Chem 453 - Experiment 4
NMR & Mass Spectroscopy and Biomolecular Structure

Fall, 2011

Introduction

- What does NMR measure?
- What information does NMR provide us about the structures of biological macromolecules
  - Will focus on the contributions of Kurt Wüthrich, the 2002 Nobel Prize winner in Chemistry.

Introduction

Historical timeline

1922 Stern (Nobel Prize, 1943) & Gerlach measure intrinsic angular momentum, I, of particles
- beam is split in inhomogeneous field; spins (*I*) are quantized

1924 Pauli (Nobel Prize, 1945): “two-valued quantum degree of freedom”
- spin quantum numbers and the Pauli Exclusion Principle

1938 Rabi (Nobel Prize, 1944) introduces the “molecular-beam magnetic-resonance detection method”
- NMR

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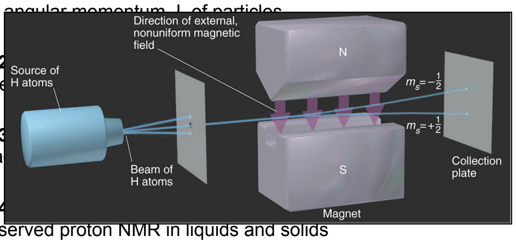

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Introduction

Historical timeline, con’d

1953 Overhauser and others report “NOE’s” and their correlation to internuclear distances
- NMR contains structural information

1966 Ernst (Nobel Prize, 1991) proposes Fourier transform NMR
- Greatly improved sensitivity and resolution

1972 Lauterbur (Nobel Prize, 2003) and others demonstrate imaging by NMR

1976 Ernst (Nobel Prize, 1991) introduces 2D spectroscopy (ideas from Jeener)

1985 Wüthrich (Nobel Prize, 2002) presents a 3D structure of a protein, after complete assignment of 2D spectra

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What NMR Measures

NMR stands for **N**uclear **M**agnet **R**esonance Spectroscopy
- Nuclear
  - NMR Spectroscopy looks at the local environment of atomic nuclei, some of which have magnetic spins (***I*** ≠ 0).

A *Mass Number*	***Z*** *Atomic Number*	***I*** *Nuclear Spin*
Odd	*Even or Odd*	*1/2, 3/2, 5/2, ...*
Even	*Even*	*0*
Even	*Odd*	*1, 2, 3, ...*

What NMR Measures

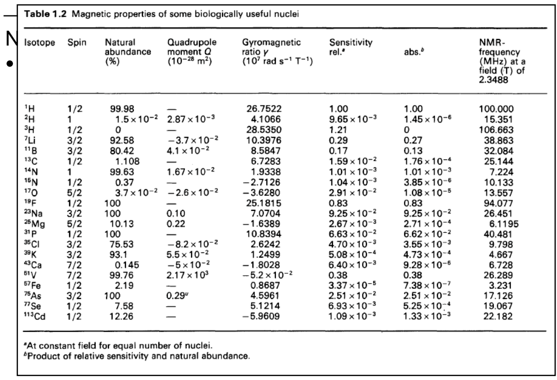

Table 1.2 Magnetic properties of some biologically useful nuclei

Isotope	Spin	Natural abundance (%)	Quadrupole moment Q (10^{-28} m^2)	Gyromagnetic ratio γ (10^7 rad s^{-1} T^{-1})	Sensitivity rel.[a]	abs.[b]	NMR-frequency (MHz) at a field (T) of 2.3488
^{1}H	1/2	99.98	—	26.7522	1.00	1.00	100.000
^{2}H	1	1.5×10^{-2}	2.87×10^{-3}	4.1066	9.65×10^{-3}	1.45×10^{-6}	15.351
^{3}H	1/2	0	—	28.5350	1.21	0	106.663
^{7}Li	3/2	92.58	-3.7×10^{-2}	10.3976	0.29	0.27	38.863
^{11}B	3/2	80.42	4.1×10^{-2}	8.5847	0.17	0.13	32.084
^{13}C	1/2	1.108	—	6.7283	1.59×10^{-2}	1.76×10^{-4}	25.144
^{14}N	1	99.63	1.67×10^{-2}	1.9338	1.01×10^{-3}	1.01×10^{-3}	7.224
^{15}N	1/2	0.37	—	−2.7126	1.04×10^{-3}	3.85×10^{-6}	10.133
^{17}O	5/2	3.7×10^{-2}	-2.6×10^{-2}	−3.6280	2.91×10^{-2}	1.08×10^{-5}	13.557
^{19}F	1/2	100	—	25.1815	0.83	0.83	94.077
^{23}Na	3/2	100	0.10	7.0704	9.25×10^{-2}	9.25×10^{-2}	26.451
^{25}Mg	5/2	10.13	0.22	−1.6389	2.67×10^{-3}	2.71×10^{-4}	6.1195
^{31}P	1/2	100	—	10.8394	6.63×10^{-2}	6.62×10^{-2}	40.481
^{35}Cl	3/2	75.53	-8.2×10^{-2}	2.6242	4.70×10^{-3}	3.55×10^{-3}	9.798
^{39}K	3/2	93.1	5.5×10^{-2}	1.2499	5.08×10^{-4}	4.73×10^{-4}	4.667
^{43}Ca	7/2	0.145	-5×10^{-2}	−1.8028	6.40×10^{-3}	9.28×10^{-6}	6.728
^{51}V	7/2	99.76	2.17×10^{3}	-5.2×10^{-2}	0.38	0.38	26.289
^{57}Fe	1/2	2.19	—	0.8687	3.37×10^{-5}	7.38×10^{-7}	3.231
^{75}As	3/2	100	0.29^{u}	4.5961	2.51×10^{-2}	2.51×10^{-2}	17.126
^{77}Se	1/2	7.58	—	5.1214	6.93×10^{-3}	5.25×10^{-4}	19.067
^{113}Cd	1/2	12.26	—	−5.9609	1.09×10^{-3}	1.33×10^{-3}	22.182

[a] At constant field for equal number of nuclei.

[b] Product of relative sensitivity and natural abundance.

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- Nuclear Magnetic
  - Nuclei with non-zero magnet spins, have a magnetic moment:

$$\mu_m = \gamma I\left(\frac{h}{2\pi}\right)$$

where:

μ_m is the magnetic moment

I is the spin angular momentum.

γ is the gyromagnetic ratio (how fast the nucleus will precess in a magnetic field.

h is Planck's constant

What NMR Measures

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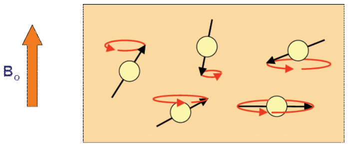
  - When placed in a strong magnetic field (**B$_o$**), nuclei with non-zero magnetic spins will precess like a tops.



