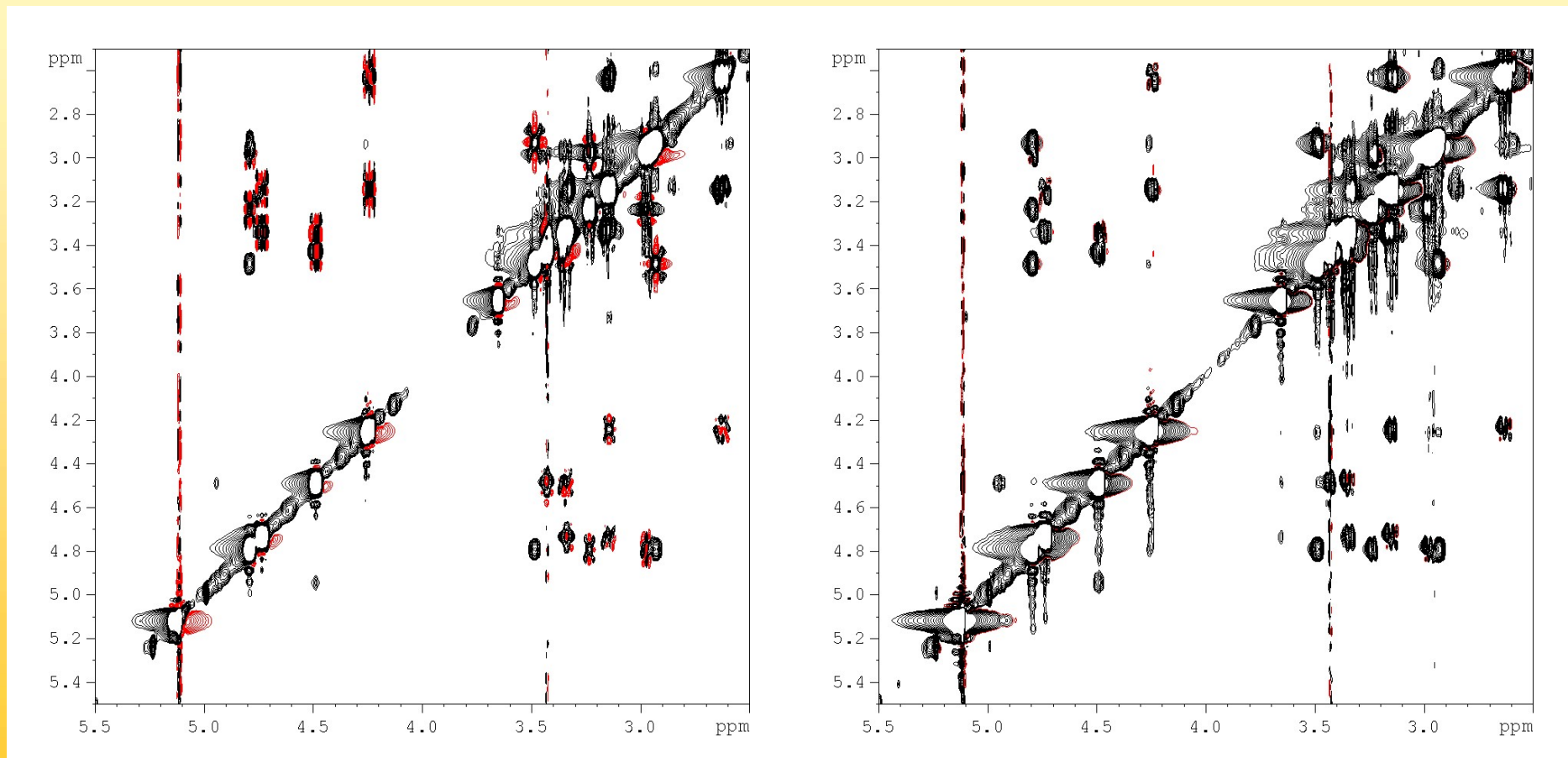
$$\xrightarrow{90^\circ H_x} H_{1x} H_{2z} \cos 2\pi\delta_{H1}t_1 \sin \pi J_{HH}t_1 - H_{1z} H_{2x} \cos 2\pi\delta_{H1}t_1 \sin \pi J_{HH}t_1$$

$$\begin{aligned}
 \xrightarrow{t_2} & H_{1y} \cos 2\pi\delta_{H1}t_1 \sin \pi J_{HH}t_1 \cos 2\pi\delta_{H1}t_2 \sin \pi J_{HH}t_2 && \text{diagonal peak} \\
 & - H_{2y} \cos 2\pi\delta_{H1}t_1 \sin \pi J_{HH}t_1 \cos 2\pi\delta_{H2}t_2 \sin \pi J_{HH}t_2 && \text{cross peak}
 \end{aligned}$$

The position of the peaks are the same but the phase is different and they are antiphase peaks

Z-Filter (ZQ-Suppression)

