

Lecture #11

Product Operator Formalism II

- Topics
 - Branch Diagrams
 - Spin Echoes
 - Multiple quantum coherences
 - 2D NMR

The Starting Point

- NMR (w/o relaxation) $\Rightarrow \hat{\sigma}(0) \xrightarrow[\text{rotates around } \hat{H}_1 \text{ for duration } t_1]{\hat{H}_1(t_1)} \xrightarrow{\hat{H}_2(t_2)} \xrightarrow{\hat{H}_3(t_3)} \dots \hat{\sigma}(t)$

- However, many of the equations can still get pretty long...

90-acquire:

$$\hat{I}_z \xrightarrow{\hat{I}_x(-\pi/2)} \xrightarrow{\hat{I}_z(\Omega t)} \xrightarrow{2\hat{I}_z\hat{S}_z(\pi Jt)} (\hat{I}_y \cos \Omega_I t + \hat{I}_x \sin \Omega_I t) \cos \pi Jt + (2\hat{I}_y\hat{S}_z \sin \Omega_I t - 2\hat{I}_x\hat{S}_z \cos \Omega_I t) \sin \pi Jt$$

90-t-180-t-acquire:

$$\hat{I}_z \xrightarrow{\hat{I}_x(\pi/2)} \xrightarrow{\hat{I}_z(\Omega t)} \xrightarrow{2\hat{I}_z\hat{S}_z(\pi Jt)} \xrightarrow{\hat{I}_y(\pi)} \xrightarrow{\hat{I}_z(\Omega t)} \xrightarrow{2\hat{I}_z\hat{S}_z(\pi Jt)} \text{some algebra} \rightarrow \hat{I}_y \cos 2\pi Jt - 2\hat{I}_x\hat{S}_z \sin 2\pi Jt$$

...and these equations are just for the I spin (not to mention simple pulse sequences).

- Thus, we'd like to find a more compact/intuitive/useful notation.

Matrix Formulation

- One approach is the use of rotation matrices.

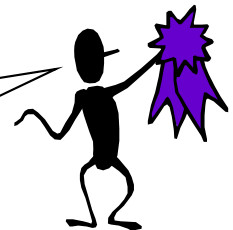
$$\hat{\sigma} \leftrightarrow \vec{\sigma} = \begin{pmatrix} 1 \\ \overline{\langle I_x \rangle} \\ \vdots \end{pmatrix} \quad \text{vector in 16-D coherence space and rotations take place in subspaces}$$

- Example: Free Precession

$$\begin{pmatrix} \hat{I}_x(t) \\ \hat{I}_y(t) \\ 2\hat{I}_x\hat{S}_z(t) \\ 2\hat{I}_y\hat{S}_z(t) \end{pmatrix} = \underbrace{\begin{pmatrix} c_I & -s_I & 0 & 0 \\ s_I & c_I & 0 & 0 \\ 0 & 0 & c_I & -s_I \\ 0 & 0 & s_I & c_I \end{pmatrix}}_{\underline{\Omega}_I} \underbrace{\begin{pmatrix} c'_I & 0 & 0 & -s'_I \\ 0 & c'_I & s'_I & 0 \\ 0 & -s'_I & c'_I & 0 \\ s'_I & 0 & 0 & c'_I \end{pmatrix}}_{\underline{J}} \begin{pmatrix} \hat{I}_x(0) \\ \hat{I}_y(0) \\ 2\hat{I}_x\hat{S}_z(0) \\ 2\hat{I}_y\hat{S}_z(0) \end{pmatrix} \quad \text{where} \quad \begin{aligned} c_I &= \cos \pi \Omega_I t, & c'_I &= \cos \pi J t \\ s_I &= \sin \pi \Omega_I t, & s'_I &= \sin \pi J t \end{aligned}$$

- Rotation matrices turn out to be ok, but not the best for describing mutually commuting rotations. However this formulation can be very helpful for arbitrary rotations.

For experts only: show that rotating around the tilted axis $2(\hat{I}_x\hat{S}_y - \hat{I}_y\hat{S}_x)$ is advantageous for analyzing strong coupling effects with product operators.



Branch Diagrams

- The master equation for product operators is

$$\hat{C}_p \xrightarrow{\hat{C}_q(\theta)} \begin{cases} \hat{C}_p & \text{if } [\hat{C}_q, \hat{C}_p] = 0 \\ \hat{C}_p \cos \theta - i[\hat{C}_q, \hat{C}_p] \sin \theta & \text{if } [\hat{C}_q, \hat{C}_p] \neq 0 \end{cases}$$

where \hat{C}_p and \hat{C}_q are any pair of product operator coherences.

- A more concise notation is known as a *branch diagram*.

$$\hat{C}_p \xrightarrow{\hat{C}_q(\theta)} \begin{cases} \hat{C}_p & \leftarrow \text{“cosine” branch} \\ -i[\hat{C}_q, \hat{C}_p] & \leftarrow \text{“sine” branch} \end{cases}$$

- Examples

Notation used when there is no rotation at all (i.e. operators commute).

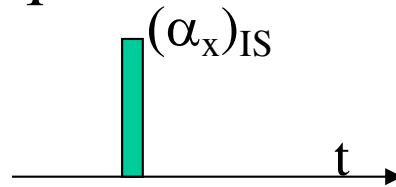
$$\hat{I}_z \xrightarrow{\hat{I}_x(\omega_1 t)} \begin{cases} \hat{I}_z \\ \hat{I}_y \end{cases}, \quad \hat{I}_x \xrightarrow{\hat{I}_z \hat{S}_z(\pi J t)} \begin{cases} \hat{I}_x \\ 2\hat{I}_y \hat{S}_z \end{cases}, \quad \begin{matrix} 2\hat{I}_x \hat{S}_x \xrightarrow{\hat{I}_z \hat{S}_z(\pi J t)} 2\hat{I}_x \hat{S}_x \\ 2\hat{I}_y \hat{S}_z \xrightarrow{\hat{I}_x(\pi/2)} \hat{S}_x(\pi/2) \rightarrow -2\hat{I}_z \hat{S}_y \end{matrix}$$

Hey, that looks like polarization transfer!

Branches also omitted when equal to zero

Branch Diagrams

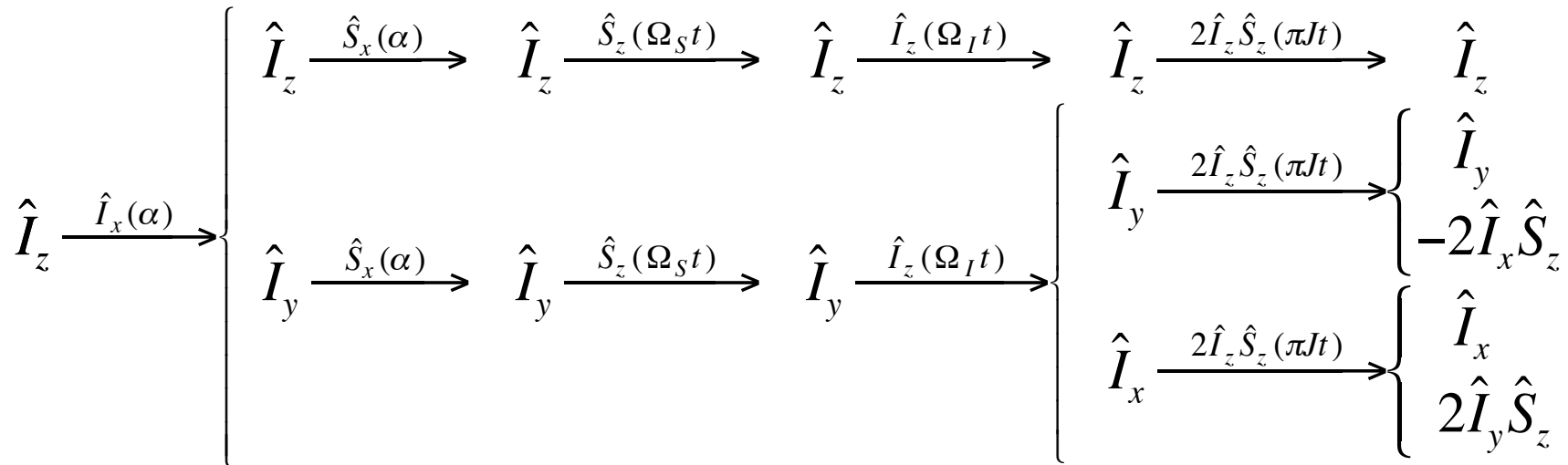
- Another example: α_x -acquire



Try generating branch diagrams for different permutations of the operators. Just be sure to only permute operators that commute! Verify that you get the same final result.