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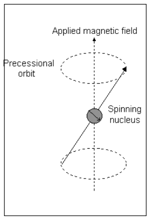

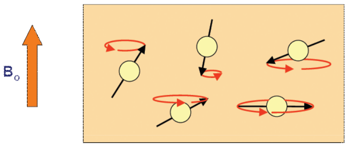

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  - For nuclei with *I* = 1/2, the magnetic spin quantum number, m_m, has one of two values
    - $m_m = +1/2$
    - $m_m = -1/2$.
  - The energy of these two quantum states is given by

$$E = -\mu_{\mathrm{m}} \bullet \mathbf{B}_o$$
$$= \gamma\left(\frac{h}{2\pi}\right) m\, \mathrm{B}_{\mathrm{o}}$$

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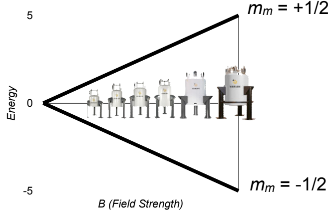
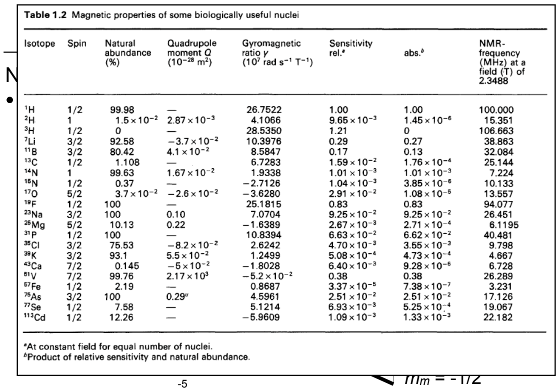
  - For nuclei with *I* = 1/2, the magnetic spin quantum number, m_m, has one of two values
  - The energy difference between these two quantum states increases with the field strength of the magnet (**B**ₒ)





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B (Field Strength)

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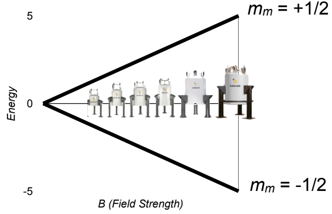

What NMR Measures

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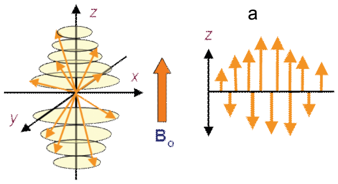
  - When all the magnetic spins are added together, there is a net excess of spins aligned with the field (m_m = -1/2) compared to against the field (m_m = +1/2)



- Due to thermal motions, the difference in populations is quite small
- For our magnet

$$\frac{N_{-1/2}}{N_{+1/2}} = 1.000064$$

for ^{1}H

What NMR Measures

- The very weak sensitivity of the NMR signal is one of the driving forces behind developing larger magnets.
- The 900 MHz magnet at the University of Wisconsin-Madison

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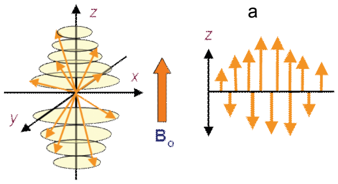

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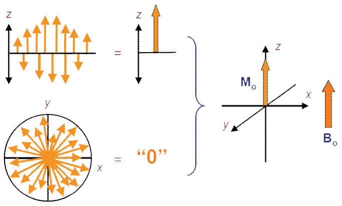
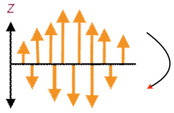
  - The excess produces a net magnet moment (**M**$_o$) that is aligned with the field.



What NMR Measures

NMR stands for **N**uclear **M**agnet **R**esonance Spectroscopy

- Nuclear Magnetic Resonance
  - If a sample in a strong magnet field is irradiated with electromagnetic radiation that is tuned to the precession (resonance) frequency of a nucleus.
    - The nucleus will absorb the radiation and flip from the m_m = -1/2 state to the m_m = +1/2 state.



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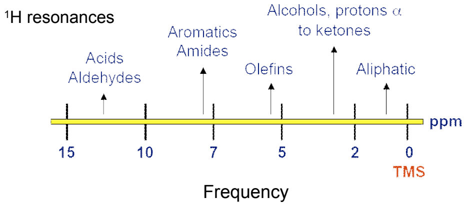
- Nuclear Magnetic Resonance
  - Depending on the local magnetic environment, different nuclei will resonate at different frequencies with the radiation.



What NMR Measures

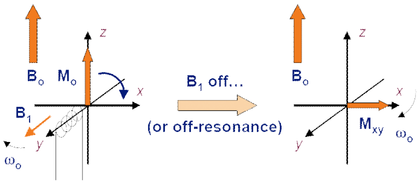
NMR stands for **N**uclear **M**agnet **R**esonance Spectroscopy

- Nuclear Magnetic Resonance Spectroscopy
  - In a bygone era, NMR spectra were obtained by scanning through the frequencies and observing which frequencies were absorbed.
    - These spectrometer were called **continuous wave NMR spectrometers**.
  - Modern NMR spectrometers use a method developed by Richard Ernst that involves Fourier transforms.
    - These spectrometers are called **FT-NMR spectrometers**.

FT-NMR Spectroscopy

Instead of exciting the nuclei one frequency at a time, the magnetization (**M**$_o$) is rotated from the z-axis onto the the x-y plane by applying a strong magnetic pulse along the y-axis.

- This is called a 90° pulse.



FT-NMR Spectroscopy

As the magnetization will rotate in the x-y plane at the precession (resonance) frequency.

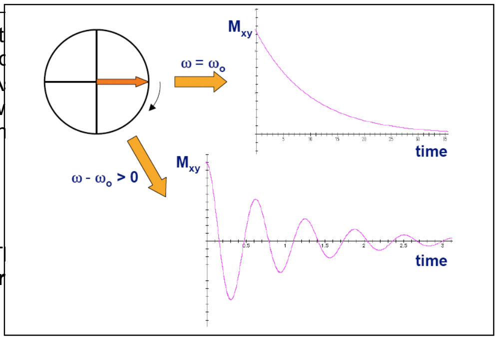
- As it sweeps past the receiver coil located on the x-axis, it will induce an electrical current in the coil that oscillates at the resonance frequency (ω_o in radians, ν_o in hertz).

$$\omega_o = \gamma B_o$$

$$\nu_o = \frac{\gamma B_o}{2\pi}$$

- This signal will decay with time to produce what is called a **free induction decay**, or **FID**.

FT-NMR Spectroscopy



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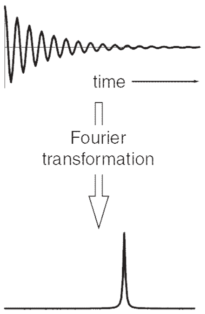
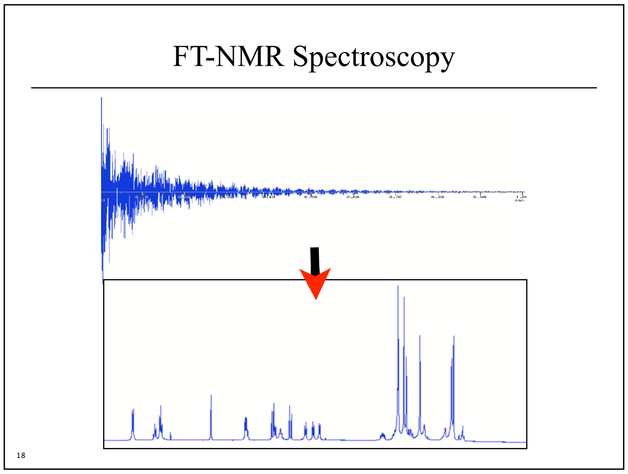
FT-NMR Spectroscopy

The NMR spectrum is obtained by carrying out a Fourier transform on the FID to extract the frequency components of the FID

- Richard Ernst was awarded his Nobel Prize in 1991, in part, for his work in developing FT-NMR.





