2-Dimensional NMR

General Information

• More complicated to set-up than $^1$H and $^{13}$C experiments

• Changes in pulses (#, length, angles, mixing times, etc.)

• Observe effect based on relationship of nuclei
  - can be homonuclear (same nuclei – e.g. H-H) or heteronuclear (different nuclei – e.g. H-C, H-P)

• Focus on Interpretation of most commonly used experiments
  - COSY
  - HETCOR (HMQC)
  - HMBC
  - INADEQUATE
  - NOESY

• LOTS of other experiments (both 1D and 2D):
  - EXSY, TOCSY, HOHAHA, INEPT, WATERGATE, and many more …

http://nmrweb.chem.ox.ac.uk/nmr-acronyms.aspx
2-Dimensional NMR

Basic Pulse Sequences

1D NMR:
- acquisition of FID immediately following pulse

2D NMR:
- pulse followed by delay period
- \( t_1 \) (evolution) varied systematically as experiment repeated (512x or 1024x)
- during mixing, information from one part of spin system is relayed to other parts (e.g. magnitization transfer – through bond or through space)
- one FID acquired for each experiment

Note: \( t_1 \) = evolution time; \( T1 \) = type of relaxation
2-Dimensional NMR

Basic Pulse Sequence

- Relaxation delay ($T_0$)
- Preparation period (excitation pulse(s))
- Evolution period $T_1$
- Acquisition pulse(s)

Acquire ($t_2$)

1st $t_1$ increment

Repeat $n$ times

1-D FID

1-D spectra, each with an incremental variable change

FTs can be performed on the vertical data sets
2-Dimensional NMR

Fourier Transform

Stacked to Contour
2-Dimensional NMR

**Common 2-D Experiments**

**Structure Evaluation**

- **COSY (CO)relation Spectroscopy**: $^1$H-$^1$H correlation
- **HETCOR (HETeronuclear CORelation Spectroscopy)**: $^1$H-$^{13}$C correlation
- **HMOC (Heteronuclear Multiple Quantum Coherence)**: $^1$H-$^{13}$C correlation
- **HMBC (Heteronuclear Multiple Bond Correlation)**: $^1$H-$^{13}$C correlation over 2-3 bonds
- **INADEQUATE (Incredible Natural Abundance Double QUAntum Transfer Experiment)**: $^{13}$C-$^{13}$C correlation
- **NOESY (Nuclear Overhauser Effect Spectroscopy)**: spatial proximity
2-Dimensional NMR

**COSY**

**General Features**

- **CO**rrelation Spectroscopy

- Allows correlation of all coupled protons (\(^1\text{H}-^1\text{H}\) correlation)

- Gives unequivical proof of proton assignments

- Very useful when peaks overlap in \(^1\text{H}\) NMR and are unable to determine coupling constants

- Very useful when there are a lot of similar coupling constants

- Cross peaks are coupled to each other

- Use double quantum filtered experiment (DQF-COSY) to suppress noise if needed
2-Dimensional NMR

COSY

Typical COSY Report

cross peaks

diagonal peak
2-Dimensional NMR

COSY

Typical COSY Report

cross peaks

diagonal peak
2-Dimensional NMR

COSY

Typical COSY Report

- $H_a$ is coupled to $H_c$
- $H_b$ is coupled to $H_c$ and $H_d$
- $H_c$ is coupled to $H_a$ and $H_b$
- $H_d$ is coupled to $H_b$ and $H_c$
- $H_e$ is coupled to $H_f$
- $H_f$ is coupled to $H_e$
2-Dimensional NMR

COSY

What is and Isn't Coupled?
2-Dimensional NMR

COSY

Identify Contiguous Carbons in Chain

- Start at likely -CH₃ resonance.
- Walk. Must be coupled to -CH₂-.
- Which is coupled to another -CH₂-.
- Which is coupled to last -CH₂O-.

what is n?
2-Dimensional NMR

COSY

Identify Contiguous Carbons in Chain

Start at likely -CH₃ resonance.

