Lecture 16: 2D NMR & Product Operators

**Agenda**
1. Evolution of MQC
2. Modulation & Linewidth
3. COSY
4. DPQF-COSY
5. HMQC
6. HMBE

**Multiple Quantum Coherence (MQC)**

In analyzing the DEPT experiment, we found the MQC $2I_x S_y$. How does this operator evolve?

**Coherence order ($p$):** When a $Z$-rotation of $\phi$ is applied to a product operator of coherence order $p$, it acquires a phase of $-e^{i\phi}$.

For example, $I_x$ is a product operator of coherence order 0.

$$A \xrightarrow{\text{rotation}} A e^{-i\phi}$$

What is the coherence order of $I_x$? It is not 1, since

$$I_x \not\rightarrow I_x e^{-i\phi}$$

We need the raising and lowering operators:

$$I_+ = I_x + iI_y \quad p = +1$$
$$I_- = I_x - iI_y \quad p = -1$$

Watch this:

$$I_x + iI_y \rightarrow \left[ I_x \cos \phi + I_y \sin \phi \right]$$
$$+ i \left[ I_y \cos \phi - I_x \sin \phi \right]$$

$$= I_x \left[ \cos \phi - i \sin \phi \right] + iI_y \left[ \frac{\sin \phi}{i} + \cos \phi \right]$$
Consider the evolution of $D_{2x}$:

$$D_{2x} = 2I_x S_x - 2I_y S_y$$

$$2I_x S_x \xrightarrow{\Delta t} \begin{bmatrix} \cos(\frac{\Delta t}{2})I_x + \sin(\frac{\Delta t}{2})(I_y) \\ \cos(\frac{\Delta t}{2})S_x + \sin(\frac{\Delta t}{2})S_y \end{bmatrix}$$

$$-2I_y S_y \xrightarrow{\Delta t} \begin{bmatrix} \cos(\frac{\Delta t}{2})I_y - \sin(\frac{\Delta t}{2})I_x \\ \cos(\frac{\Delta t}{2})S_y + \sin(\frac{\Delta t}{2})S_x \end{bmatrix}$$

Collect like terms:

$$D_{2x} \left[ \left( 2I_x S_x - 2I_y S_y \right) \right] \begin{bmatrix} \cos(\frac{\Delta t}{2}) \cos(\Delta \tau t) - \sin(\frac{\Delta t}{2}) \sin(\Delta \tau t) \\ \cos(\frac{\Delta t}{2}) \sin(\Delta \tau t) + \sin(\frac{\Delta t}{2}) \cos(\Delta \tau t) \end{bmatrix}$$

$$D_{2y} \left[ \left( 2I_y S_y + 2I_x S_x \right) \right] \begin{bmatrix} \cos(\frac{\Delta t}{2}) \sin(\Delta \tau t) - \sin(\frac{\Delta t}{2}) \cos(\Delta \tau t) \\ \cos(\frac{\Delta t}{2}) \cos(\Delta \tau t) + \sin(\frac{\Delta t}{2}) \sin(\Delta \tau t) \end{bmatrix}$$

Recall that:

$$\cos(A + B) = \cos A \cos B - \sin A \sin B$$

$$\sin(A + B) = \cos A \sin B + \sin A \cos B$$

$$\cos \left[ (\Omega_I + \Omega_S) t \right] D_{2x} + \sin \left[ (\Omega_I + \Omega_S) t \right] D_{2y}$$

This is analogous to the evolution of $I_x$, except that the frequency is the double quantum frequency. For two coupled spins, MQC does not evolve with J-coupling (not shown here). Overall:

\[ (\Omega_I + \Omega_S) t \]
\[ = (I_+) e^{ix} \]

So \( I_+ \) is always \( p=+1 \) and \( I_- \) is always \( p=-1 \).

What about \( I_x \)? It is half \( p=+1 \) and half \( p=-1 \):

\[
I_+ = I_x + iI_y \quad \text{Similarly,} \quad I_- = I_x - iI_y
\]

\[
\frac{1}{2} (I_+ + I_-) = I_x
\]

The operator \( 2I_x S_y \) is half \( p=0 \) and \( p=\pm 1 \):

\[
2I_x S_y = 2 \left[ \frac{1}{2} (I_+ + I_-) \right] \left[ \frac{1}{2i}(S_+ - S_-) \right]
\]

\[
= \frac{1}{2i} \left[ 2I_x S_y - I_x S_+ - I_x S_- + I_x S_- - I_x S_+ \right]
\]

\[
p = +1 \quad p = 0 \quad p = 0 \quad p = -1
\]

For "composites," one sums the coherence order for each component.