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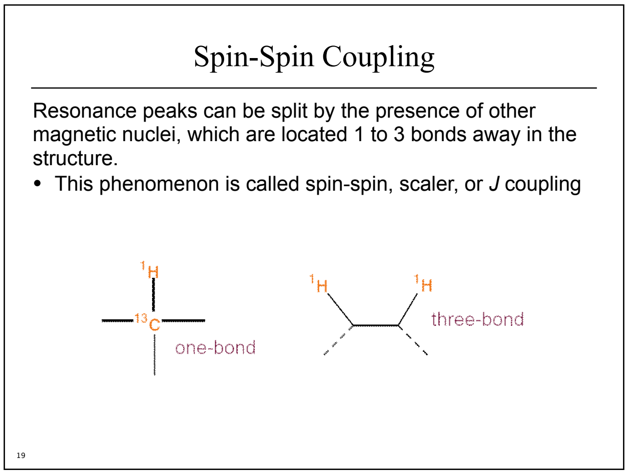
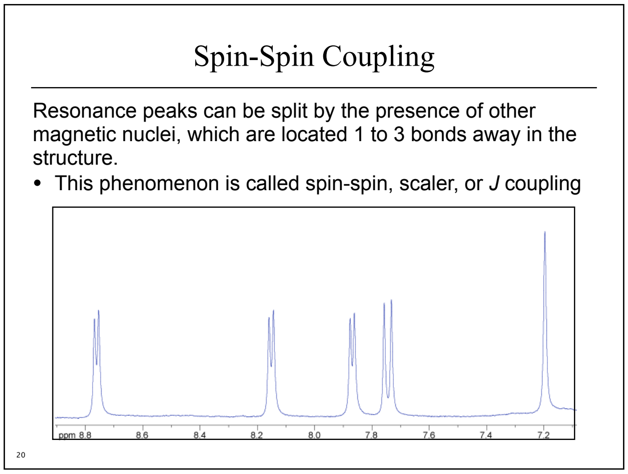


Spin-Spin Coupling

Resonance peaks can be split by the presence of other magnetic nuclei, which are located 1 to 3 bonds away in the structure.

- This phenomenon is called spin-spin, scaler, or *J* coupling



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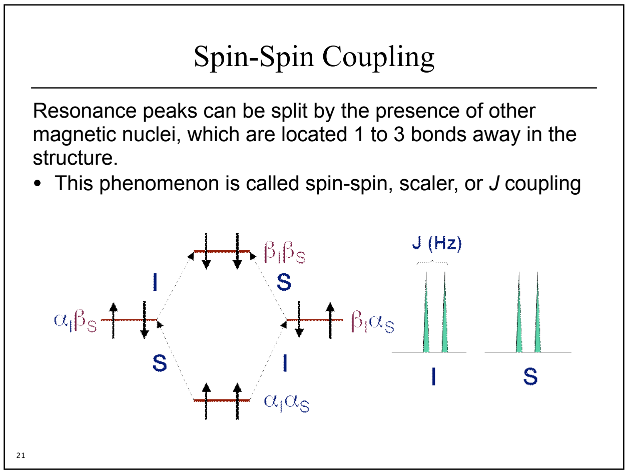

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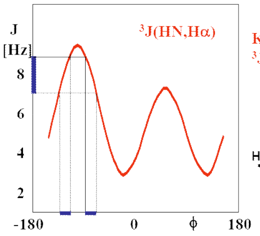
Spin-Spin Coupling

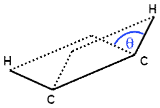
The frequency difference for the split peaks is called the **coupling constant**, *J*.

- 3-bond coupling constants contain information about the dihedral angle between the two nuclei.



Karplus relation

$^3J(\theta) = A\cdot\cos^2(\theta) + B\cdot\cos(\theta) + C$



The Contributions of Kurt Wüthrich

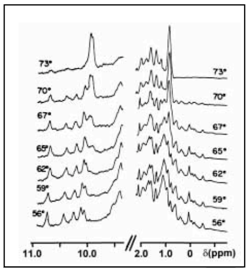
In 2002, Kurt Wüthrich shared the Nobel Prize in Chemistry for his contributions in applying NMR spectroscopy to the study of biological macromolecules

- Like Richard Ernst, Wüthrich work at the ETH Institute in Zurich, Switzerland
- His Nobel Prize winning contributions span a 35-year period.

The Contributions of Kurt Wüthrich

The NMR Spectra of proteins contains structural information.

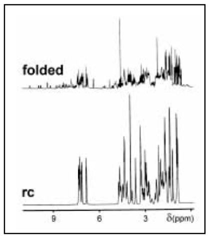
- The thermal denaturation of lysozyme (1960's).

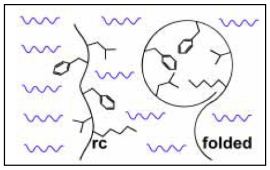


The Contributions of Kurt Wüthrich

The NMR Spectra of proteins contains structural information.

- Comparison of ^1H spectrum for bovine pancreatic trypsin inhibitor (BPTI) with that expected for the unfolded form of the protein (1970's).





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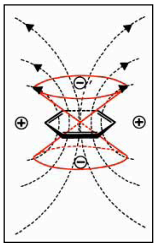
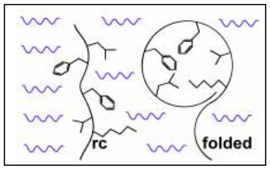
- “Ring current shifts”.





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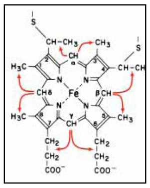
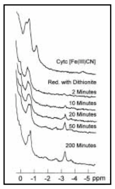
The NMR Spectra of proteins contains structural information.

- A lot of the early NMR studies on proteins were done on heme-containing proteins.
  - The “ring current shifts” arising from the heme groups would shift some of the resonances out from under the envelope, where they could be studied





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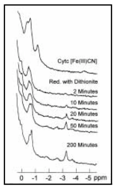
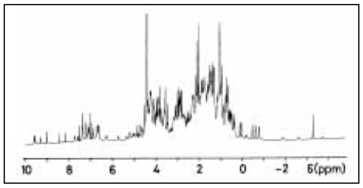
Advances in NMR technologies in the 1970’s opened up new avenues for study.

- Fourier Transform NMR
- Superconducting magnets with higher, more stable fields



1968
220 MHz
continuous-wave NMR



1980
360 MHz
FT-NMR

The Contributions of Kurt Wüthrich

Recognized that the Nuclear Overhauser effect (NOE) contained information that could be used to solve for the solution structure of biomacromolecules.

$$\text{NOE} \propto \frac{1}{\langle r \rangle^{6}} \cdot f(\tau_c)$$

- An NOE is observed as change in intensity that occurs in one resonance peak when another resonance peak is irradiated.
- It arrises from through-space dipole-dipole interactions between different nuclei.

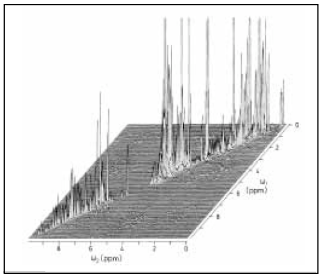
The Contributions of Kurt Wüthrich

The emergence of FT-NMR spectrometers led to the development of multi-pulse, 2-dimensional NMR experiments.

