Fundamentals of NMR
MRI Workshop
Dayananda Sagar Institutes
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K.V.RAMANATHAN
NMR Research Centre
Indian Institute of Science Bangalore
NMR

It is an Ubiquitous Technique

Physics
Chemistry
Structural Biology
Material Science

Medicine
Food Technology
Forensic Science
Plant/Soil Science

Well Logging (Oil Exploration)
In Airport for Detection of Explosives
SHORT HISTORY OF NMR

--- Understanding of Magnetism (late 19th century)
--- Stern and Gerlach detect nuclear magnetic moment (1933)
--- Observation of NMR in Bulk Matter
   Failed Attempts - C.J. Gorter (1936)
--- Magnetic Resonance Methods (1937)
   Nobel Prize to I.I. Rabi (1944)
Felix Bloch
Nobel Prize 1952

For discovery of NMR in Bulk Matter (1945)

Edward Purcell
Nobel prize 1952
--- Discovery of Chemical Shift (1949)
--- First Commercial Spectrometer (1953)
--- Magic Angle Spinning, in 50’s
--- Fourier Transform NMR, in 60’s
--- Two Dimensional NMR in 70’s
--- NMR Imaging (MRI) in 70’s
--- 80’s onwards
   → Multi Dimensional NMR
   → Protein Structure in Liquids and Solids
      723 residue protein, 81 kD
   → Functional Imaging
Nobel prize in chemistry 1991

RICHARD R ERNST

“Development of Methodology of High resolution NMR”
Nobel prize in chemistry 2002

KURT WÜTHRICH

“Three dimensional Structure of Biomolecules”
Nobel Prize in Medicine - 2003

Paul Lauterbur

Peter Mansfield
CONTRIBUTIONS OF INDIAN SCIENTISTS

• G. SURYAN, IISc, NMR IN FLOWING LIQUIDS, RADIATION DAMPING.

• S.S. DHARMATI, TIFR, DISCOVERY OF CHEMICAL SHIFT

• C.L. KHETRAPAL, IISc, NMR OF ORIENTED MOLECULES

• ANIL KUMAR, IISc, TWO-DIMENSIONAL NMR
WHAT TECHNOLOGICAL DEVELOPMENTS THAT HAVE CONTRIBUTED TO THE SUCCESS OF NMR?

• DEVELOPMENT OF SUPERCONDUCTING MAGNET TECHNOLOGY

• FOURIER TRANSFORM TECHNIQUES/ DIGITAL SIGNAL PROCESSING METHODS

• AVAILABILITY OF MINI-COMPUTERS

• ADVANCED R.F. ELECTRONICS
\[ \Delta E = \gamma \hbar H_0 \]

**RESONANCE SPECTROSCOPY**

Source → Sample → Detector

**MAGNETIC RESONANCE SPECTROSCOPY**
What is the basic condition to observe Nuclear Magnetic Resonance?

*Nuclear Spin Quantum Number* $(I) \neq 0$

**Even atomic mass & number**

$I = 0$  
eg., $(^{12}\text{C}, ^{16}\text{O})$

**Even atomic mass & odd number**

$I = \text{Whole integer} \rightarrow (^{14}\text{N}, ^{2}\text{H}, ^{10}\text{B})$

**Odd atomic mass**

$I = \text{Half integer} \rightarrow (^{1}\text{H}, ^{13}\text{C}, ^{15}\text{N}, ^{31}\text{P})$
Nuclear spin behaves like a tiny magnet

It also has a magnetic moment $\mu$

Spin angular momentum and magnetic moment are related to each other as

$$\mu = \gamma I h / 2\pi$$
What happens to a nuclear spin in a magnetic field?

A tiny magnet, (compass needle) always aligns itself parallel to an external magnetic field.

Spins also align in a magnetic field.

The magnetic moment moves in a cone keeping an angle with the magnetic field.

LARMOR PRECISION
For an ensemble of spins

$\vec{M} \times \vec{z} \times \vec{y}$

平均磁化沿磁场（Z）方向

**XY component of the magnetic moment cancels out due to random phase.**

**Average magnetization along the field (Z) direction**
It turns out that \( \nu \) is the same as the Larmor Precession Frequency.
Energy separation is directly proportional to magnetic field and also the magnetic moment of the nuclei.