That leads to heavy distortions in the peaks (left spectrum) and prevents a reliable integration and thus distance determination, that would be possible with the spectrum on the right

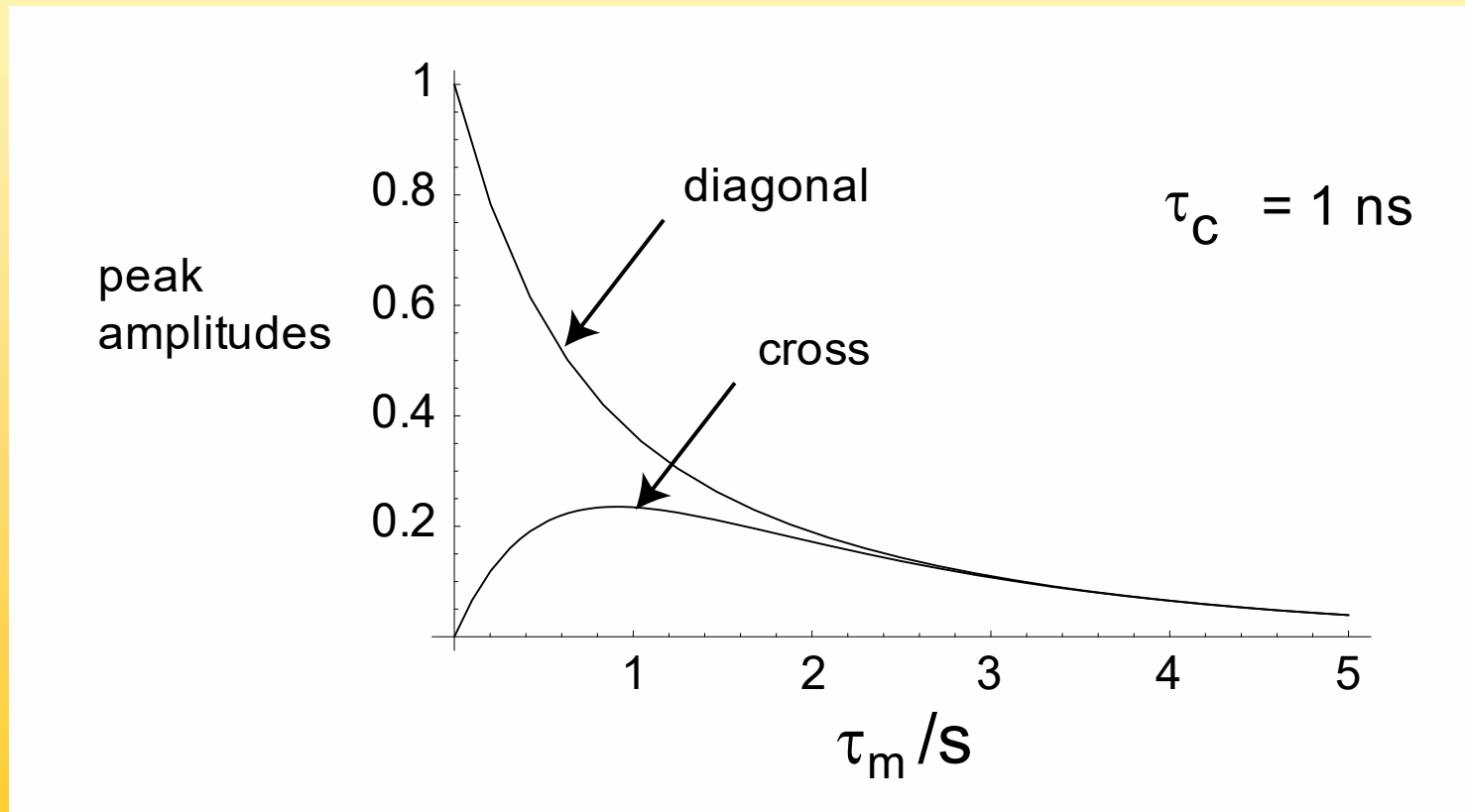


Z-Filter (ZQ-Suppression)

But there is a difference that we can exploit:

$$H_{1z} \xrightarrow{\tau_m} H_{1z} [\{1 + \exp(-2\sigma\tau_m)\} \exp(-(\rho - \sigma)\tau_m)] + H_{2z} [\{1 - \exp(-2\sigma\tau_m)\} \exp(-(\rho - \sigma)\tau_m)]$$

This is dependent on τ_m but not as an oscillation !