- Richard Ernst also contributed to the development of 2D-experiments
- These experiments greatly expanded the resolution and efficiency of collecting spin-spin (*J*) and dipole-dipole (NOE) data on large molecules
  - For example:
    - 2D-COSY (spin-spin, through bond, coupling)
    - 2D-NOESY (dipole-dipole, through space, coupling)

The Contributions of Kurt Wüthrich

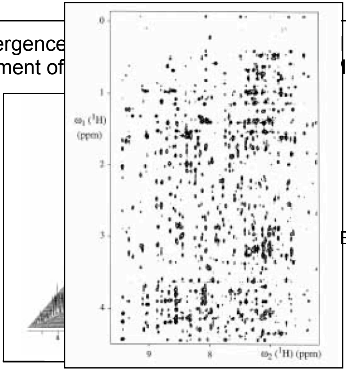
The emergence of FT-NMR spectrometers led to the development of multi-pulse, 2-dimensional NMR experiments.



2D-NOESY spectrum of BUSI IIA at 500 MHz

The Contributions of Kurt Wüthrich

The emergence … to the
development of … R experiments.



2D-NOESY spectrum of BUSI IIA at 500 MHz

The Contributions of Kurt Wüthrich

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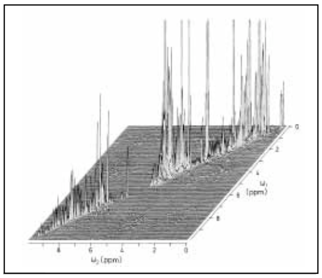
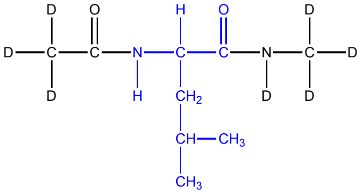


2D-NOESY spectrum of BUSI IIA at 500 MHz

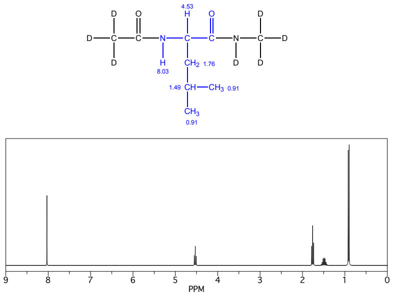
The Contributions of Kurt Wüthrich

^{1}H-NMR spectrum of the amino acid leucine



The Contributions of Kurt Wüthrich

^{1}H-NMR spectrum of the amino acid leucine



The Contributions of Kurt Wüthrich

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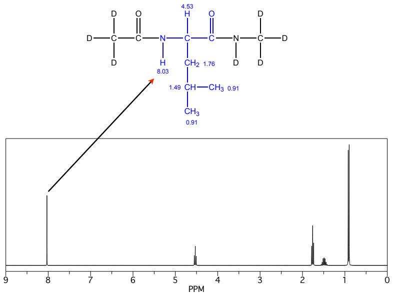

The Contributions of Kurt Wüthrich

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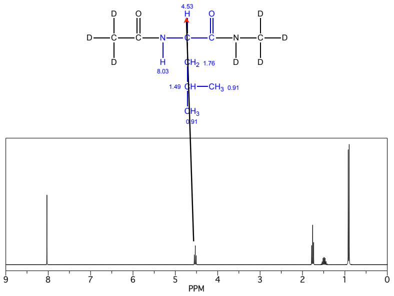

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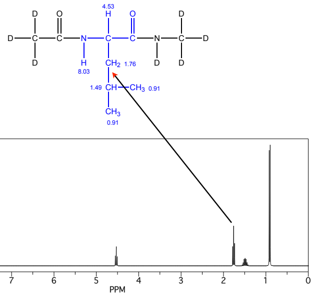

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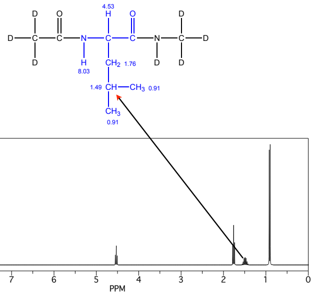

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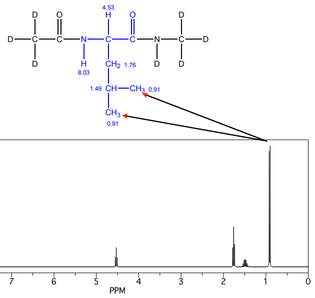

The Contributions of Kurt Wüthrich

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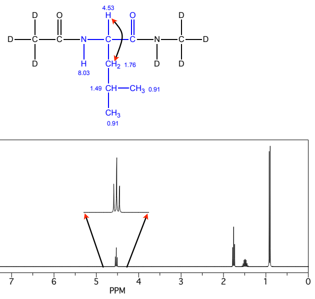
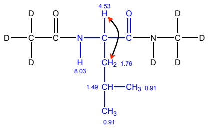
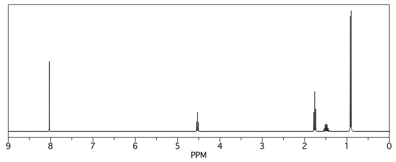
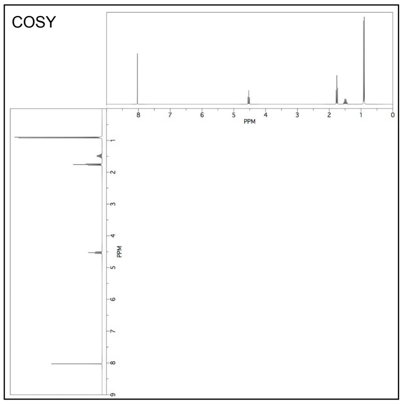


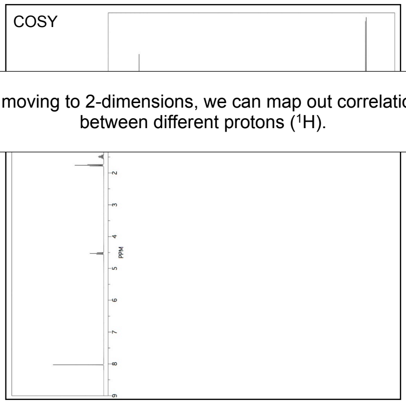
The Contributions of Kurt Wüthrich

^{1}H-NMR spectrum of the amino acid leucine

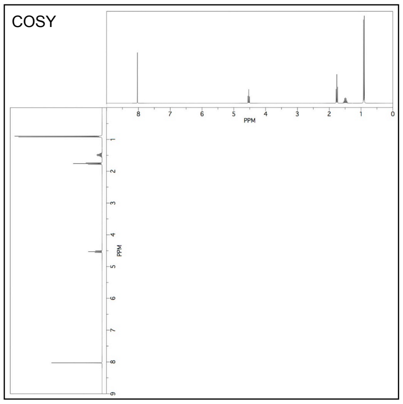




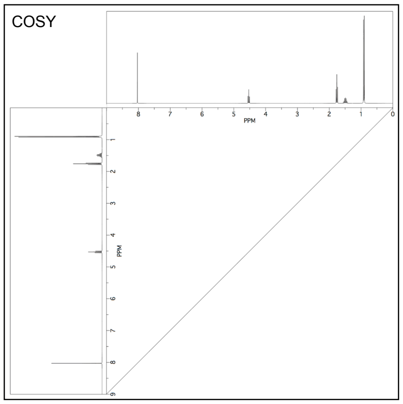




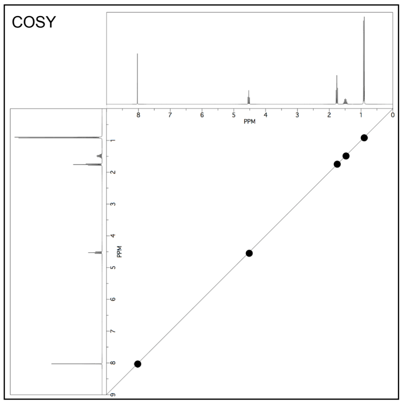
By moving to 2-dimensions, we can map out correlations between different protons (^{1}H).