Thus, we can write \( 2I_x S_y \) as a \( QA \) and \( DA \) part:

\[
2I_x S_y = \frac{1}{2i} \left( I_x S_+ - I_x S_- \right) + \frac{1}{2i} \left( -I_x S_+ + I_x S_- \right)
\]

\[
PQ \quad QA
\]

We can define multiple quantum operators:

\[
DQ_x = \frac{1}{2i} \left( I_x S_+ - I_x S_- \right)
\]

\[
DQ_y = \frac{1}{2i} \left( I_x S_+ + I_x S_- \right)
\]

\[
ZQ_x = \frac{1}{2i} \left( I_x S_+ + I_x S_- \right)
\]

\[
ZQ_y = \frac{1}{2i} \left( I_x S_+ - I_x S_- \right)
\]

Why do these have \( x \) and \( y \) labels?
A key idea is that anti-phase states are the source of these MBCs:

\[
2I_x S_z \xrightarrow{90_x (I)} -2I_x S_y \text{ (ZAC, DAc)}
\]

\[
2I_x S_z \xrightarrow{90_y (I)} 2(-I_z) S_x \text{ (Sac)}
\]

Change phase x→y

Now we can look at DEPT again:

\[
\begin{align*}
\text{We have} & \quad -I_y \xrightarrow{\text{inversion}} -I_y \cos(\pi J I C) + 2I_x S_z \sin(\pi J I C) \\
& \quad \downarrow 180_x (I), 90_x (S) \\
& \quad I_y \cos(\pi J I C) \text{ } \downarrow 2I_x S_y \sin(\pi J I C) \\
& \quad \text{trans. terms only} \\
& \quad \{ -2I_x S_y \sin(\pi J I C) \\
& \quad \downarrow 180_x (S) \\
& \quad + 2I_x S_y \sin(\pi J I C) \\
& \quad \downarrow \beta_y (I) \\
\} \\
& \quad 2(I_x \cos \beta + -I_z \sin \beta) S_y \sin(\pi J I C)
\end{align*}
\]
\[ \begin{align*}
&= \cos \beta \sin(\pi Jt) \ 2I_x S_y \quad \text{not observable} \\
&+ \sin \beta \sin(\pi Jt) \ 2I_x S_y \quad \text{anti-phase term only.} \\
&\downarrow \quad \text{apply decoupling} \\
&= -\sin \beta \sin(\pi Jt) \left[ \cos(\pi Jt) \ 2I_x S_y - \sin(\pi Jt) \ 2S_x \right] \\
&\downarrow \\
&+ \sin \beta \sin^2(\pi Jt) \ S_x
\end{align*} \]

For \( \tau = \frac{1}{2J}, \ \beta = \frac{\pi}{2} \), there is complete transfer.

**Schematic**

1) generate anti-phase on \( I \)
2) use 90° pulse to turn anti-phase to MQC
3) although not shown here, the \( Jy \) pulse is a kind of MESP transfer that carries even \( g_J \) differences
4) the anti-phase on \( S \to \) in-phase on \( S \) in the final delay.

Note that MQC can have coupling evolution if it's not just an IS system (IS\(_x\), IS\(_y\)).

**2D NMR**

For 2D NMR, we form the signal via quadrature detection:

\[ M = \mathbf{M}_x + i \mathbf{M}_y = \mathbf{e}^{-i\omega t} \]

With relaxation, we have:
\[ S(t) = S_0 \exp(i\Omega t) \exp(-Rt) \xrightarrow{\text{FT}} S_0 [A(w) + iD(w)] \]

This is purely absorption in the real FT and purely dispersion in the imaginary FT. For 2D-NMR experiments, the time-domain signal is of the form:

\[ S(t_1, t_2) = S_0 \cos(\Omega t_1) \exp(-Rt_1) \left[ \exp(i\Omega t_2) \exp(-Rt_2) \right] \]

This represents a crosspeak at (\Omega_1, \Omega_2). Note that:

\[ \exp(i\Omega t) \exp(-Rt) \xrightarrow{\text{FT}} A(w) + iD(w) \]
\[ \cos(i\Omega t) \exp(-Rt) \xrightarrow{\text{cosFT}} A(w) \]
\[ \sin(i\Omega t) \exp(-Rt) \xrightarrow{\text{sinFT}} D(w) \]

Thus for \( S(t_1, t_2) \):

\[ S(t_1, t_2) \xrightarrow{\text{cosFT}(t_1)} A_1(\Omega_1) [A_2(\Omega_2) + iD_2(\Omega_2)] \]

"Mixed modulation" occurs when some peaks are sinc and some peaks are cosine-modulated. Since one can only perform one kind of FT on all the data, this gives phase twists:

\[ \cos(i\Omega t) \exp(-Rt) \xrightarrow{\text{sinFT}} D(w) \]
\[ \sin(i\Omega t) \exp(-Rt) \xrightarrow{\text{cosFT}} D(\Delta) \]
Our next goal is to understand the popular COSY-90 experiment.