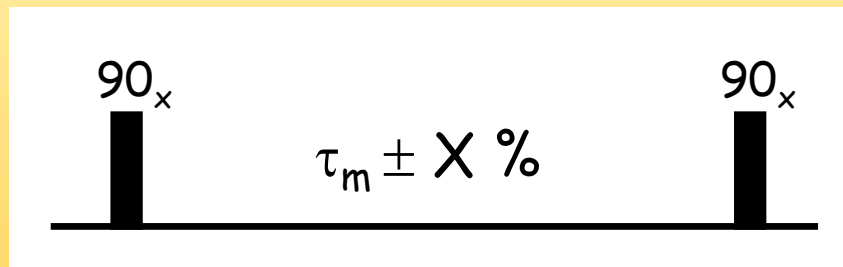


Z-Filter (ZQ-Suppression)

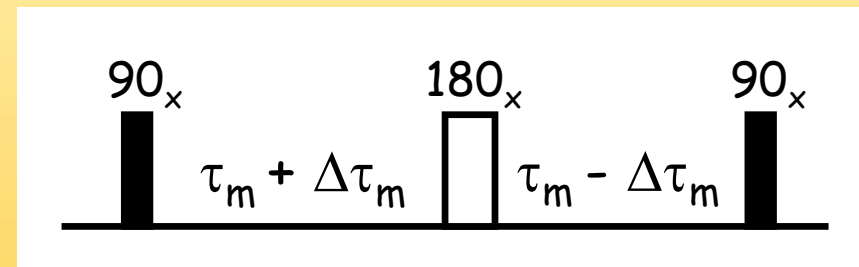
$$H_{1-}H_{2+} - H_{1+}H_{2-} \xrightarrow{\tau_m} H_{1-}H_{2+} \exp(-i[\Omega_2 - \Omega_1] \tau_m) - H_{1+}H_{2-} \exp(-i[\Omega_1 - \Omega_2] \tau_m)$$

Whereas this oscillates with τ_m ! That means that we can achieve a cancellation of the signals from ZQCs if we vary the evolution of ZQCs and add up the result. There are two ways of doing that:

Random variation of τ_m



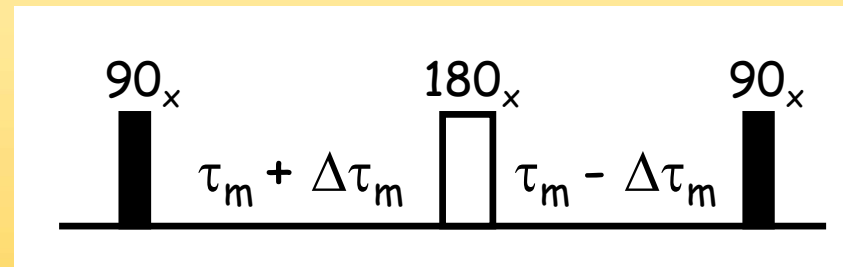
systematic movement of an 180° pulse



If you want to be accurate with your mixing time then the second solution is for you

Z-Filter (ZQ-Suppression)

But there is a potential problem: the NOESY should be executed with a phase cycle of 4, even if supported by gradients, maybe even 8 for suppression of central signals. If we now repeat every FID with a decent number of increments for τ_m then we easily end up with 80 scans or more for every FID, which makes the experiment extremely lengthy

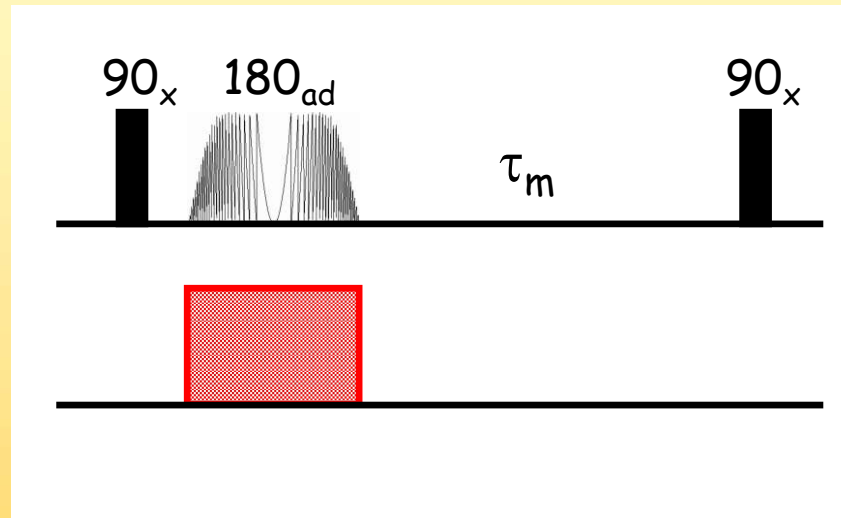


An impressive solution to that problem was designed in James Keelers group and can be found here:

Angewandte Chemie Int. Ed. **42**, 3938-3941 (2003)

Z-Filter (ZQ-Suppression)