COSY



COSY



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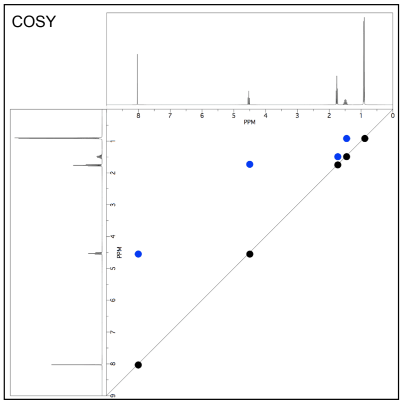

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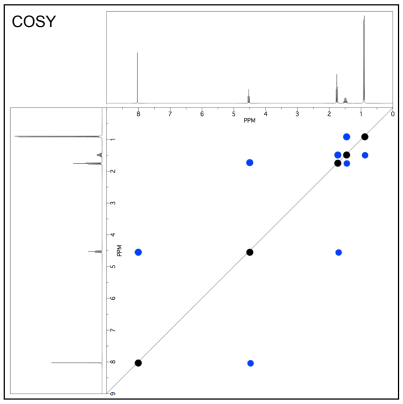

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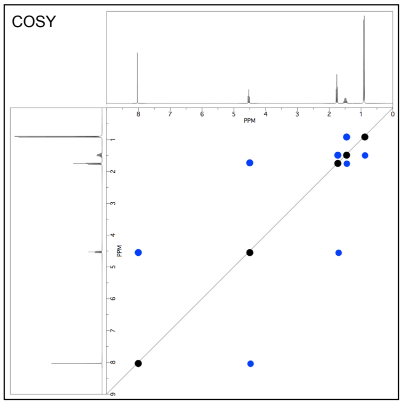

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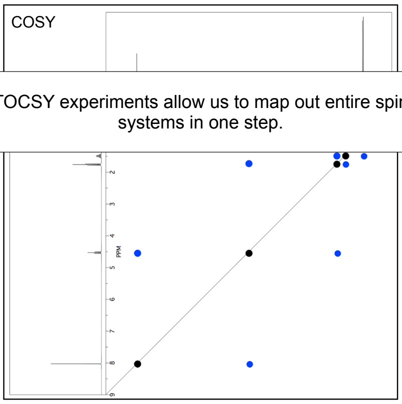

TOCSY experiments allow us to map out entire spin systems in one step.

COSY

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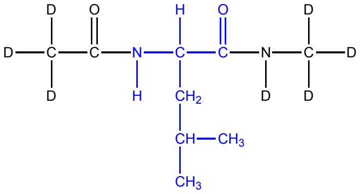

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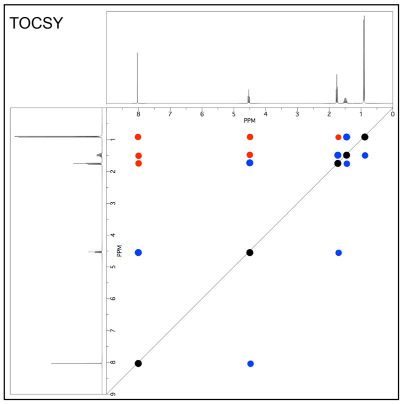

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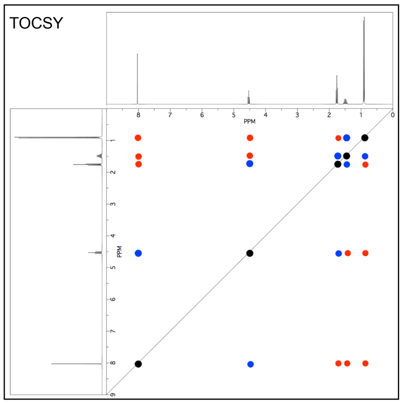

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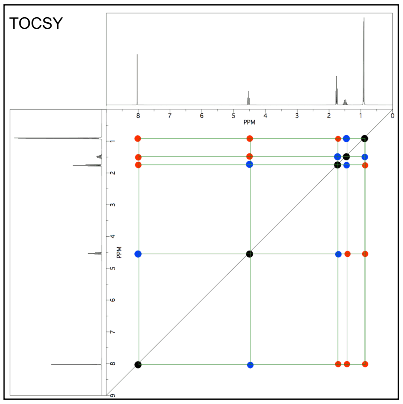

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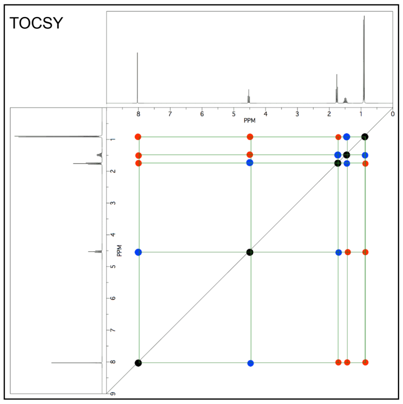
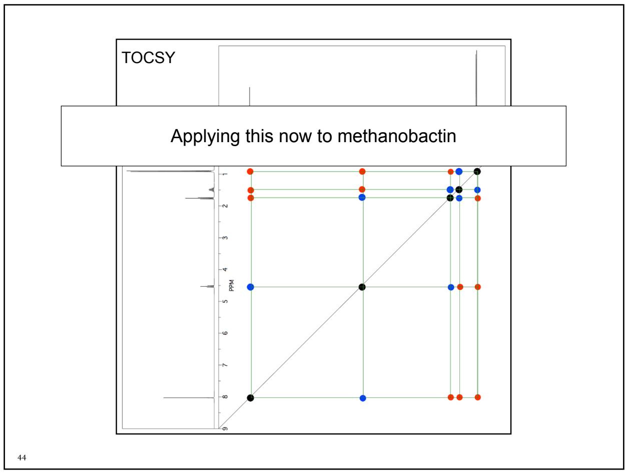
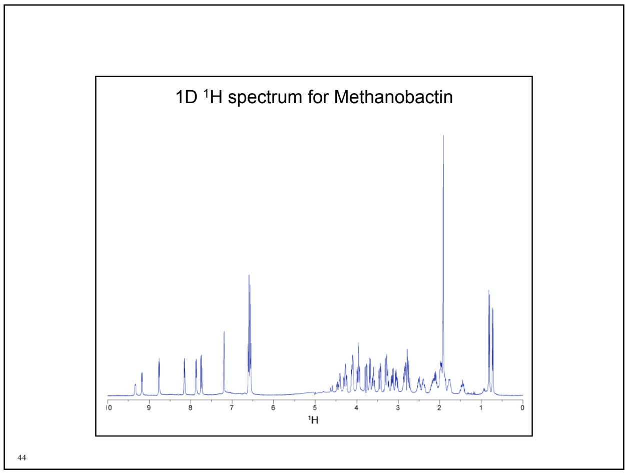