For the I spin....



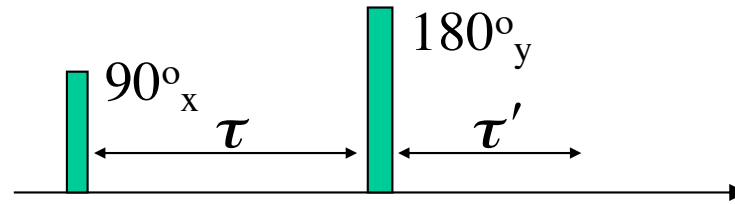
Can now just “read off” the values of interest, e.g. the \hat{I}_x branch is:

→ $\hat{I}_x \cos \pi J t \sin \Omega_I t \sin \alpha$

Whatever happened to the bras, kets, wavefunctions, Hilbert space, Liouville space, superoperators, and all that other stuff I really liked? Sniff. Sniff.




The 180°: Chemical Shift



- Let's consider the magnetization right after the 90° and focus on chemical shift (i.e. ignore J-coupling effects for now).

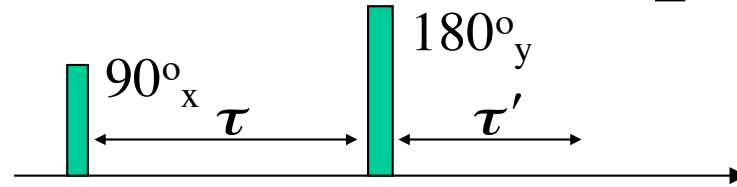
$$\hat{I}_y \xrightarrow{\hat{I}_z(\Omega_I \tau)} \left\{ \begin{array}{l} \hat{I}_y \xrightarrow{\hat{I}_y(\pi)} \hat{I}_y \xrightarrow{\hat{I}_z(\Omega_I \tau')} \left\{ \begin{array}{l} \hat{I}_y \\ \hat{I}_x \end{array} \right. \\ \hat{I}_x \xrightarrow{\hat{I}_y(\pi)} -\hat{I}_x \xrightarrow{\hat{I}_z(\Omega_I \tau')} \left\{ \begin{array}{l} -\hat{I}_x \\ \hat{I}_y \end{array} \right. \end{array} \right. \stackrel{?}{=} \hat{I}_y \xrightarrow{\hat{I}_y(\pi)} \hat{I}_y \xrightarrow{\hat{I}_z(\Omega_I (\tau' - \tau))} \left\{ \begin{array}{l} \hat{I}_y \\ \hat{I}_x \end{array} \right.$$

- Reading off the terms yields...

$$\begin{aligned} \hat{I}_y &\longrightarrow \hat{I}_y (\cos \Omega_I \tau' \cos \Omega_I \tau + \sin \Omega_I \tau' \sin \Omega_I \tau) + \hat{I}_x (\sin \Omega_I \tau' \cos \Omega_I \tau - \cos \Omega_I \tau' \sin \Omega_I \tau) \\ &\longrightarrow \hat{I}_y \cos \Omega_I (\tau' - \tau) + \hat{I}_x \sin \Omega_I (\tau' - \tau) \end{aligned}$$


Hence, for chemical shift, $\tau - 180^\circ - \tau' \equiv 180^\circ - (\tau' - \tau)$

The 180°: J-Coupling



- Ignore chemical shift effects, let's consider three cases.

- Case 1. 180°_y selective on I spin

$$\hat{I}_y \xrightarrow{\hat{I}_z \hat{S}_z (\pi J \tau)} \left\{ \begin{array}{l} \hat{I}_y \xrightarrow{\hat{I}_y (\pi)} \hat{I}_y \xrightarrow{\hat{I}_z \hat{S}_z (\pi J \tau')} \begin{cases} \hat{I}_y \\ -2\hat{I}_x \hat{S}_z \end{cases} \\ 2\hat{I}_x \hat{S}_z \xrightarrow{\hat{I}_y (\pi)} -2\hat{I}_x \hat{S}_z \xrightarrow{\hat{I}_z \hat{S}_z (\pi J \tau')} \begin{cases} -2\hat{I}_x \hat{S}_z \\ -\hat{I}_y \end{cases} \end{array} \right. \stackrel{?}{=} \hat{I}_y \xrightarrow{\hat{I}_y (\pi)} \hat{I}_y \xrightarrow{2\hat{I}_z \hat{S}_z (\pi J (\tau' - \tau))} \left\{ \begin{array}{l} \hat{I}_y \\ -2\hat{I}_x \hat{S}_z \end{array} \right.$$

$$\hat{I}_y \longrightarrow \hat{I}_y (\cos \pi J \tau' \cos \pi J \tau - \sin \pi J \tau' \sin \pi J \tau) - 2\hat{I}_x \hat{S}_z (\sin \pi J \tau' \cos \pi J \tau + \cos \pi J \tau' \sin \pi J \tau)$$

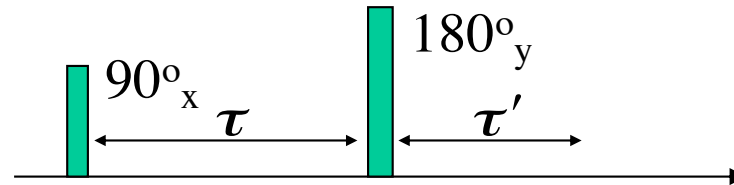
$$\longrightarrow \hat{I}_y \cos \pi J (\tau' - \tau) - 2\hat{I}_x \hat{S}_z \sin \pi J (\tau' - \tau)$$



- Case 2. 180°_y selective on S spin - analogous to Case 1.