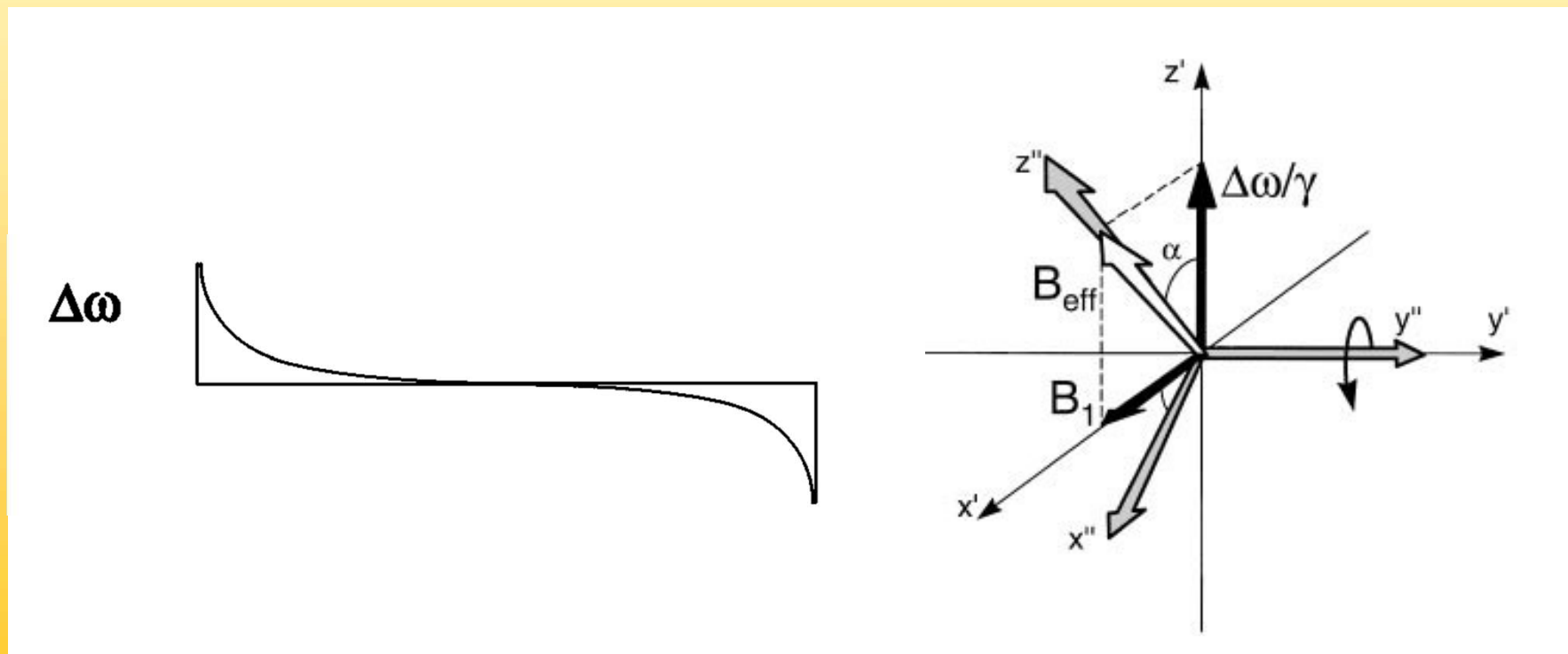
They use a combination of an adiabatic 180° pulse and a gradient to obtain a z-filter in one go:



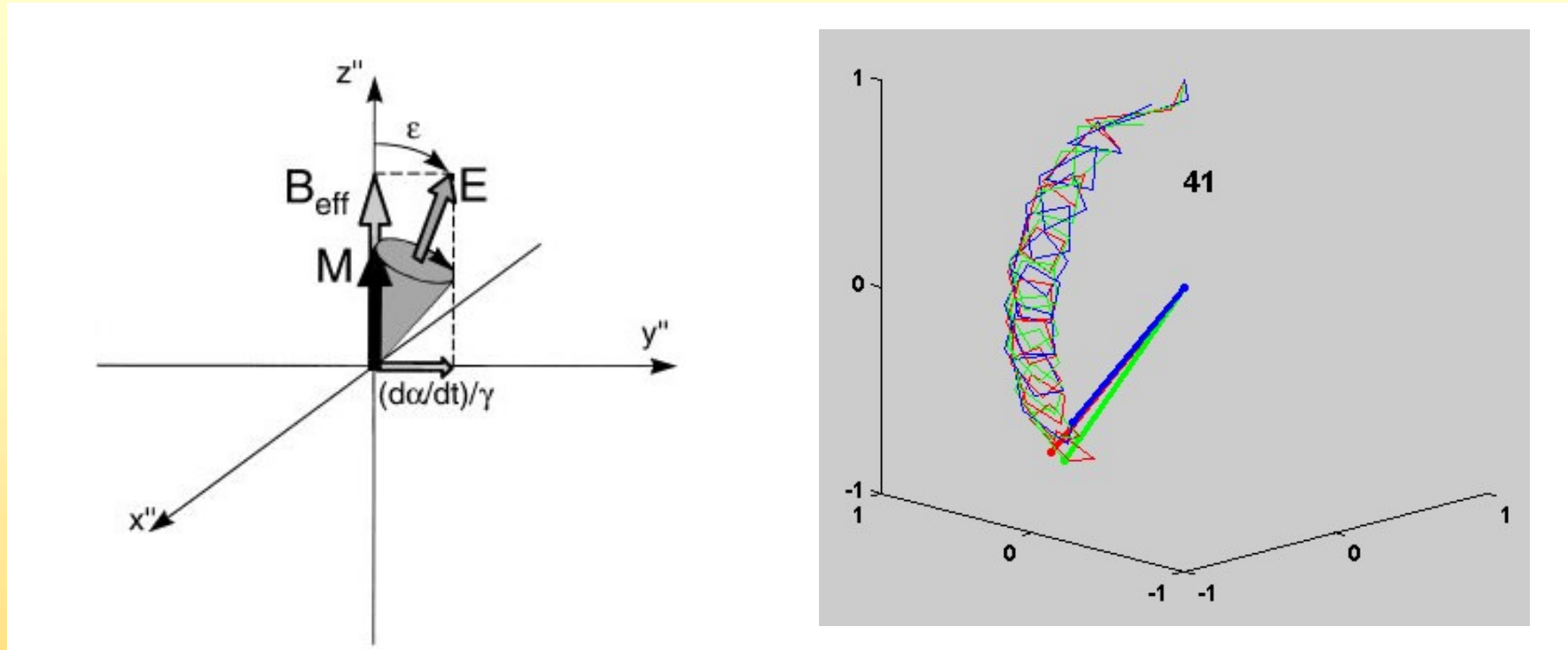
To understand this we have to take a closer look at an adiabatic pulse, that is performing an adiabatic fast passage