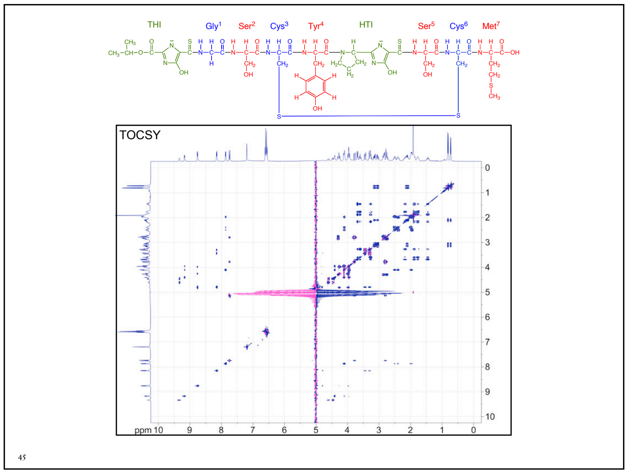


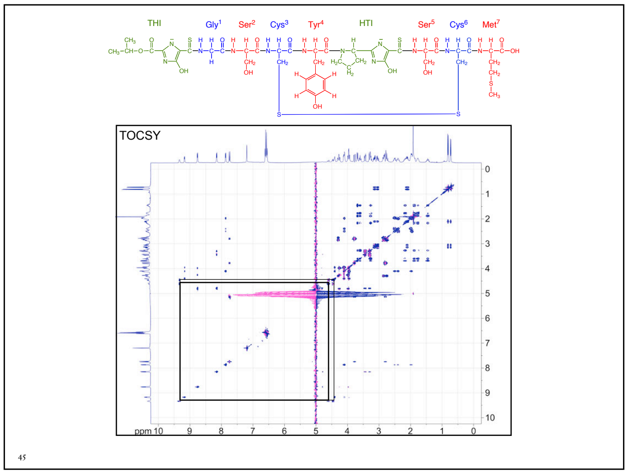
TOCSY

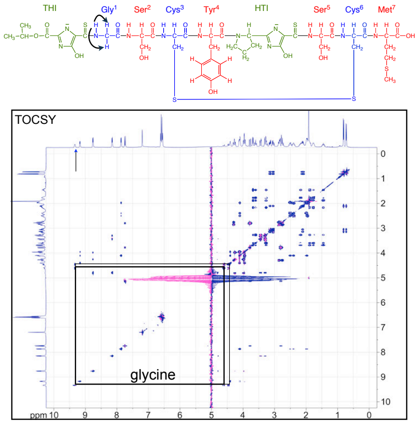
Applying this now to methanobactin

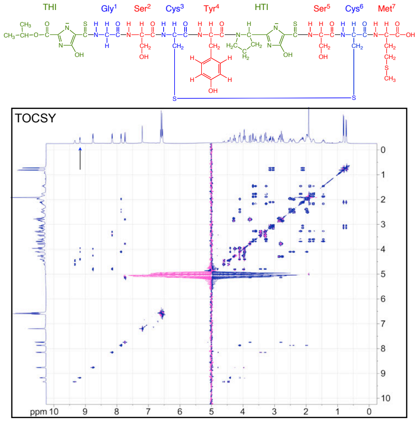


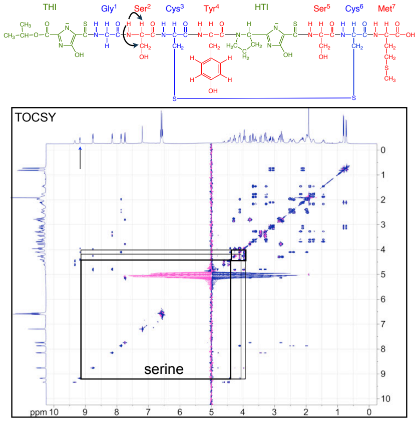
1D ^{1}H spectrum for Methanobactin

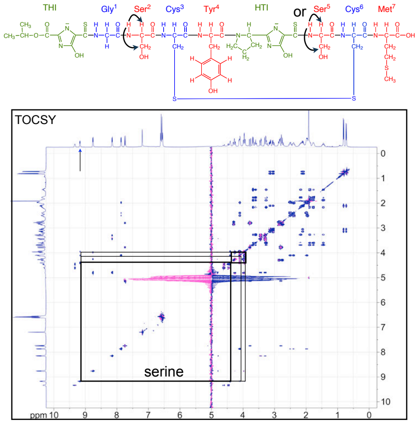


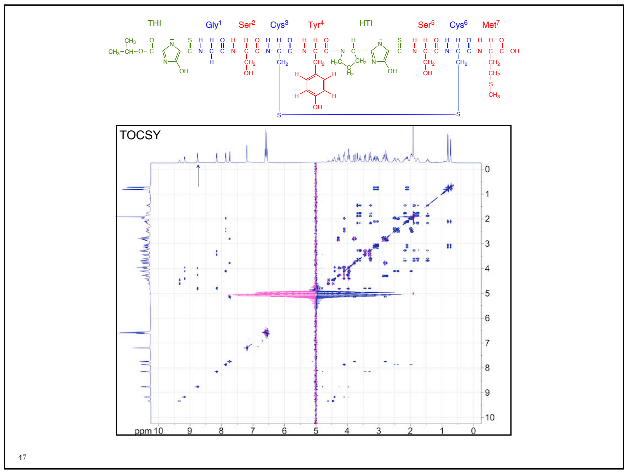


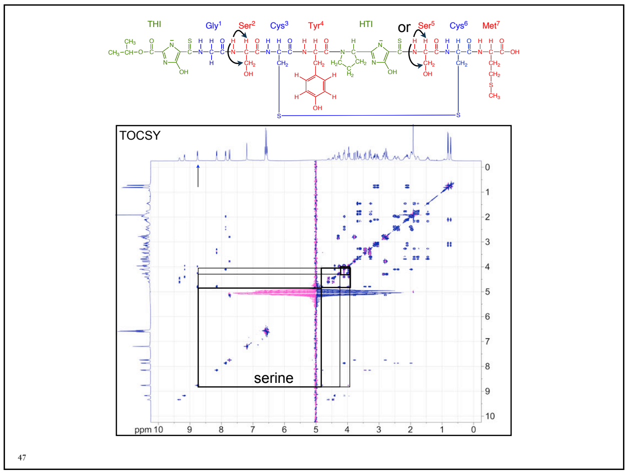

THI
Gly^{1}
Ser^{2}
Cys^{3}
Tyr^{4}
HTI
Ser^{5}
Cys^{6}
Met^{7}
TOCSY
glycine
ppm 10 9 8 7 6 5 4 3 2 1 0