Before we begin, let me remind you:

1. The signal is fumed as \( S(t) = \begin{bmatrix} c_1 + i c_2 \end{bmatrix} \exp(-i \Omega t) \)
   if the product operator during acquisition are \( c_1 \hat{I}_x \) and \( c_2 \hat{I}_y \).

2. \( S_x \) is an in-phase term:
   \[
   S_x \rightarrow S_x \cos(\Omega_3 t_z) + S_y \hat{\delta} \sin(\Omega_3 t_z)
   \]
   \[
   \begin{bmatrix}
   S_x \cos(\pi J t_z) + 2 \hat{I}_y S_x \sin(\pi J t_z) \\
   S_y \cos(\pi J t_z) + 2 \hat{I}_x S_y \sin(\pi J t_z)
   \end{bmatrix}
   \]

3. \( -2 \hat{I}_y S_z \) is an anti-phase term:
   \[
   -2 \hat{I}_y S_z \rightarrow -2 \hat{I}_y S_z \cos(\Omega_3 t_z) + 2 \hat{I}_x S_z \sin(\Omega_3 t_z)
   \]
   \[
   -\cos(\Omega_3 t_z) \begin{bmatrix}
   \cos(\pi J t_z) & 2 \hat{I}_y S_z - \sin(\pi J t_z) \hat{I}_x \\
   \hat{\delta} \sin(\Omega_3 t_z) & \cos(\pi J t_z) \hat{I}_x + \sin(\pi J t_z) \hat{I}_y
   \end{bmatrix}
   \]
\[ \cos \Theta \xrightarrow{\text{terms only}} \quad + \cos (\Delta \tau t_2) \sin (\pi J t_2) \, I_x \]
\[ \quad + \sin (\Delta \tau t_2) \sin (\pi J t_2) \, I_y \]

\[ S(t) = \sin (\pi J t_2) \left[ \cos (\Delta \tau t_2) + i \sin (\Delta \tau t_2) \right] \]
\[ = \frac{1}{2i} \left[ \exp (i \pi J t_2) - \exp (-i \pi J t_2) \right] \exp \left[ i \Delta \tau t_2 \right] \]
\[ = \frac{1}{2i} \left[ \exp \left[ i (\Delta \tau + \pi J) t_2 \right] - \exp \left[ i (\Delta \tau - \pi J) t_2 \right] \right] \]

**This is anti-phase and 90° out of phase with \(-2I_x S_y\).**

\[ \text{COSY:} \quad I_x \xrightarrow{90°} -I_y \quad \rightarrow \quad -I_y \cos (\Delta \tau t_1) + I_x \sin (\Delta \tau t_1) \]

\[ \text{SIN(SIN(\Delta \tau t_1))} \left[ -I_y \cos (\pi J t_1) + 2I_x S_y \sin (\pi J t_1) \right] \]
\[ \text{SIN(COS(\Delta \tau t_1))} \left[ I_x \cos (\pi J t_1) + 2I_y S_x \sin (\pi J t_1) \right] \]

\[ \text{\downarrow 90°} \]
\[ \text{CO} \]
\[ \text{SIN(COS(\Delta \tau t_1))} \left[ -I_x \cos (\pi J t_1) + 2I_y (-S_y) \sin (\pi J t_1) \right] \]
\[ \text{SIN(SIN(\Delta \tau t_1))} \left[ I_x \cos (\pi J t_1) + 2I_y S_x \sin (\pi J t_1) \right] \]

**Observable terms only**

\[ \sin (\Delta \tau) \cos (\pi J t_1) \, I_x \]
\[ \sin (\Delta \tau) \sin (\pi J t_1) \, Z \quad \xrightarrow{\text{diagonal peak}} \]
\[ \sin (\Delta \tau) \sin (\pi J t_1) \, Z \quad \xrightarrow{\text{cross-peak}} \]
\[ \sin (\Delta \tau) \cos (\pi J t_1) \, Z \quad \xrightarrow{\text{cross-peak}} \]
ANALYSIS OF COSY-RO STARTING WITH $S_2$ WOULD LEAD TO THE OTHER HALF OF THE SPECTRUM.