Z-Filter (ZQ-Suppression)

Here the offset of the pulse, i.e. the frequency with that it is executed, is changed over the length of the pulse, in a full adiabatic passage this is done from far off resonance at lower frequency to far off resonance at higher frequency (or vice versa). That influences the position of the effective field that is rotating the magnetization.



Z-Filter (ZQ-Suppression)



The effective field is moving from the z-axis ($\Delta\omega/\gamma$ is dominating) towards the x,y-plane (B_1 is dominating) and to the -z-axis in the end ($\Delta\omega/\gamma$ is dominating again). If this is done slowly enough the "adiabatic condition" is fulfilled and the magnetization, that is rotating around the effective field, is following that path.

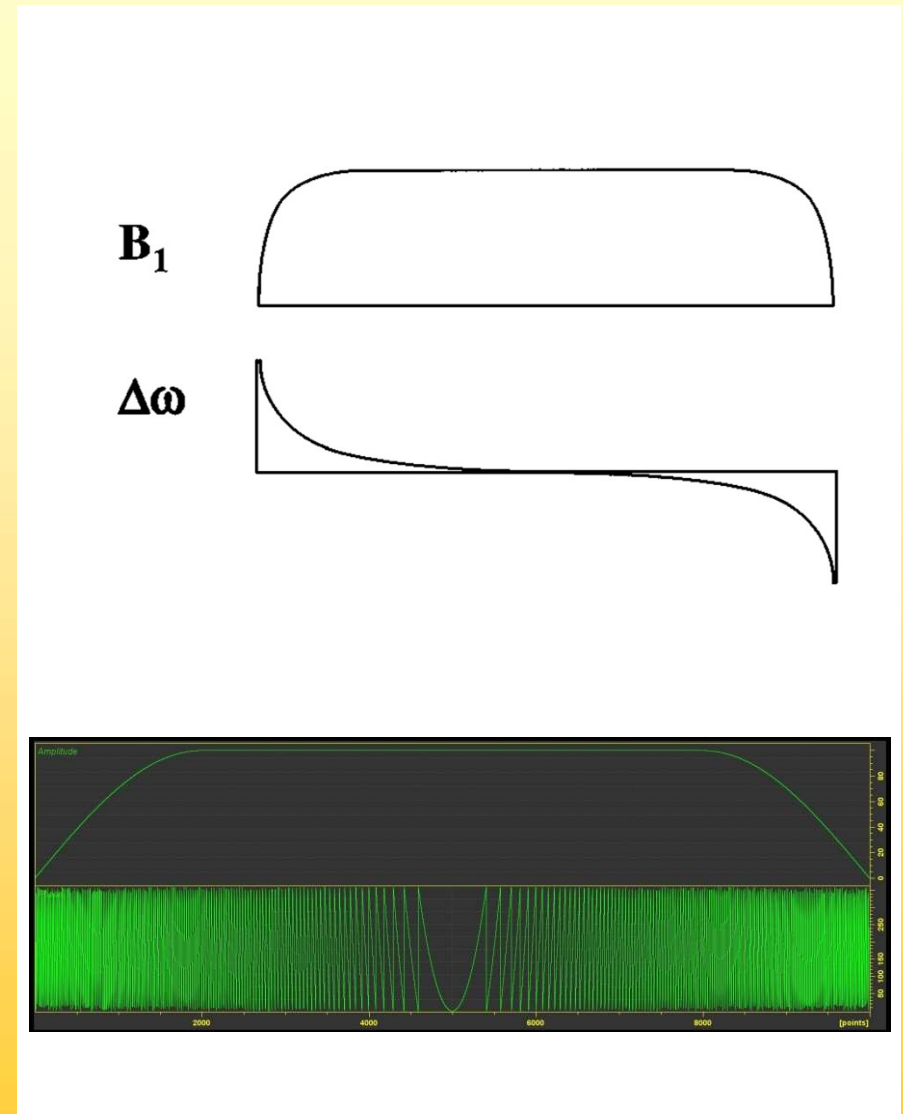
Z-Filter (ZQ-Suppression)