Higher the magnetic field and larger the magnetic moment, higher the resonance frequency.

\[ E \] Proton Carbon

\[ B_0 \]
SIMPLE BLOCK DIAGRAM OF A NMR SPECTROMETER
AN NMR spectrometer has following components

- An intense, Homogeneous and stable magnetic field
- A “probe” which enables the coils to excite and detect the signal
- A high-power rf transmitter capable of delivering short pulses
- A sensitive receiver to amplify the NMR signals
- A digitizer to convert the analogue NMR signals to digital form
- A pulse programmer to produce precise timed pulses and delays
- A computer to control everything and to process data
NMR Spectrum of the protein Lysozyme (14.3 kDa)
What are the advantages of High Field Magnets

High chemical shift dispersion  --- Improvement in selectivity of spectral editing schemes

High sensitivity  \((H_1 / H_2)^{3/2}\)

Simplification / First order spectra

TROSY effect

\(T_1\) elongation at high field ?  Not an advantage !!!
IRON CORE MAGNETS - HYSTERESIS

Approximate Magnetic Field: $\approx 2.3 \text{ T} \Rightarrow 100 \text{ MHz}$

Diagram labels:
- Magnetic Field
- Current

Diagram shows a saturation curve with a point at $\approx 2.3 \text{ T}$ corresponding to $100 \text{ MHz}$. 
Modern nmr spectrometers make use of superconducting magnets (air core) in persistent current mode.

Super conducting material is in the form of a thin wire of NbTi or Nb$_3$Sn alloy, which has zero resistance at temperatures less than 9K. This is achieved by immersing the superconducting wire in a bath of liquid helium (boiling point 4.2K)

Magnet is designed such that the sample is at Room temperature. Liquid Nitrogen is used to minimise the evaporation of liquid helium.
Iron Magnets : Max. Field 2.5 Tesla
(~100 MHz for Protons)

Supercon : > 21 Tesla
(~900 MHz for Protons)

Stability and homogeneity required for High resolution NMR :

0.1 Hz @ 1 GHz i.e., ≈ 1 part in $10^{10}$
External view of a Superconducting NMR magnet
TYPICAL SUPERCONDUCTING MAGNET 900 MHz

Superconducting material currently used for producing high magnetic Fields of 21 Tesla and above is Nb₃Sn.
Vacuum chamber

The aluminized Mylar insulation reflects the infra-red heat radiation from the inside of the room temperature surface.

Liquid Nitrogen vessel

to act as a refrigerant to block radiation from reaching the liquid helium vessel.
Superconducting coil

This magnet contains approximately 19 kms of superconducting wire

The Liquid Helium Baffle

For infra-red radiation shield and protects the superconducting magnet from any fluctuations in the liquid helium reservoir
MAGNET CHARGING

- S.C. Magnet Coil
- S.C. Switch
- Charging Leads
- Heater

Method to achieve persistent current mode
• Stray Magnetic fields
• 5 gauss lines
• Ultra shielded magnets save space
For homogeneous magnetic fields, we need SHIM COILS

The applied magnetic field can be written as

\[ B = B_0 + \left( \frac{\partial B}{\partial x} \right)x + \left( \frac{\partial B}{\partial y} \right)y + \left( \frac{\partial B}{\partial z} \right)z + \left( \frac{\partial^2 B}{\partial x^2} \right)x^2 \\
+ \left( \frac{\partial^2 B}{\partial x \partial y} \right)xy + \ldots + \left( \frac{\partial^3 B}{\partial x^3} \right)x^3 + \ldots \]

Each shim coil will produce a counteracting tiny magnetic field with a particular spatial profile so as to cancel the residual field inhomogeneities.