Hence, for selective 180° s $\tau - 180^\circ - \tau' \equiv 180^\circ - (\tau' - \tau)$

The 180°: J-Coupling



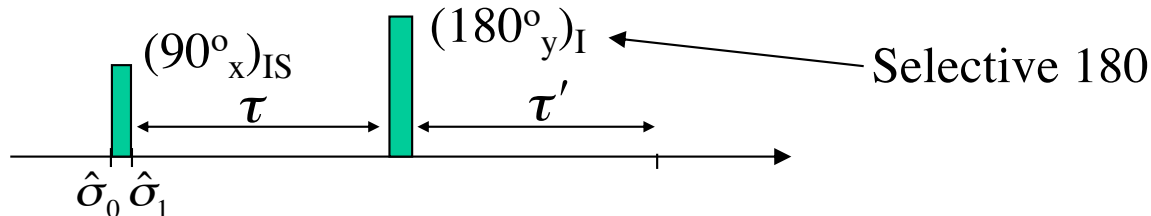
- Case 3. 180°_y nonselective

$$\hat{I}_y \xrightarrow{\hat{I}_z \hat{S}_z (\pi J \tau)} \left\{ \begin{array}{l} \hat{I}_y \xrightarrow{\hat{I}_y(\pi)} \hat{I}_y \xrightarrow{\hat{S}_y(\pi)} \hat{I}_y \xrightarrow{\hat{I}_z \hat{S}_z (\pi J \tau')} \left\{ \begin{array}{l} \hat{I}_y \\ -2\hat{I}_x \hat{S}_z \end{array} \right. \\ -2\hat{I}_x \hat{S}_z \xrightarrow{\hat{I}_y(\pi)} 2\hat{I}_x \hat{S}_z \xrightarrow{\hat{S}_y(\pi)} -2\hat{I}_x \hat{S}_z \xrightarrow{\hat{I}_z \hat{S}_z (\pi J \tau')} \left\{ \begin{array}{l} -2\hat{I}_x \hat{S}_z \\ -\hat{I}_y \end{array} \right. \end{array} \right.$$

Collecting terms and simplifying...

$$\hat{I}_y \longrightarrow \hat{I}_y \cos \pi J (\tau' + \tau) - 2\hat{I}_x \hat{S}_z \sin \pi J (\tau' + \tau) \longrightarrow \text{J-modulation continues uninterrupted.}$$

Spin Echo Example



where $\hat{\sigma}_0 \propto \hat{I}_z$ and $\hat{\sigma}_1 \propto \hat{I}_y$.

- Branch diagram has 64 branches, since rotations to compute are...

$$\hat{\sigma}_1 \xrightarrow{\hat{S}_z(\Omega_S \tau)} \xrightarrow{2\hat{I}_z \hat{S}_z(\pi J \tau)} \boxed{\xrightarrow{\hat{I}_z(\Omega_I \tau)} \xrightarrow{\hat{I}_y(\pi)} \xrightarrow{\hat{I}_z(\Omega_I \tau')}} \xrightarrow{\hat{S}_z(\Omega_S \tau')} \xrightarrow{2\hat{I}_z \hat{S}_z(\pi J \tau')} \hat{\sigma}_2$$

...but we need not compute them all.

$$\boxed{\xrightarrow{\hat{I}_y(\pi)} \xrightarrow{\hat{I}_z(\Omega_I(\tau' - \tau))}}$$

- Substituting, rearranging commuting terms, and continuing....

$$\hat{\sigma}_1 \xrightarrow{\hat{S}_z(\Omega_S \tau)} \boxed{\xrightarrow{2\hat{I}_z \hat{S}_z(\pi J \tau)} \xrightarrow{\hat{I}_y(\pi)} \xrightarrow{2\hat{I}_z \hat{S}_z(\pi J \tau')}} \xrightarrow{\hat{S}_z(\Omega_S \tau')} \xrightarrow{\hat{I}_z(\Omega_I(\tau' - \tau))} \hat{\sigma}_2$$

$$\hat{\sigma}_1 \xrightarrow{\hat{S}_z(\Omega_S \tau)} \xrightarrow{\hat{I}_y(\pi)} \xrightarrow{\hat{S}_z(\Omega_S \tau')} \boxed{\xrightarrow{2\hat{I}_z \hat{S}_z(\pi J(\tau' - \tau))} \xrightarrow{\hat{I}_z(\Omega_I(\tau' - \tau))}} \hat{\sigma}_2$$

$$\hat{\sigma}_1 \xrightarrow{\hat{I}_y(\pi)} \xrightarrow{\hat{S}_z(\Omega_S(\tau' + \tau))} \xrightarrow{2\hat{I}_z \hat{S}_z(\pi J(\tau' - \tau))} \xrightarrow{\hat{I}_z(\Omega_I(\tau' - \tau))} \hat{\sigma}_2$$

for $\tau = \tau'$: $\hat{\sigma}_1 \xrightarrow{\hat{I}_y(\pi)} \xrightarrow{\hat{S}_z(2\Omega_S \tau)} \hat{\sigma}_2$ Ω_I, J refocused Ω_S not refocused

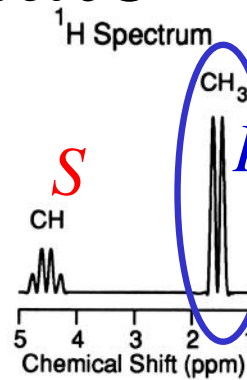
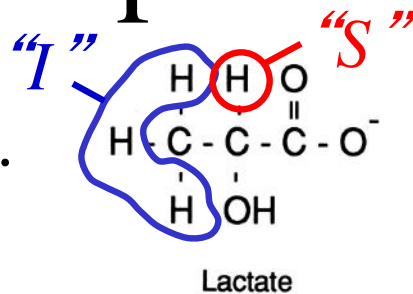
- Non-selective 180

$$\hat{\sigma}_1 \xrightarrow{\hat{I}_y(\pi)} \xrightarrow{\hat{S}_y(\pi)} \xrightarrow{\hat{S}_z(\Omega_S(\tau' - \tau))} \xrightarrow{2\hat{I}_z \hat{S}_z(\pi J(\tau' + \tau))} \xrightarrow{\hat{I}_z(\Omega_I(\tau' - \tau))} \hat{\sigma}_2$$

for $\tau = \tau'$: $\hat{\sigma}_1 \xrightarrow{\hat{I}_y(\pi)} \xrightarrow{\hat{S}_x(\pi)} \xrightarrow{2\hat{I}_z \hat{S}_z(2\pi J \tau)} \hat{\sigma}_2$ Ω_I, Ω_S refocused, J not refocused

Example: Lactate

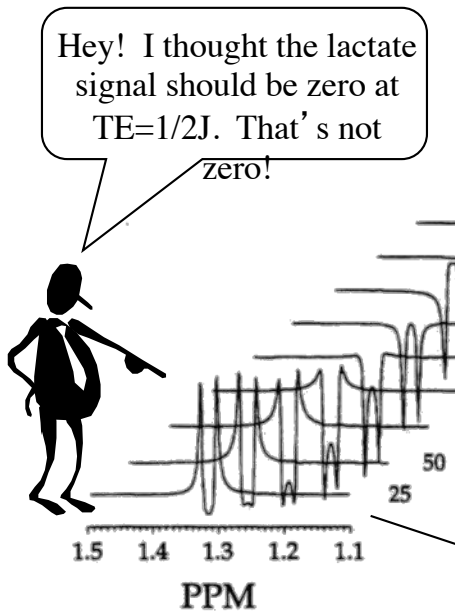
- Lactate involved in anaerobic metabolism.