This has two consequences:

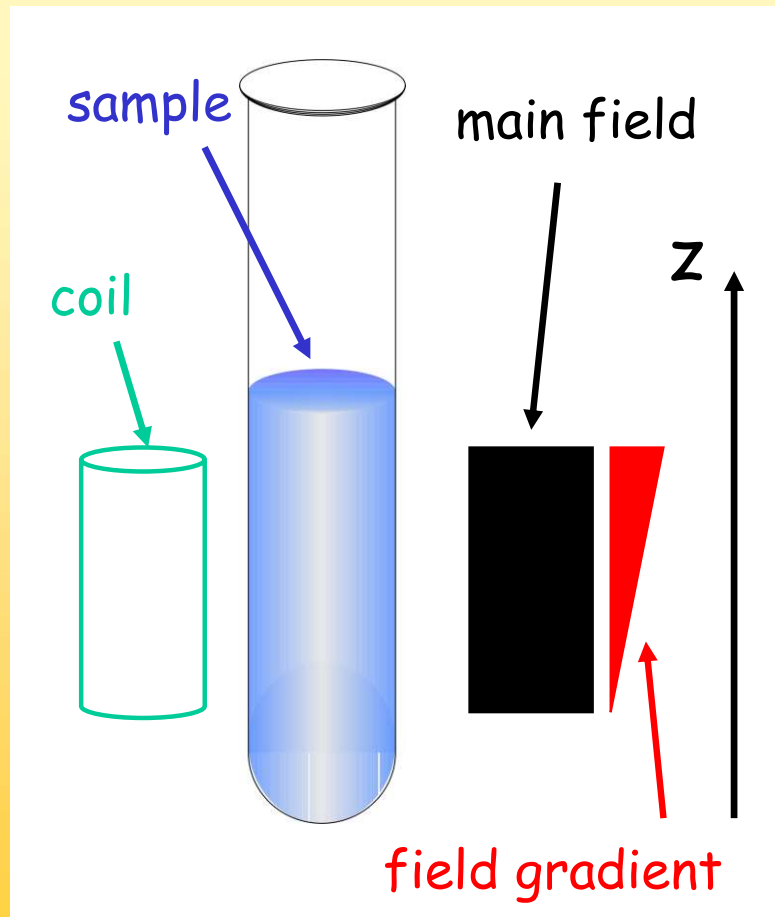
The pulse can invert magnetization over a wide range of frequencies, since it starts far off resonance from the spectral range anyway.

And it does not hit all magnetization vectors at the same time as a conventional pulse does.

That means a typical adiabatic pulse like a smoothed chirp can invert a range a 60 kHz but it inverts the magnetization vectors over that range "one at a time"