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CRYO SHIMS

ROOM TEMP. (R.T.) SHIMS
Break Through in 1970s

- Availability of dedicated Mini-Computers
- Signal Averaging
- F.T. Algorithms
CW (Frequency Sweep) NMR

or

Pulsed Fourier Transform NMR?
R.F. Pulse for (μ secs) → Signal from the Sample

Free Induction Decay (FID) → Time

FT → Frequency
Advantages of F.T.Method

- Faster by the Ratio of Spectral-width to Line-width
- Several New Experiments Became Possible
Two Dimensional NMR

- Preparation
- Evolution $t_1$
- Mixing
- Acquisition $t_2$

$f_1$

$t_1$ is the variable delay time
$t_2$ is the normal acquisition time

Double Fourier transform of the data results in frequencies in two dimensions

Time domain signal along $t_2$

Time domain signal along $t_1$ is also periodic

Can build Pseudo FID by looking at the points for each frequency along $t_2$
Two dimension NMR time and frequency data

Frequency domain spectrum after double Fourier Transformation

Time domain data
COSY spectrum
NMR spectra of a dimeric GpA mutant

3D $^1$H-$^{15}$N NOESY-HSQC spectrum
Protein Activation and Drug Inhibition of Calcium-binding Domains

Folding and Proteinase Inhibition by Cystatins

http://www.shef.ac.uk/~nmr/jpw_proj.html#cam
The coplanar Trps [blue] bind to the flat cellulose. Relacement of adjacent glutamine (red) by glycine changes tryptophan orientation and the cell fails to bind to cellulose (right).

CELLULOSE BINDING DOMAIN
(of a plant cell wall hydrolase — a catalytic enzyme)
PROBE

Small coil is used to excite and detect the NMR signal.

Input RF frequency and probe frequency should be matched (tuning).

Transmitter/Receiver impedance and probe impedance should be matched.

Magnetic field gradient coils are extremely useful.
The NMR coil is where the action is

Basic Probe circuit

Resonance frequency \( \nu = 1/ \frac{2\pi}{\sqrt{(LC)}} \)

The coil and the capacitors, \( C_1 \) and \( C_2 \), form a resonant circuit. The inductance of the coil, \( L \), and the (approximate) sum of \( C_1 + C_2 \) determine the resonance frequency

\( C_2 \) provides transformation of the high impedance parallel resonant circuit to a lower impedance (50 ohms) to match the output impedance of a transmitter and the input impedance of a receiver.
Impedance Matching

Radio-frequency waves cannot be efficiently sent over regular wires. To prevent signal losses, "transmission lines" are used.

The transmission line and the load at the other end must have the same impedance.

If the impedances differ, a "mismatch" condition exists, leading to "standing waves" or "reflection".

This means that the rf power is not efficiently transferred, leading to a loss.
With perfect matching, we obtain the shortest possible pulse width, the best possible signal to noise and, if decoupling is used, the most efficient decoupling.

The impedance of the pulse and decoupler transmitters, and the connecting cables of an NMR spectrometer is usually 50 Ohm. The probe must therefore present a 50 Ohm load impedance to avoid the above problems.
Different types of coils

Solenoid, Saddle and Cage Coils
Double Tuning

VIRTUAL GROUND

OPEN QUARTER $\lambda$ CABLES HAVE ZERO IMPEDENCE FOR CORRESPONDING $\nu$
**SPECIALITY OF INSTRUMENTATION FOR HIGH RESOLUTION NMR**

- High R.F. and Magnetic field stability.
- All R.F. is generated by crystal controlled oven stabilized single R.F. source.
- Magnetic field stability ensured by Field-Frequency Lock.
Pulse FTNMR Spectrometer

Block Diagram 250MHz  (Super Heterodyne Circuit)

Synthesizer \(\rightarrow\) 150 \(\rightarrow\) Mixer \(\rightarrow\) 250 \(\rightarrow\) Transmitter \(\rightarrow\) PROBE

Magnet

X 10

Switch

Preamp

Pulse Programmer

Computer

Magnet

Detectors

IF Receiver

100MHz

150

250

100MHz

250

100MHz

150

100MHz

100MHz

100MHz

100MHz
Synthesiser is the source of rf gate and attenuator is used to create pulses under computer control.

Rf source is usually at low level of few mW. This needs to be amplified to a power of 100 W.