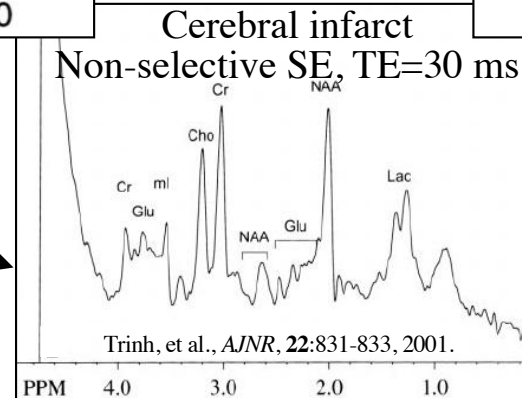
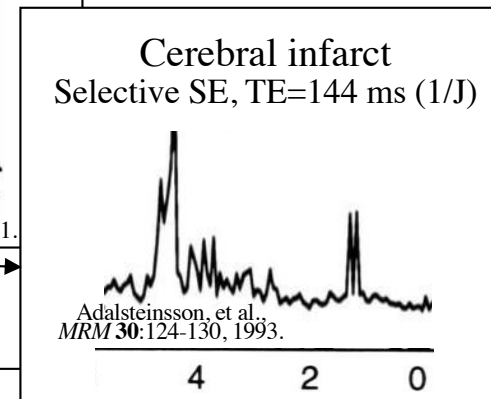
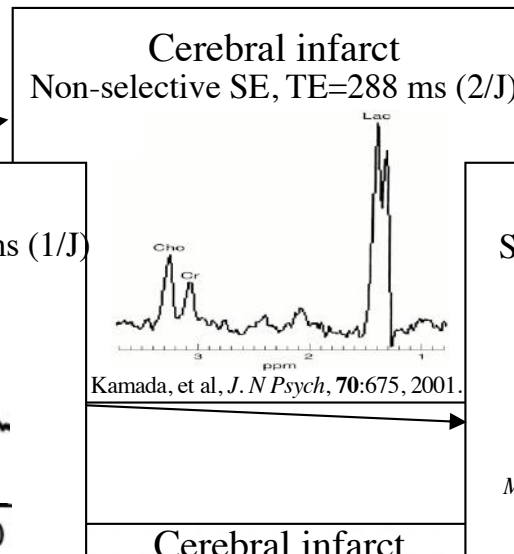
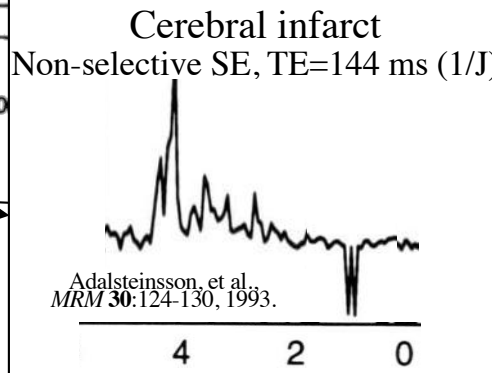
Technically... an AX₃ system

We'll focus on this doublet.

Hey! I thought the lactate signal should be zero at TE=1/2J. That's not zero!



Lactate phantom
Non-selective SE

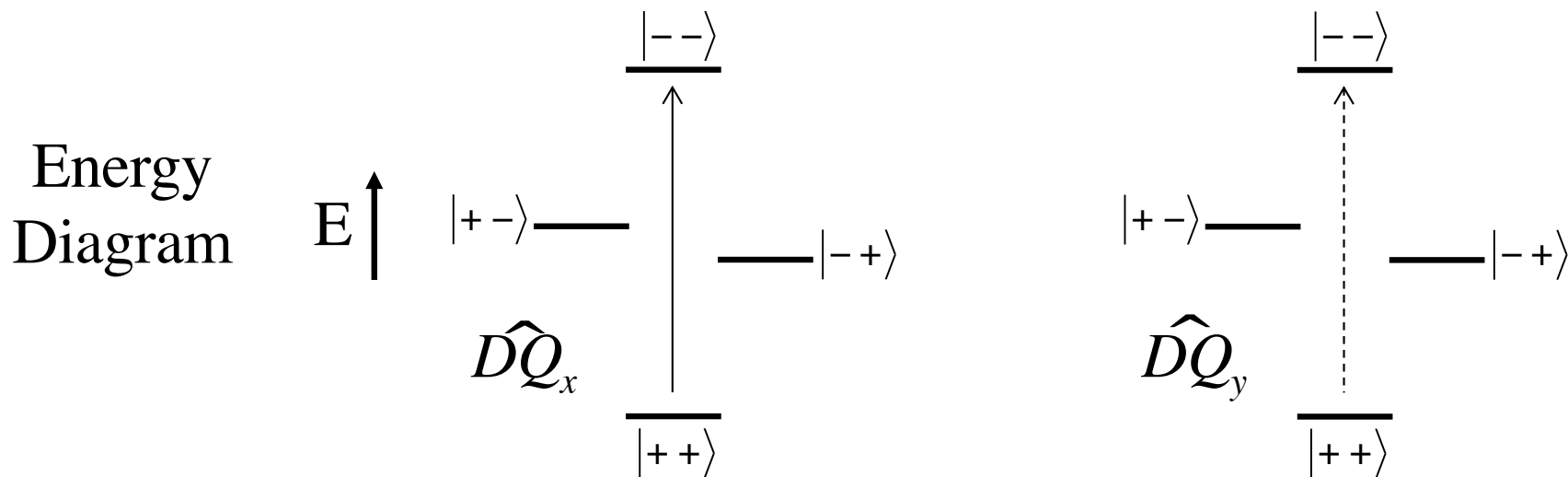


Double Quantum Coherence

- Some two-spin operators that we haven't said much about are the multiple quantum coherences $2\hat{I}_x\hat{S}_x$, $2\hat{I}_x\hat{S}_y$, $2\hat{I}_y\hat{S}_x$, $2\hat{I}_y\hat{S}_y$.
- $2\hat{I}_x\hat{S}_x$, $2\hat{I}_x\hat{S}_y$, $2\hat{I}_y\hat{S}_x$, $2\hat{I}_y\hat{S}_y$ are not directly observable.
- Linear combinations form double and zero quantum coherences.

$$\hat{DQ}_x = \frac{1}{2}(2\hat{I}_x\hat{S}_x - 2\hat{I}_y\hat{S}_y)$$

$$\hat{DQ}_y = \frac{1}{2}(2\hat{I}_y\hat{S}_x + 2\hat{I}_x\hat{S}_y)$$

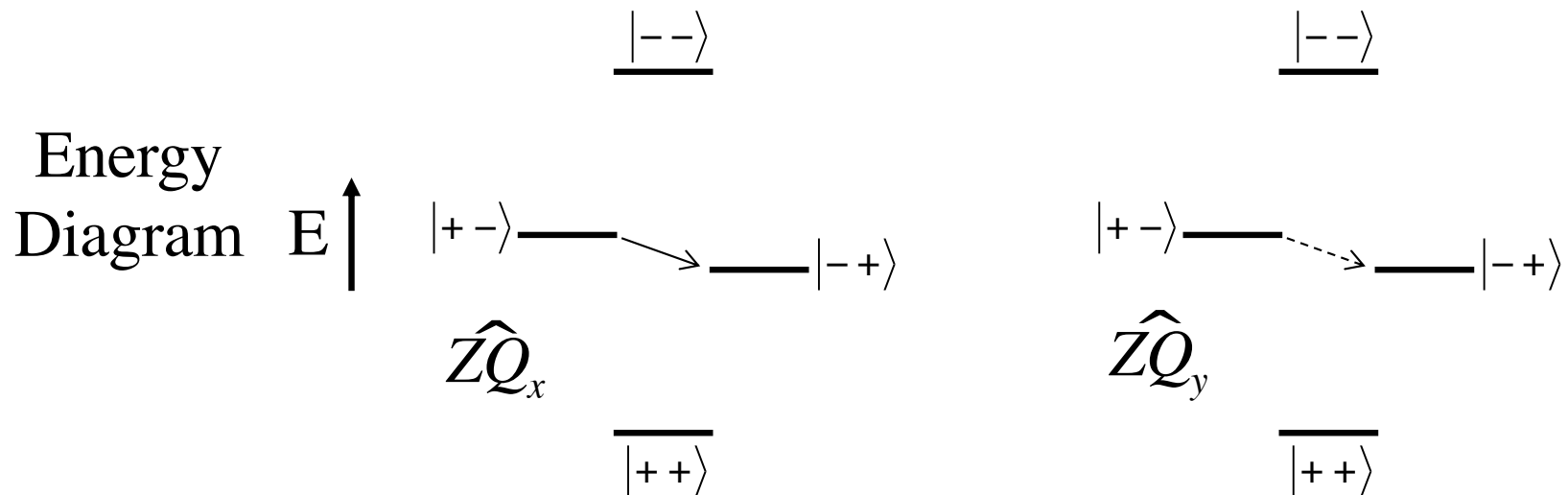


Zero Quantum Coherence

- Similarly, zero quantum coherence is defined by:

$$\hat{ZQ}_x = \frac{1}{2}(2\hat{I}_x\hat{S}_x + 2\hat{I}_y\hat{S}_y)$$

$$\hat{ZQ}_y = \frac{1}{2}(2\hat{I}_y\hat{S}_x - 2\hat{I}_x\hat{S}_y)$$



DQ and ZQ: Free Precession

- J-Coupling

$$[\hat{I}_x \hat{S}_x, \hat{I}_z \hat{S}_z] = [\hat{I}_y \hat{S}_y, \hat{I}_z \hat{S}_z] = 0 \Rightarrow \hat{DQ}_x \xrightarrow{2\hat{I}_z \hat{S}_z (\pi J t)} \hat{DQ}_x \text{ and } \hat{ZQ}_x \xrightarrow{2\hat{I}_z \hat{S}_z (\pi J t)} \hat{ZQ}_x$$

$$[\hat{I}_x \hat{S}_y, \hat{I}_z \hat{S}_z] = [\hat{I}_y \hat{S}_x, \hat{I}_z \hat{S}_z] = 0 \Rightarrow \hat{DQ}_y \xrightarrow{2\hat{I}_z \hat{S}_z (\pi J t)} \hat{DQ}_y \text{ and } \hat{ZQ}_y \xrightarrow{2\hat{I}_z \hat{S}_z (\pi J t)} \hat{ZQ}_y$$

- Chemical Shift

Using the commutator tables, it is straightforward to show that...

$$\hat{DQ}_x \xrightarrow{\hat{I}_z (\Omega_I t)} \xrightarrow{\hat{S}_z (\Omega_S t)} \hat{DQ}_x \cos(\Omega_I + \Omega_S)t + \hat{DQ}_y \sin(\Omega_I + \Omega_S)t$$

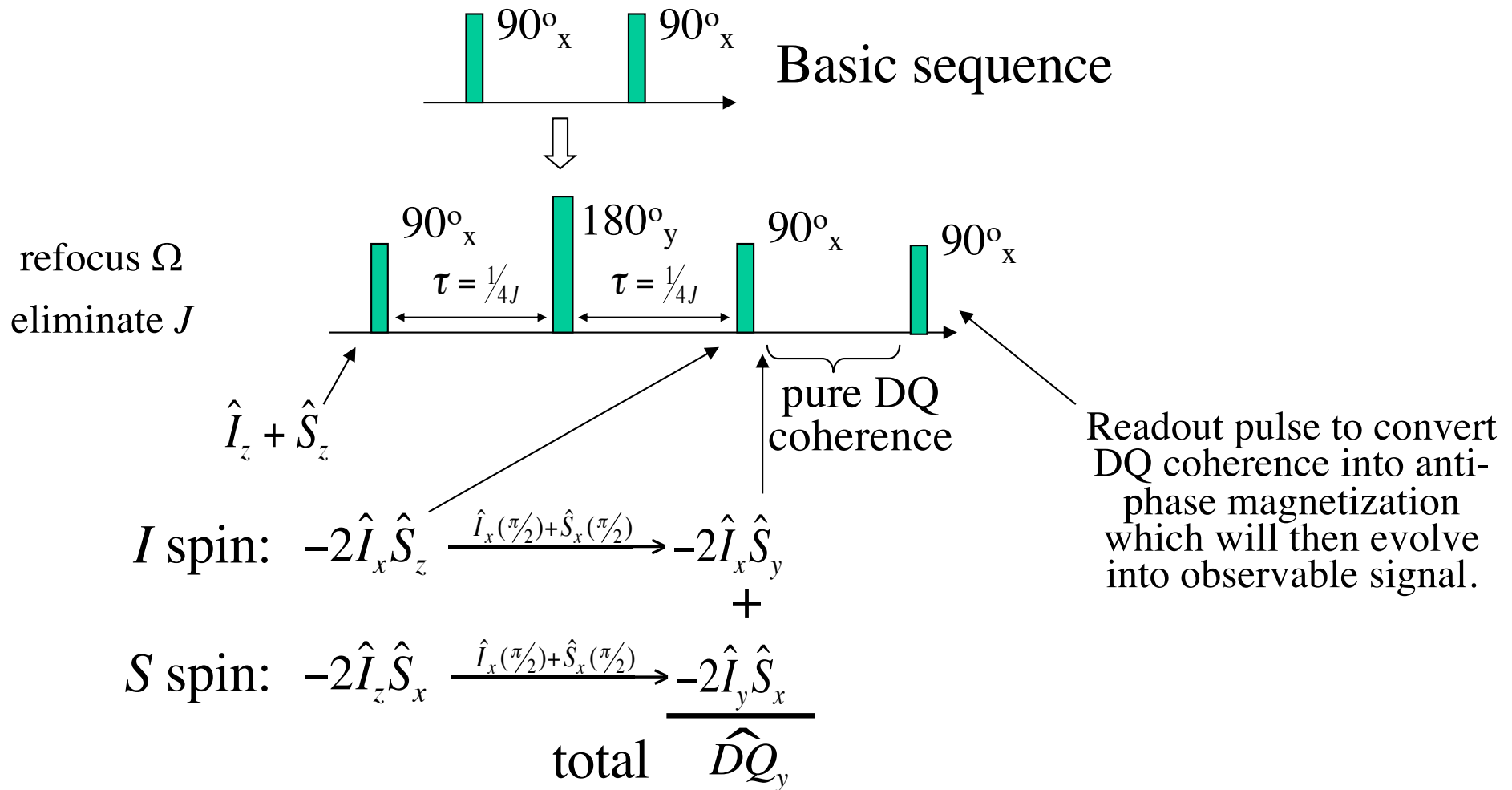
↑
Precesses at the *sum* of chemical shifts

$$\hat{ZQ}_x \xrightarrow{\hat{I}_z (\Omega_I t)} \xrightarrow{\hat{S}_z (\Omega_S t)} \hat{ZQ}_x \cos(\Omega_I - \Omega_S)t + \hat{ZQ}_y \sin(\Omega_I - \Omega_S)t$$

↑
Precesses at the *difference* of chemical shifts

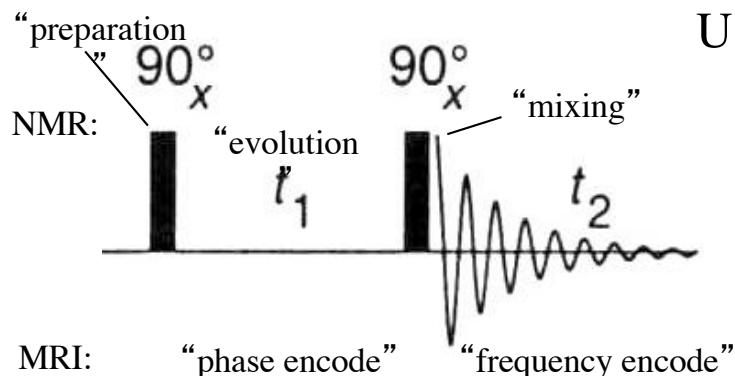
These differential precession frequencies are especially important when using gradients to select particular coherences.