Gradients and coherence levels

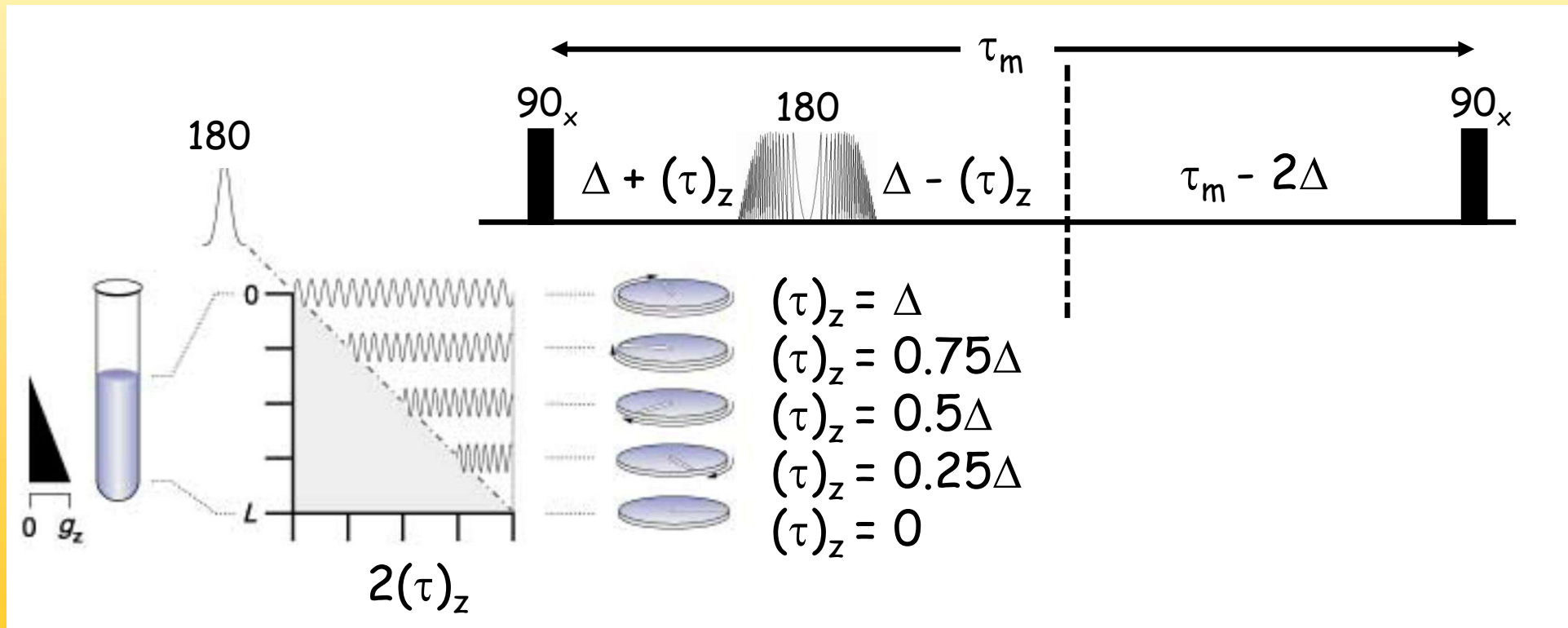


We have already calculated what a gradient does to the sample volume:
We use a gradient of 5 G/cm , that means the frequencies at both ends of the sample differ by 40 kHz .
If we apply an adiabatic 180° pulse during that gradient it will still invert all spins but not all at the same time, the moment of inversion will depend on the position in the sample.

Z-Filter (ZQ-Suppression)

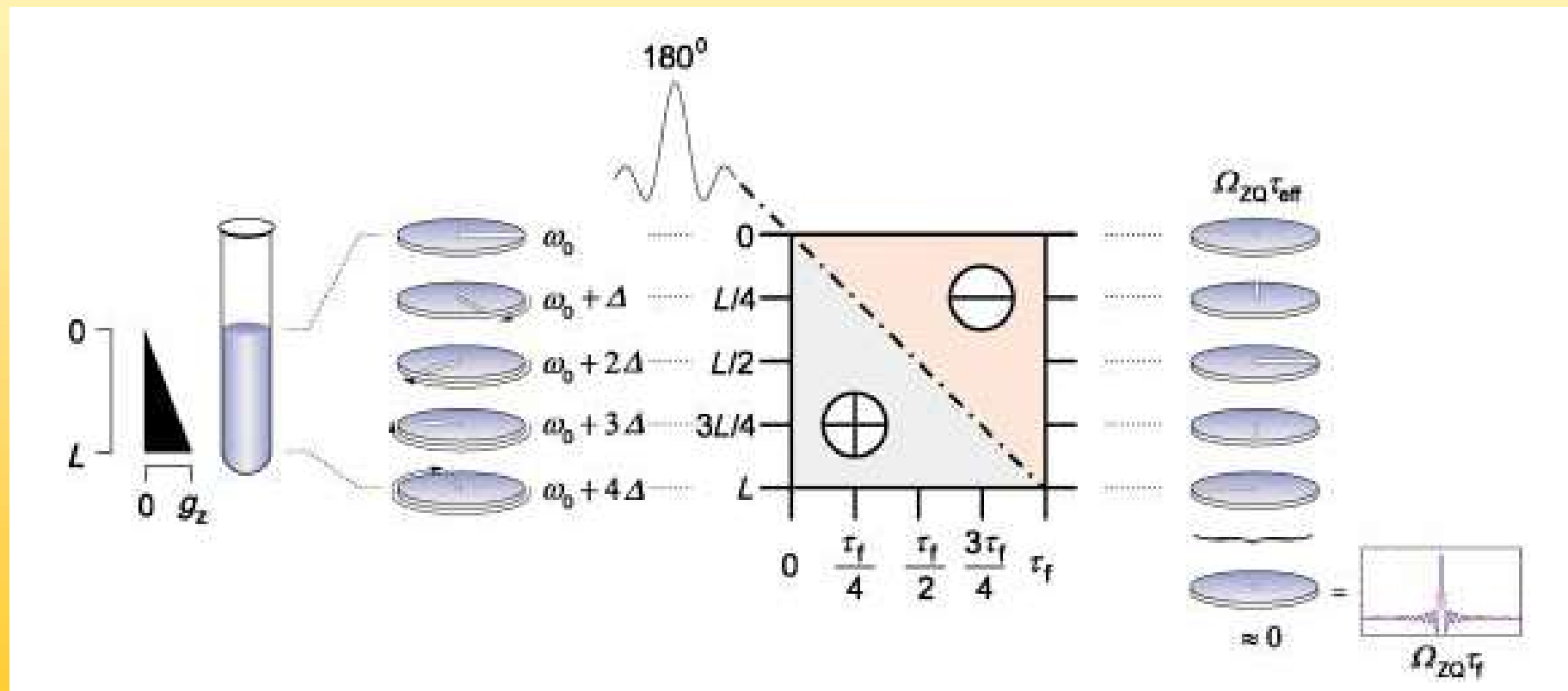
While the z-magnetization does not care about the inversion, the ZQCs do.