Power of the rf at the coil defines the 90 degree pulse.
TRANSMITTER

- HIGHER POWER IS PREFERRED
- SHORTER PULSE WIDTHS LARGER EXCITATION PROFILE
- BLANKING
RECEIVER

- LOW NOISE CONFIGURATION
- BETTER IMAGE REJECTION
- I.F.FREQUENCY
Angalog to Digital Conversion

ADC is used to convert the NMR signal from voltage to a binary number. ADC samples the signal at regular intervals resulting in the representation of FID as data points.

Largest number is defined by the number of binary bits that ADC uses ($2^n$ steps)

16 or 32 bits is commonly used in NMR
Digital signal Processing

- Nyquist Frequency
- Advantages of Oversampling
ENSURES $B_0$ STABILITY

(It is easier to produce highly stable and accurate frequencies with crystal controlled oscillators)

ENABLES HOMOGENEITY ADJUSTMENT
2H LOCK CHANNEL

R.F. SOURCE ➔ TRANSMITTER

Probe

Magnet ➔ Switch ➔ RECEIVER

Amp.

Field Correction Coil ➔ Dispersion Signal ➔ Display

Absorption signal
Absorption signal

Dispersion signal

Voltage

H
Lock transmitter / receiver generates the rf pulse at the reference frequency

Lock signal coming from the coil is amplified and fed into the lock receiver

The correction circuit will know when the lock signal is drifting from the reference frequency

Dispersive signal used gives equal but opposite intensities on either side of the reference signal. The integrator sums the intensities to zero, when the lock is on resonance.

When the integrated sum is not zero, the corrective circuit sends the current which augments or detracts in such a way that the sum is zero.
METHODS OF INCREASING S/N

“n” scans increases signal to noise (S/N) by $\sqrt{n}$

OVER SAMPLING
Nyquist frequency requires $DW = 1/(2SW)$
Sampling @ $> DW$ above improves S/N

CRYOGENICALLY COOLED PROBES
Noise decreases with temperature
It helps to cool both the coil and the preamplifier
S/N increases by a ~ 4
Other features of high resolution NMR spectrometers

Decoupling Nucleus X from Y

Helps: Simplification of spectra, Assignment and Information the system

Computer and software:

Large Data sets
Multi dimensional FT
Digital Signal processing
Linear prediction
- Have become essential
- Usually single axis \((z)\) is enough.

Uses: Cleans up the spectrum well, faster and newer experiments have become possible
GRADIENT COILS

MRI

-Absolutely essential – 3 axis x,y,z
-Linear field gradients encode for spatial distribution of protons
Magnetic Resonance Imaging

MRI
Fourier Imaging
Anil Kumar, D. Welti, R.R. Ernst, J. Magn. Res. 18, 69 (1975)
Echo-planar imaging
P. Mansfield
Science, 254, 43-50, 1991
Coronal Image of a Human Head
Sagittal Image of a Human Head
Axial Image of a Human Head
Other Related Areas of Development:

• MR Angiography
• Magnetic Resonance Spectroscopy (MRS)
• Functional Imaging
A 3T MRI Instrument
On-going/Future Developments

• Fast multi-dimensional NMR methods
  Single Scan 2D NMR methods
  G-Matrix Transform
  Projection Reconstruction
  Covariance Spectroscopy

• Multiple Receivers
  For eg. Proton and Carbon spectra acquired simultaneously

• Multiple Samples
  Using magnetic field gradients to distinguish sample tubes
SUMMARY

• TECHNOLOGICAL DEVELOPMENTS AND SCIENTIFIC PROGRESS GO HAND IN HAND.

• BOTH AREAS GAIN BY SCIENTISTS AND TECHNOLOGISTS WORKING TOGETHER.

Before I Conclude.....
NMR RESEARCH CENTRE
SIX NMR SPECTROMETERS UNDER ONE ROOF
700 MHz Solution NMR Spectrometer

300 MHz Solids NMR Spectrometer

500 MHz Solution NMR Spectrometer

400 MHz Solution NMR Spectrometer

AV-500 MHz Solution NMR Spectrometer

NMR Research Centre
National Facility
THANK YOU
FOR YOUR ATTENTION