DQ-ZQ Example



2D NMR: COSY

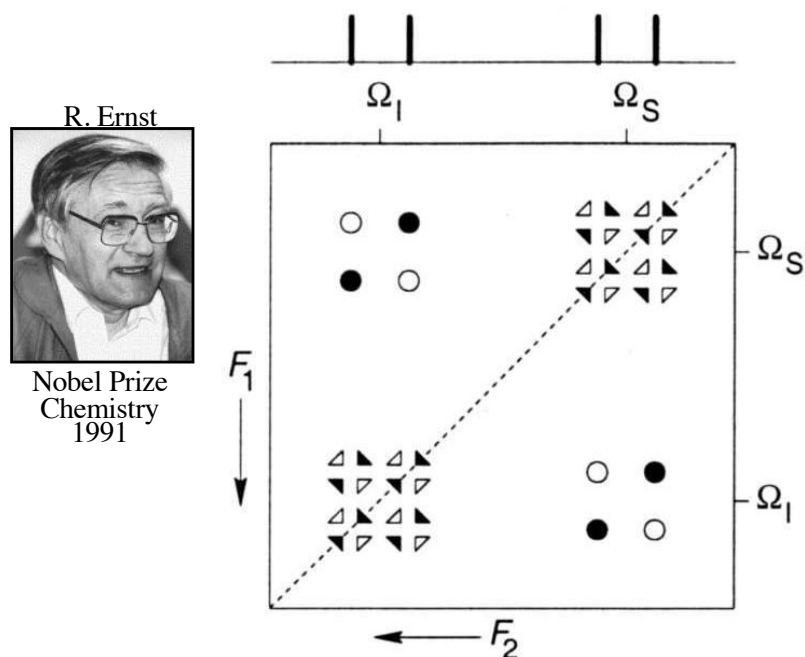
- General building block for many 2D NMR sequences.



Using branch diagrams, the final detectable signal will be...

$$\begin{aligned} \hat{I}_y + \hat{S}_y \propto & \cos \pi J t_1 \sin \Omega_I t_1 \cos \pi J t_2 \sin \Omega_I t_2 \\ & + \cos \pi J t_1 \sin \Omega_S t_1 \cos \pi J t_2 \sin \Omega_S t_2 \\ & + \sin \pi J t_1 \sin \Omega_I t_1 \sin \pi J t_2 \sin \Omega_I t_2 \\ & + \sin \pi J t_1 \sin \Omega_S t_1 \sin \pi J t_2 \sin \Omega_S t_2 \end{aligned}$$

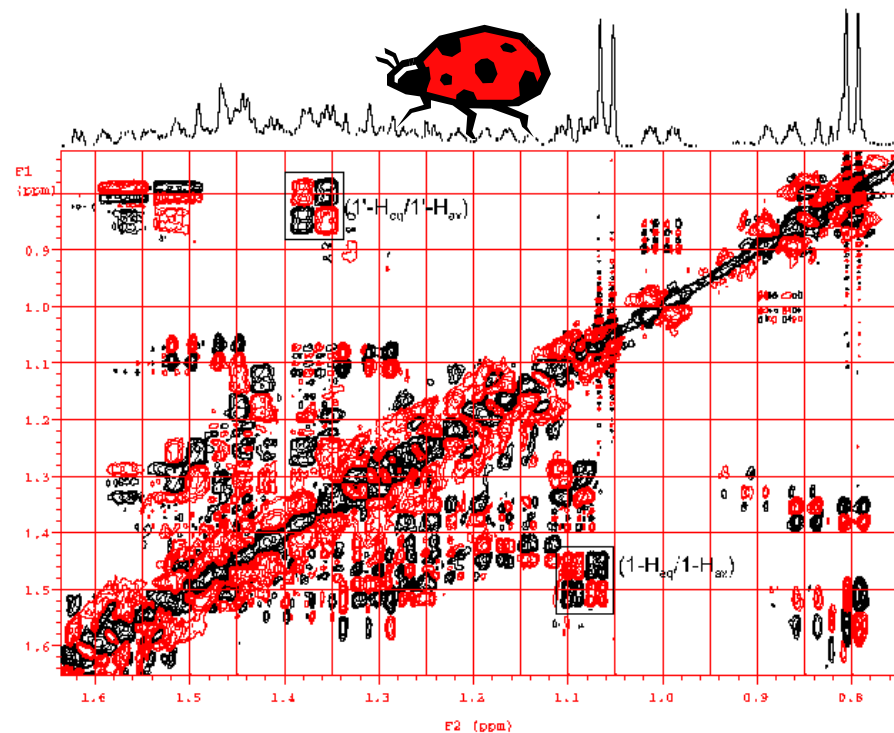
- Collect data for multiple t_1 s, then inverse 2DFFT.



K. Wüthrich



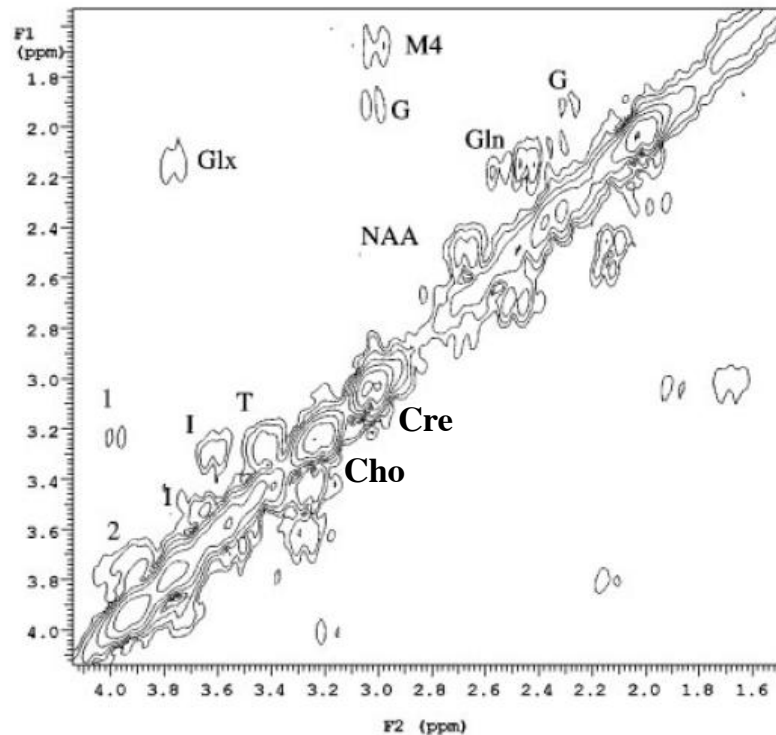
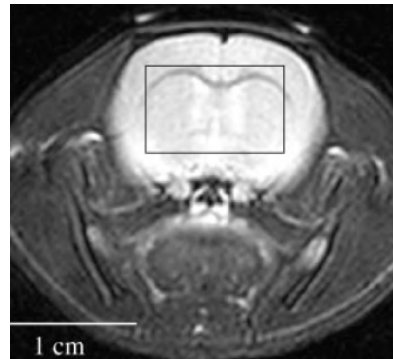
Nobel Prize Chemistry 2002



COSY spectrum of chemical that make ladybugs taste bad (psylloborine, $C_{26}H_{40}N_2$)₅
Schröder, et al, *Tetrahedron* 54:12243 1998.