The sample is split up in infinitesimal small slices by the gradient and in each the 180 pulse is doing its job at a different time. That means in each slice the ZQCs are refocussed to a different degree



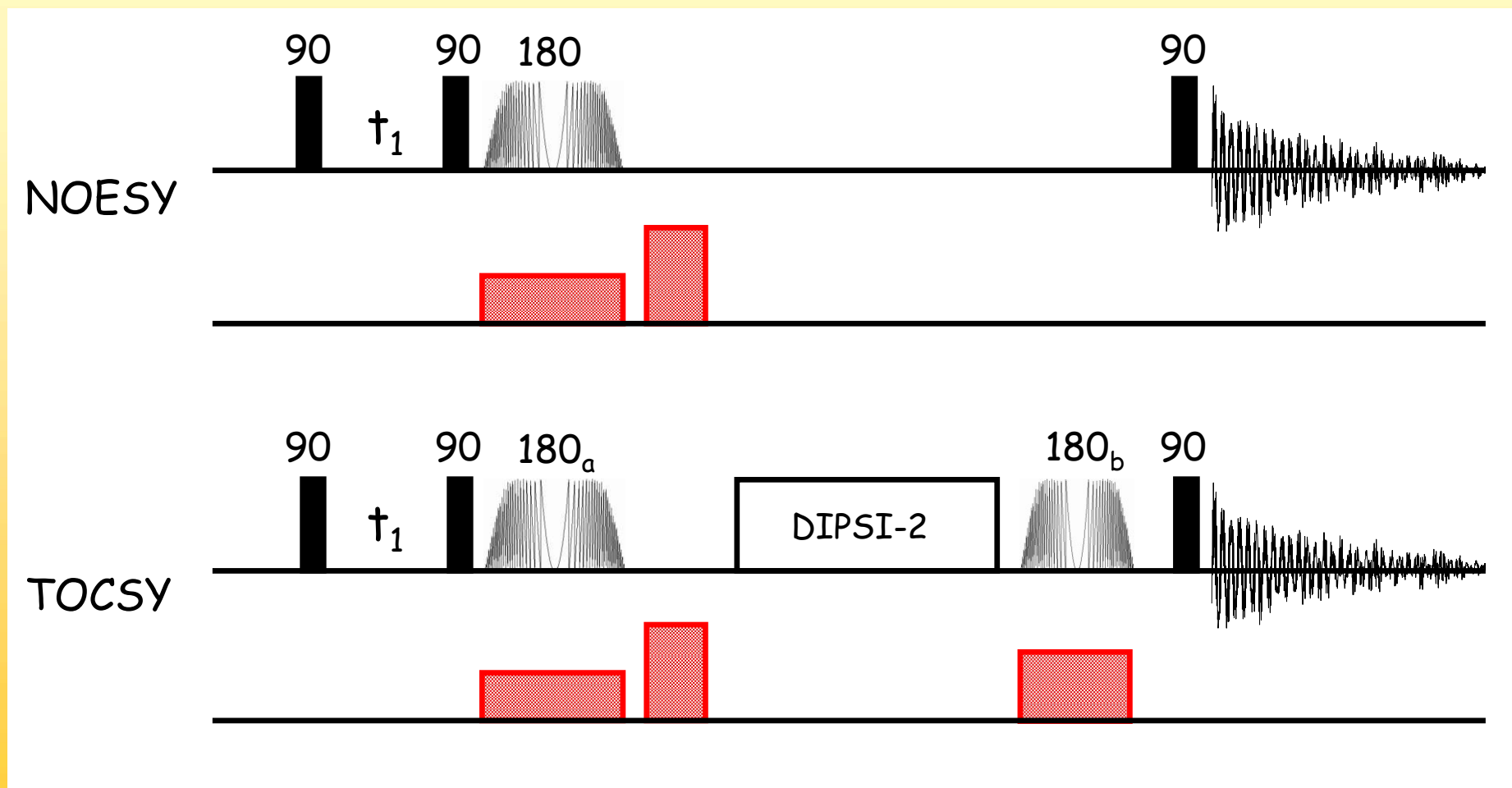
Z-Filter (ZQ-Suppression)

And while the z-magnetization remains as if there was no 180° pulse, the sum of all ZQCs will be zero, the ZQCs are cancelled without a cumbersome repetition of the experiments beyond the requirements of signal-to-noise.



Z-Filter (ZQ-Suppression)

This can be used in a variety of experiments, for example:



That's it

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