$X \rightarrow 90^\circ_\perp \rightarrow \text{IN-PHASE + ANTI-PHASE}$

$90^\circ_\perp \downarrow \quad \downarrow 90^\circ_\perp \quad \text{TRANSFERS FROM} \quad 2 \rightarrow 5$

DIAGONAL PEAK \hspace{1cm} OFF-DIAGONAL PEAK

\begin{align*}
\text{Crosspeak:} & \\
-2 \Im \left[ \sin(a_{22} t_2) \sin(c_{22} t_2) \right] \\
\text{As we know, in } t_2, \text{ this is } & \frac{1}{2i} \left[ \exp \left[ i (a_{22} + \pi J) t_2 \right] - \exp \left[ i (a_{22} - \pi J) t_2 \right] \right] \\
\text{In } t_1, \text{ this is:} & \\
& \frac{1}{2i} \left[ \exp \left( a_{21} t_1 \right) - \exp \left( a_{12} t_1 \right) \right] \frac{1}{2i} \left[ \exp \left( a_{21}^* \pi J t_1 \right) - \exp \left( a_{12}^* \pi J t_1 \right) \right] \\
& = \frac{1}{4} \left[ \exp \left( a_{21} + \pi J t_1 \right) + \exp \left( a_{12} - \pi J t_1 \right) \right] \\
& \quad - \exp \left( a_{21} + \pi J t_1 \right) - \exp \left( a_{12} - \pi J t_1 \right) \\
& = \frac{1}{4} \left[ \cos \left( a_{21} + \pi J t_1 \right) + \sin \left( a_{21} + \pi J t_1 \right) \right] \\
& \quad + \cos \left( a_{12} - \pi J t_1 \right) - \sin \left( a_{12} - \pi J t_1 \right) \\
& = \frac{1}{4} \left[ \cos \left( a_{21} + \pi J t_1 \right) + \cos \left( a_{12} - \pi J t_1 \right) \right] \\
& \quad - \sin \left( a_{21} + \pi J t_1 \right) - \sin \left( a_{12} - \pi J t_1 \right) \\
\text{Thus,} & \\
X(t_1) \xrightarrow{\text{cofft}} & -A_1(a_{21} + \pi J) + A_2(a_{12} - \pi J) \\
-i S(t_2) \xrightarrow{\text{fft}} & \left[ A_2 \left( a_{22} + \pi J \right) + i D_2 \left( a_{22} - \pi J \right) \right] \\
\text{Reax} & \\
\text{calculation} & \left[ A_0 \left( a_{22} - \pi J \right) + -i D_2 \left( a_{22} - \pi J \right) \right]
The real FT is:

\[
\begin{align*}
S(t) &= \frac{1}{2} \left[ \exp \left( i (\Omega x + \pi J) t \right) \mp \exp \left( i (\Omega x - \pi J) t \right) \right] \\
&= \frac{1}{2} A_1 (\Omega x + \pi J) + \frac{i}{2} A_2 (\Omega x - \pi J)
\end{align*}
\]

A similar analysis will show that:

\[
\cos (\pi \frac{J}{2}) \sin (\Omega x_1) I_x
\]

gives rise to:

\[
S(t) \approx \frac{1}{2} \left[ \sin (\Omega x + \pi J) t_1 \mp \sin (\Omega x - \pi J) t_1 \right] \\
&= \frac{1}{2} \left[ S_{\text{abs}} (\Omega x + \pi J) \mp S_{\text{disp}} (\Omega x - \pi J) \right]
\]

This gives rise to:

Note that since a COSY FT is required for the cross peaks and a SINE FT is required for the diagonal peaks, it is impossible to phase both to absorption. Hence, COSY-90 is presented in absolute value mode with phase-twist line shapes.
PROBLEMS WITH COSY:

(1) anti-phase cross-peaks vs. in-phase diagonal peaks (we want to see the cross-peaks, but with limited resolution, the cross-peaks will tend to cancel whereas the diagonal peaks will tend to reinforce)

(2) phase-twist line-shapes

(3) artifacts that do not arise from J-coupling

DQF - COSY solves these issues:

\[ i_{35} \]

Without specifying how this is possible yet, imagine that we remove all but the DQ terms after COSY:

The MBC term that remains is:

\[ -2I_x s_y \sin(\pi J t) \cos(\pi A t) \]

\[ -2I_x s_y = \frac{1}{2} (DQ_y - ZQ_y) \]

\[ \frac{1}{2} DQ_y = \frac{1}{2} (2I_x s_y + 2I_x s_x) \]

\[ \frac{1}{2} (2I_x s_z + 2I_y s_x) \]

same phase relationship \( (x', x) \) no phase twist

diagonal peaks cross-peaks both have anti-phase structure