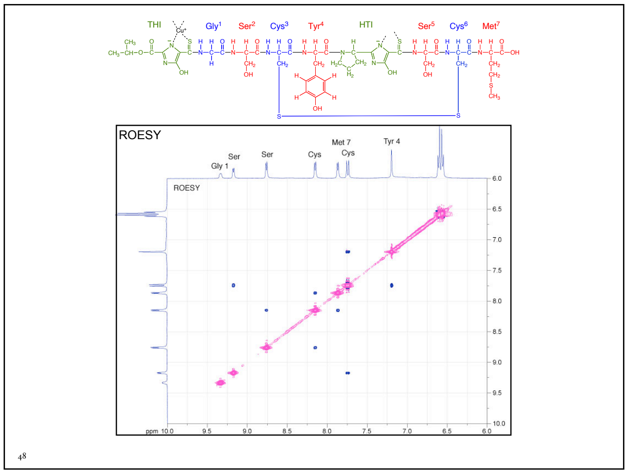

THI
Gly^{1}
Ser^{2}
Cys^{3}
Tyr^{4}
HTI
Ser^{5}
Cys^{6}
Met^{7}
TOCSY
ppm 10 9 8 7 6 5 4 3 2 1 0

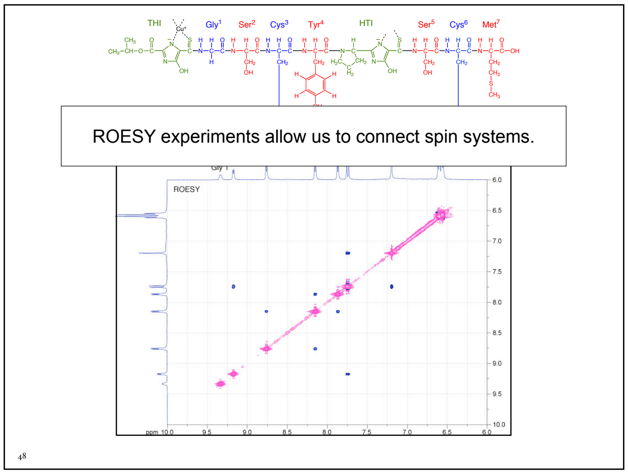

THI
Gly^{1}
Ser^{2}
Cys^{3}
Tyr^{4}
HTI
Ser^{5}
Cys^{6}
Met^{7}
TOCSY
serine
ppm 10 9 8 7 6 5 4 3 2 1 0

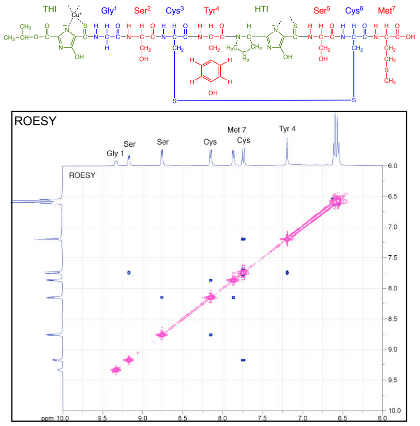

THI
Gly^{1}
Ser^{2}
Cys^{3}
Tyr^{4}
HTI
or
Ser^{5}
Cys^{6}
Met^{7}
TOCSY
serine
ppm 10 9 8 7 6 5 4 3 2 1 0



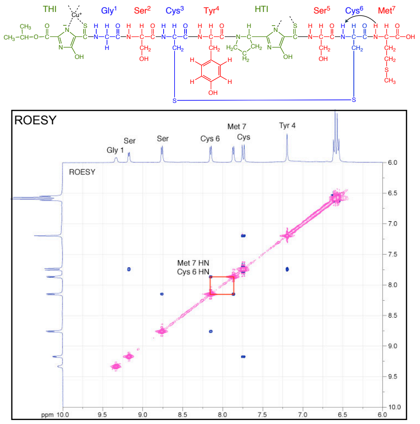




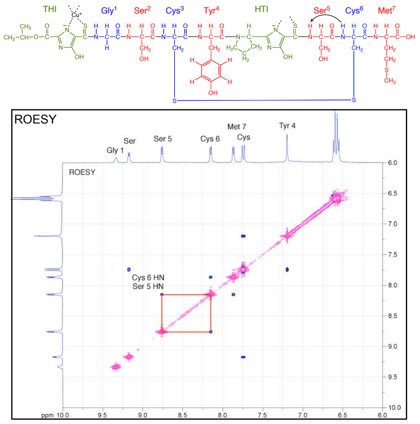

ROESY experiments allow us to connect spin systems.


THI
Gly1
Ser2
Cys3
Tyr4
HTI
Ser5
Cys6
Met7
ROESY
Gly 1
Ser
Ser
Cys
Met 7
Cys
Tyr 4
ROESY
ppm 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0
6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10.0

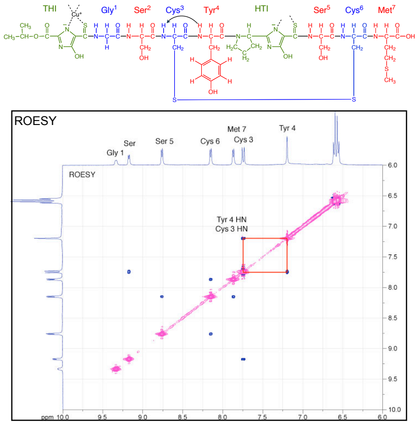
48


THI
Gly1
Ser2
Cys3
Tyr4
HTI
Ser5
Cys6
Met7
ROESY
Gly 1
Ser
Ser
Cys 6
Met 7
Cys
Tyr 4
ROESY
Met 7 HN
Cys 6 HN
ppm 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0
6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10.0

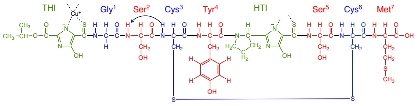
49

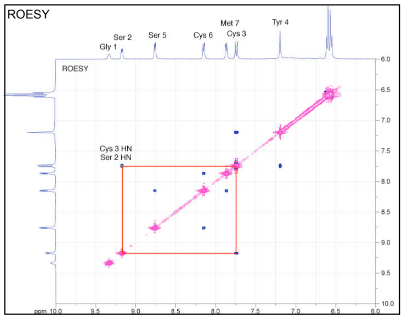

THI
Gly1
Ser2
Cys3
Tyr4
HTI
Ser5
Cys6
Met7
ROESY
Gly 1
Ser
Ser 5
Cys 6
Met 7
Cys
Tyr 4
ROESY
Cys 6 HN
Ser 5 HN
ppm 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0
6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10.0

50


THI
Gly1
Ser2
Cys3
Tyr4
HTI
Ser5
Cys6
Met7
ROESY
Gly 1
Ser
Ser 5
Cys 6
Met 7
Cys 3
Tyr 4
ROESY
Tyr 4 HN
Cys 3 HN
ppm 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0
6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10.0

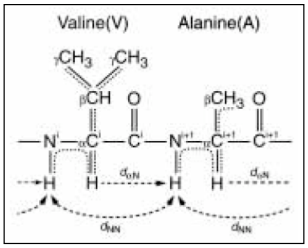
51





The Contributions of Kurt Wüthrich

Wüthrich and coworkers developed methods of making sequencial resonance assignments for all of ^{1}H resonances in a protein.