Walk. Must be coupled to -CH₂-. Which is coupled to another -CH₂-. Which is coupled to last -CH₂O-.
2-Dimensional NMR

COSY

isopentyl acetate
2-Dimensional NMR

COSY

isopentyl acetate
2-Dimensional NMR

COSY

1-thiol-β-D-glucose tetraacetate
2-Dimensional NMR

COSY

1-thiol-β-D-glucose tetraacetate
2-Dimensional NMR

COSY vs. DQF-COSY

ipsenol

COSY

DQF-COSY
2-Dimensional NMR

HETCOR

General Features

- **HET**eronuclear **COR**elation Spectroscopy
- Allows correlation of protons and attached carbons
- Takes advantage of $J_{CH}$
- Compliments DEPT
- Particularly useful for identification of diastereotopic protons
- Direct correlation - no cross peaks!
- Largely replaced by HMQC
2-Dimensional NMR

HETCOR

Typical HETCOR Spectrum
2-Dimensional NMR

HETCOR

isopentyl acetate
2-Dimensional NMR

HETCOR

isopentyl acetate

[Diagram of a 2D NMR spectrum with labels for 
1H, 13C, and peaks corresponding to carbon and proton signals.]

[Chemical structure of isopentyl acetate with carbon atoms labeled 1 to 6.]
2-Dimensional NMR

HETCOR

4-methyl-2-pentanol

'Methylene' protons adjacent to chiral centers may not be identical.

There is one more "line" than might be expected from the structure.
2-Dimensional NMR

HETCOR

4-methyl-2-pentanol

5, 6
1
3b
3a
4
2
2-Dimensional NMR

HMQC

**General Features**

• **H**eteronuclear **M**ultiple **Q**uantum **C**oherence

• Allows correlation of protons and attached carbons – has largely replaced HETCOR

• Takes advantage of $J_{HC}$

• Experimentally very different, but gives same information as HETCOR

• Lower digital resolution than HETCOR, **BUT**:  
  ~8x more sensitive!  
  ~64x faster!
2-Dimensional NMR

HETCOR vs. HMQC

ipsenol

observed nucleus is $^{13}\text{C}$

observed nucleus is $^1\text{H}$
2-Dimensional NMR

**HMQC**

More Diastereotopic Protons!
2-Dimensional NMR

HMQC

Can "Look Inside" Multiplets!
2-Dimensional NMR

**HMBC**

**General Features**

- Heteronuclear Multiple Bond Coherence

![Diagram of HMBC](image)

- Allows long range correlation of protons and attached carbons
- Minimizes $^2J\,^{1}H-^{13}C$ coupling; leaves $^3J$ and $^4J\,^{1}H-^{13}C$ coupling
- Allows correlation "through" heteroatoms and quaternary carbons
- Long-range H-C coupling constants can be measured from resulting spectra
- Very useful, but can be very complex
2-Dimensional NMR

HMBC

ipsenol

- C-4 is within $^3J_{HC}$ of H-3, H-3', H-2, OH, H-5 and H-5'

- C-7 is seen to be within 3 bonds of H-5 and H-5' even through the quaternary center at C-6!
2-Dimensional NMR

INADEQUATE

General Features

• Incredible Natural Abundance Double QUantum Transfer Experiment

• Indicates what carbons are attached to each other (carbons with no coupling do not appear)

• VERY powerful tool

• Unambiguous correlation; one of easiest 2-D methods to interpret

• Rarely used \( \rightarrow \) depends on \(^{13}\text{C}^{13}\text{C}\) coupling
  - probability of having one \(^{13}\text{C}\) at a single position about 0.001
  - probability of having two \(^{13}\text{C}\) next to each other 0.00001 (~1 in 10,000!)

• Need lots of sample and lots of time (days!) to overcome
2-Dimensional NMR

INADEQUATE

Typical Inadequate Spectrum

Horizontal pairs correspond to $^1J(\text{CC})$ correlations.
2-Dimensional NMR

NOESY

General Features

- Nuclear Overhauser Effect 2-D Correlation Spectroscopy
- Through space NOE relationships – not observed beyond ~ 5Å

3-5 Å

- Like COSY in that look for cross peaks
- Warning: rapid exchange can also give cross peaks
2-Dimensional NMR

NOESY

Ph \begin{array}{c}
\text{O} \\
\text{N} \\
\text{S} \\
\text{H} \\
\text{CO}_2\text{H}
\end{array}

\begin{array}{c}
\text{O} \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{H}
\end{array}

\text{H}_5 \\
\text{H}_3 \\
\text{CH}_2 \\
\text{CH}_3'S
2-Dimensional NMR

NOESY
2-Dimensional NMR