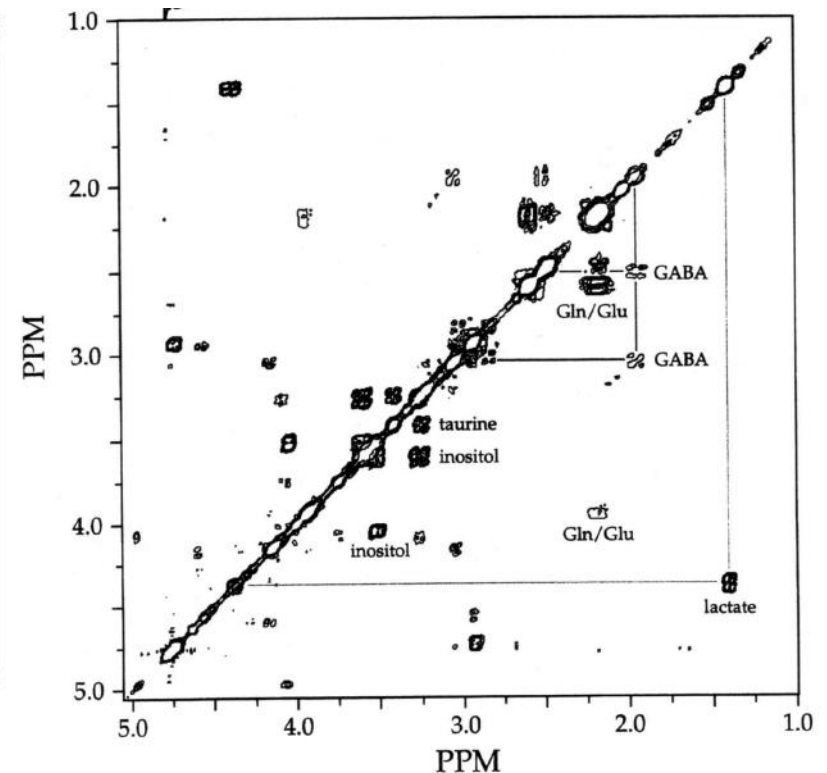
2D NMR: COSY Rat Brain

7 T in vivo rat brain
2D COSY



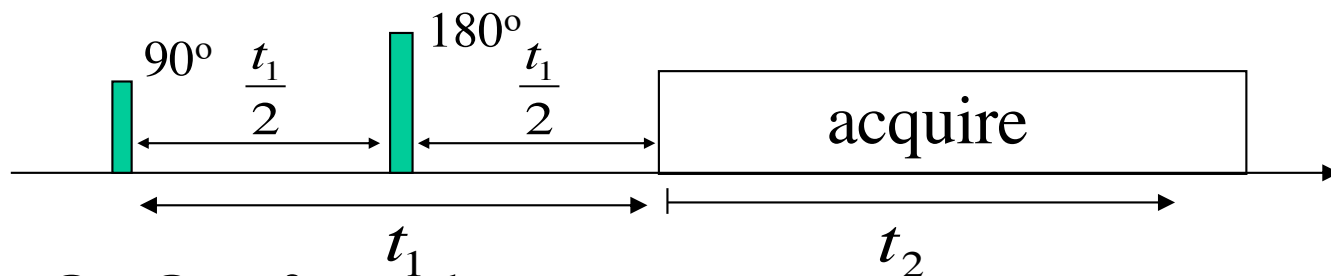
(Welch, et al., NMR in Biomed,
16:47, 2003)

7 T 2D COSY spectrum of
PCA extract from rat brain



(de Graaf, *In Vivo NMR Spectroscopy*,
Wiley & Sons, 2002)

2D NMR: 2D-J

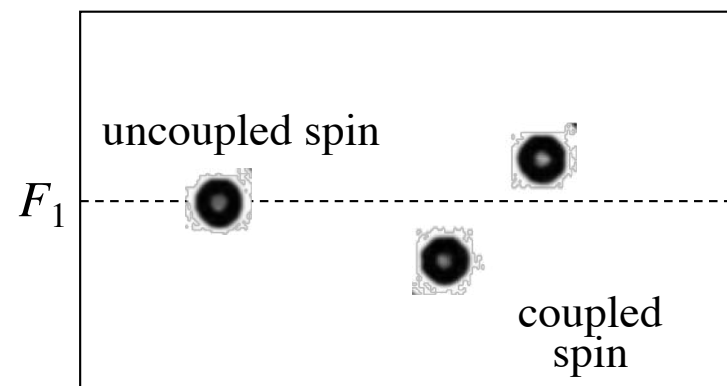


Ω_I, Ω_I refocused

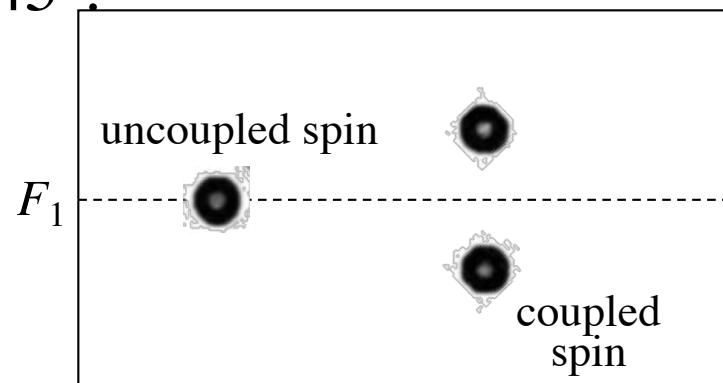
\therefore only J evolution during t_1

Both J and Ω evolution during t_2

- Acquire data for multiple values of t_1 .
- 2D-FFT yield 2D-J spectrum.

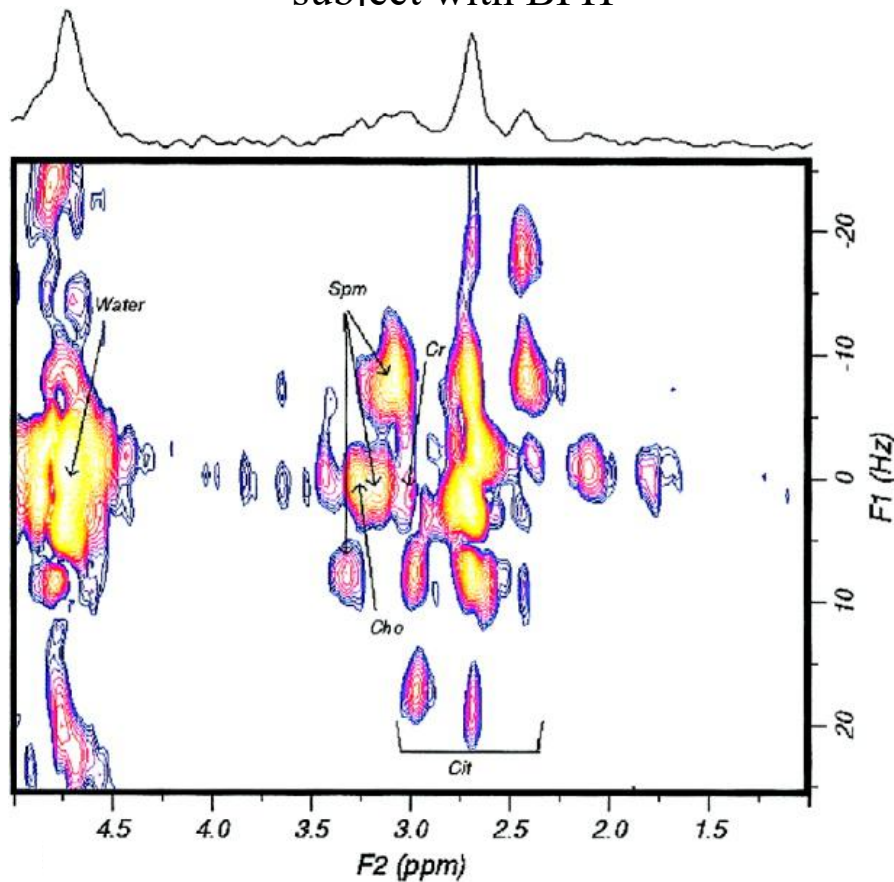


- Spectrum often processed by “tilting” 45°.