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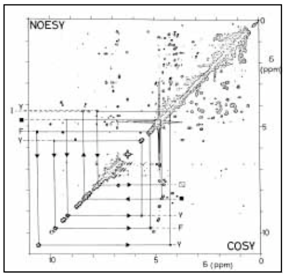
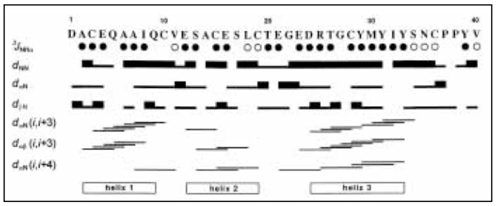


The Contributions of Kurt Wüthrich

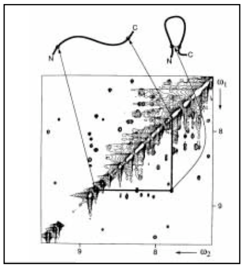
With the assignments in hand, they could then go on and use the COSY and NOESY data to determine the local structure of a polypeptide backbone

- α-helices
- β-sheets



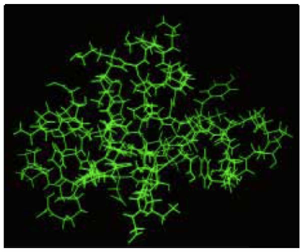
The Contributions of Kurt Wüthrich

The NOESY data can also be used find long range interactions, which can be used to predict the tertiary structure of biomacromolecules.



The Contributions of Kurt Wüthrich

In 1985, Wüthrich and coworkers published the first 3-dimensional solution structure of a protein that was determined using NMR spectroscopy.



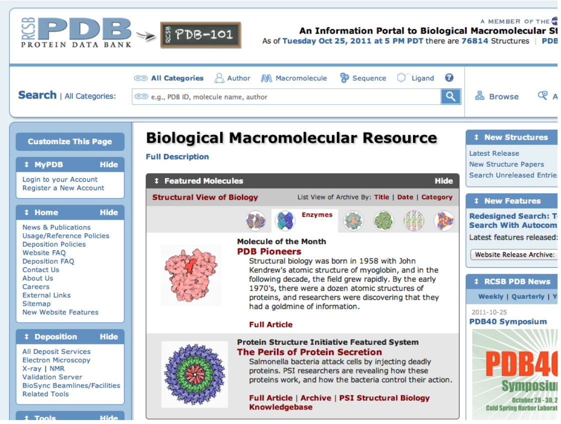
Solution structure of bull seminal proteinase inhibitor (BUSI) IIA

The Contributions of Kurt Wüthrich

There protocol has since been used to solve the solution structures of numerous proteins.

Table 1. Standard protocol for NMR structure determination of proteins

Step [a]		BUSI IIA [b]
I	Sample preparation	Protein isolated from natural source; natural isotope distribution; 16 mM solutions in H_2O and in ^2H_2O, respectively
II	NMR spectroscopy	2D ^1H NMR
IIIa	Resonance assignments	Sequential NOEs
IIIb	Conformational constraints	$[^1H,^1H]$-NOEs, $^3J_{HN\alpha}$, $^3J_{\alpha\beta}$
IIIc	Structure calculation	Metric matrix distance geometry
IIId	Structure refinement	Restrained energy minimization



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Molecule of the Month

PDB Pioneers

Structural biology was born in 1958 with John Kendrew's atomic structure of myoglobin, and in the following decade, the field grew rapidly. By the early 1970's, there were a dozen atomic structures of proteins, and researchers were discovering that they had a goldmine of information.

Full Article

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The Perils of Protein Secretion

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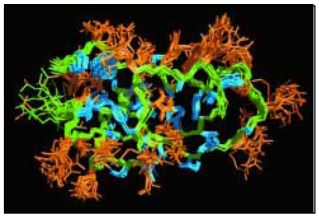
PDB40 Symposium

The Contributions of Kurt Wüthrich

In 1985, Wüthrich and coworkers published the first 3-dimensional solution structure of a protein that was determined using NMR spectroscopy.

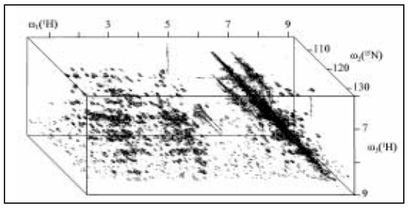


Solution structure of bovine pancreatic tripsin inhibitor

The Contributions of Kurt Wüthrich

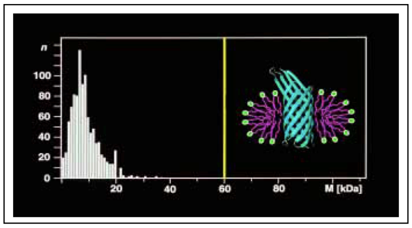
Modern higher dimensional and indirect detection experiments are further stream-lining the protocol.

- With one day the goal being to fully automate the process.



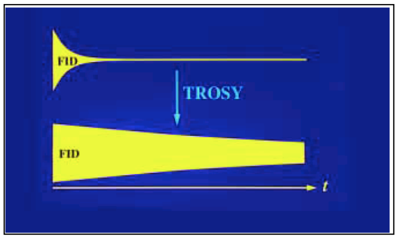
The Contributions of Kurt Wüthrich

Wüthrich and coworkers have gone on to develop experiments that can greatly expand the size of macromolecule whose structure can be determined.



The Contributions of Kurt Wüthrich

In 1997 they published and NMR experiment called TROSY (Transverse Relaxation Optimization Spectroscopy), which has be used to study systems as large as 870,000 Da.



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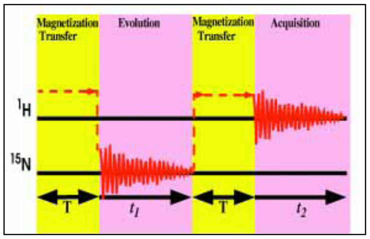
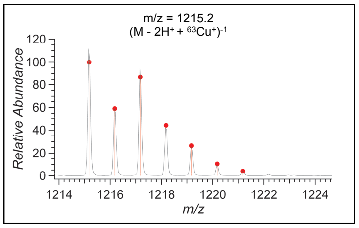


Mass Spectroscopy

Accurate mass determination on mb using our Agilent 6120 ESI-TOF mass spectrometer

Mass Spectroscopy

The isotope pattern reflects the relative distribution for each isotope in a sample



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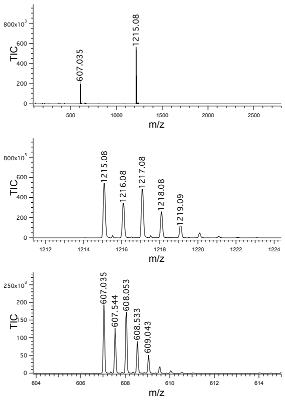
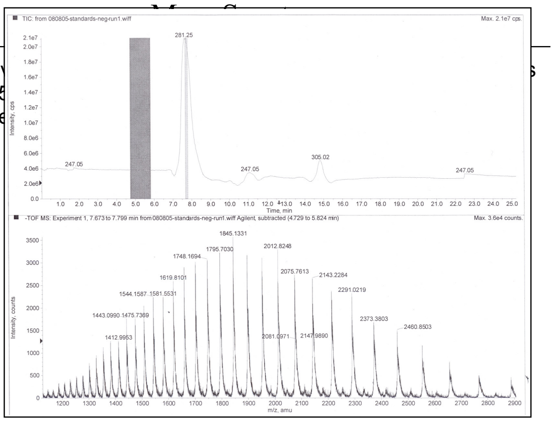


Mass Spectroscopy

Even though the highest m/z accessible on our instrument is 3500, the molecular weights of large proteins can still be determined.

Ev 35 de s



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The End