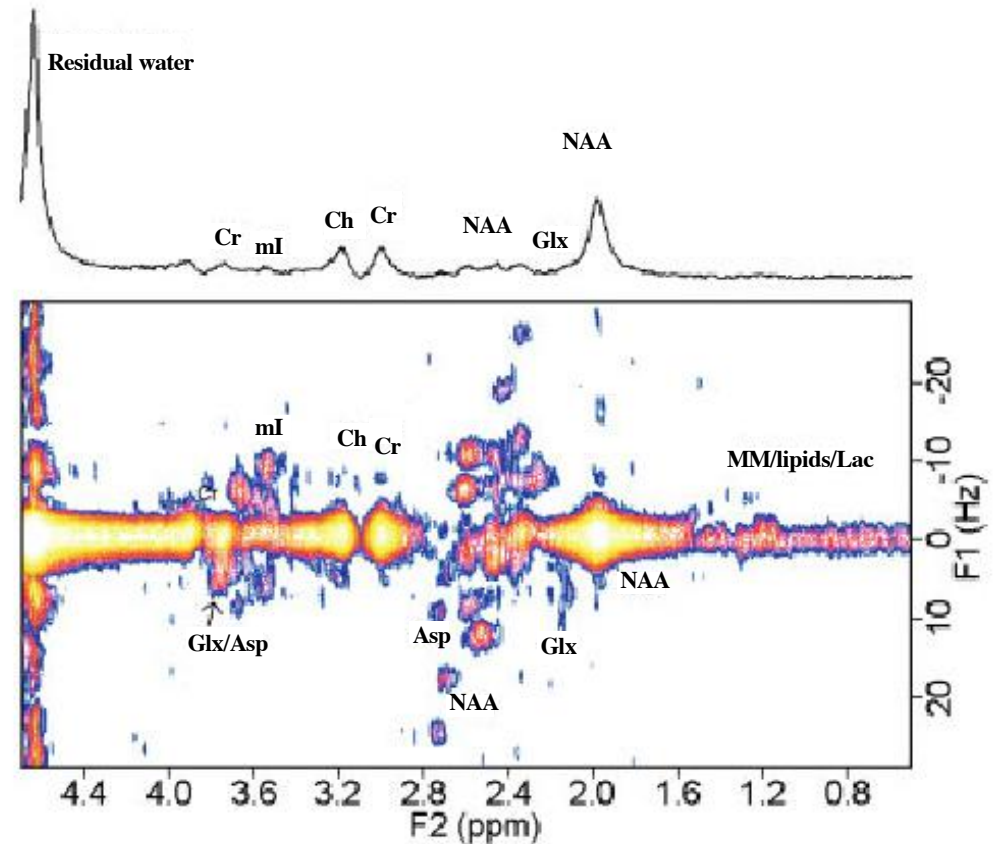
2D NMR: In Vivo 2D-J

2D-J prostate spectrum from 60-year-old subject with BPH



Yue, et al., *MRM*, 47:1059-1064, 2002

2D-J brain spectrum from normal adult



Thomas, et al., *NMR Biomed*, 16:245-51 2003.

Is in vivo 2D NMR useful? ... depends on asking the right questions. ₁₈

POF practice: polarization transfer

Biography: Richard Ernst

Born at Winterthur in Switzerland, Ernst was educated at the Federal Institute of Technology, Zurich, where he obtained his PhD in 1962. He spent the period from 1963 until 1968 working as a research chemist for Varian Associates, Palo Alto, California, before returning to the Federal Institute where he was appointed professor of physical chemistry in 1976.



The technique of nuclear magnetic resonance (NMR) described by I. I. Rabi in 1944, and developed by Felix Bloch and Edward Purcell in the late 1940s, quickly became a recognized tool for the exploration of atomic nuclei. As nuclei possess a magnetic moment they will tend to align themselves with any strong magnetic field. If, however, nuclei are subjected to radiowaves of the appropriate frequency, they will be raised to a higher energy level, and align themselves in a different direction with respect to the field. With the removal of the radio signal, the nuclei will revert to their original energy state by emitting radiation of a characteristic frequency. The frequency of the radiation emitted allows nuclei to be identified, and the structure of certain molecules determined.

But, the process was time-consuming because, in order to find which radiofrequency a sample responded to, it was necessary to sweep the applied frequency through a range of frequencies. Ernst developed a technique in which the sample was subjected to a single high-energy radio pulse. In this way numerous nuclei would respond and emit an apparently jumbled signal. But Ernst showed that, with the aid of Fourier analysis and a computer, the signal could be unraveled into its separate components. Ernst's procedure considerably increased the sensitivity of NMR.

In 1970 Ernst made a further advance. He found that if he subjected his samples to a sequence of high-energy pulses instead of to a single pulse, it enabled him to use NMR techniques to study much larger molecules. Ernst's 'two-dimensional analysis', as it became known, opened the way to investigate complex biological molecules such as proteins. His work also laid the foundation for the development by Peter Mansfield and others of MRI (magnetic resonance imaging).

For his work on NMR Ernst was awarded the 1991 Nobel Prize for chemistry.

Biography: Kurt Wüthrich

Born in Aarberg, Switzerland, Wüthrich was educated in chemistry, physics, and mathematics at the University of Berne before pursuing his Ph.D. under the direction of Silvio Fallab at the University of Basel, awarded in 1964. He continued post-doctoral work with Fallab for a short time before leaving to work at the University of California, Berkeley for two years from 1965 with Robert E. Connick. That was followed by a stint working with Robert G. Shulman at the Bell Telephone Laboratories in Murray Hill, New Jersey from 1967 to 1969.



Wüthrich returned to Switzerland, to Zürich, in 1969, where he began his career there at the ETH Zürich, rising to Professor of Biophysics by 1980. He currently maintains a laboratory both at the ETH Zürich and at The Scripps Research Institute, in La Jolla, California.

During his graduate studies Wüthrich started out working with electron paramagnetic resonance spectroscopy and the subject of his Ph. D thesis was "the catalytic activity of copper compounds in autoxidation reactions". During his time as a postdoc in Berkeley he began working with the newly developed and related technique of nuclear magnetic resonance spectroscopy to study the hydration of metal complexes. When Wüthrich joined the Bell Labs, he was put in charge of one of the first superconducting NMR spectrometers, and started studying the structure and dynamics of proteins. He has pursued this line of research ever since.

After returning to Switzerland, Wüthrich collaborated with among others nobel laureate Richard R. Ernst on developing the first 2 dimensional NMR experiments, and established the nuclear Overhauser effect as a convenient way of measuring distances within proteins. This research later led to the complete assignment and of resonances for among others the bovine pancreatic trypsin inhibitor and glucagon.

He was awarded the Louisa Gross Horwitz Prize from Columbia University in 1991 and half of the Nobel Prize in Chemistry in 2002 for "his development of nuclear magnetic resonance spectroscopy for determining the three-dimensional structure of biological macromolecules in solution". He taught at Duke University as Handler Memorial Lecturer in 2007.