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Introduction



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NMR: Nuclear Magnetic Resonance

- Definition**
 NMR is a physical phenomenon that occurs when applying a radio frequency to atomic nuclei in a magnetic field.

γ -rays	x-rays	UV	VIS	IR	μ -wave	radio
10^{-10}	10^{-8}	10^{-6}	10^{-4}	10^{-2}	10^0	10^2
wavelength (cm)						


● Gamma rays	Nuclear transitions
● X-rays	Electronic transitions (inner electrons)
● UV-Vis	Electronic transitions (outer electrons)
● IR	Vibration transitions
● radiofrequencies resonance)	NMR and EPR (electronic paramagnetic resonance)

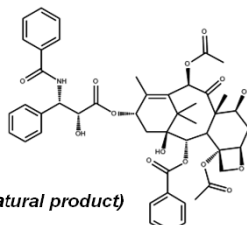
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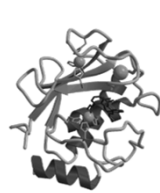
Typical Applications of NMR

- 1) Structural (chemical) elucidation
 - Natural product chemistry
 - Synthetic organic chemistry
 - analytical tool of choice of synthetic chemists
 - used in conjunction with MS and IR
- 2) Study of dynamic processes
 - reaction kinetics
 - study of equilibrium (chemical or structural)
- 3) Structural (three-dimensional) studies
 - Proteins, Protein-ligand complexes
 - DNA, RNA, Protein/DNA complexes
 - Polysaccharides
- 4) Drug Design
 - Structure Activity Relationships by NMR
- 5) Medicine-MRI






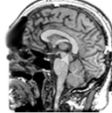
Taxol (natural product)




NMR Structure of MMP-13 complexed to a ligand



MRI image of the Human Brain




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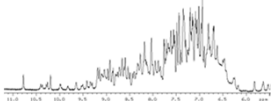

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NMR

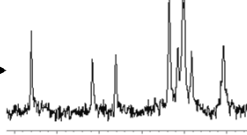
NMR \longrightarrow **Flexibility / adaptability**


- NMR liquid state
 - Structural determination
 - ❖ Low and medium molecular weight compounds
 - ❖ High molecular weight compounds 10kDa
 -
- NMR solid state
 - Organic and inorganic compounds
 - Biopolimers (proteins, DNA RNA)
 -
- Magnetic Resonance Imaging Spectroscopy (MRI)
 - MRI functional
 - Micro-imagen
 - MRI Locating









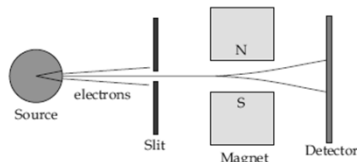


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The first observable evidence of nuclear magnetic moment



1921 Otto Stern & Walther Gerlach: Beam of electrons split into two paths when passed through an inhomogeneous magnet due to the electron's magnetic moment.



1943 Stern wins Nobel Prize in Physics

Angular momentum (p)

Magnetic moment (μ)

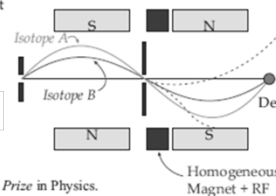


1938 I.I. Rabi (Columbia) refines the Stern & Gerlach technique to observe the effect from the nuclear magnetic moment. Using a homogeneous magnet (with field strength B) and applying a specific radio frequency he observed that a beam of atoms split into separate paths. This showed that there were quantized energy levels separated by:

$$\Delta E = \pm (\mu / p) B$$

$$\Delta E = \pm (\mu / p) B_0$$

with this method.



1944 Rabi wins the Nobel Prize in Physics.

1944 Rabi wins Nobel Prize in Physics

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First NMR signals 1946



1945-6 Edward Purcell with Henry C. Torrey and Robert V. Pound (MIT) observe NMR signal from paraffin wax (December 15, 1945).



1945-6 Felix Bloch, with W.W. Hansen and Martin Packard (Stanford) use a different method they call *nuclear induction* to observe proton signal from H_2O in early January 1946.



Both groups agreed that they were observing the same phenomena and called it NMR. (Bloch's method is closer to techniques used today).

1944 Bloch and Purcell win the Nobel Prize in Physics



First NMR signals 1946

Phys. Rev. 70 474 (1946)

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Chemical Shifts 1950-1



1950 Proctor and Yu accidentally discover that two different nitrogens of NH_4NO_3 resonate at different frequencies.

1950 Other reports of similar differences in resonance frequencies of different compounds for proton (water vs. mineral oil) and fluorine (CF_3 vs. aromatic F).

1951 Arnold, Dharmatti and Packard (Stanford) are the first to report different resonance frequency for protons in the same molecule.



First published 'high-resolution' ^1H NMR spectrum (1951)

The Chemical Shift was discovered

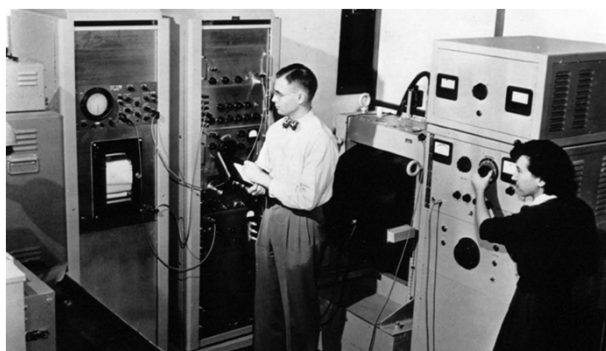
The three peaks of methanol was observed by Packard group

The operating field of magnet was 7.600 gauss. ^1H frequency 32.4 MHz



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First NMR Applications Laboratory, 1952

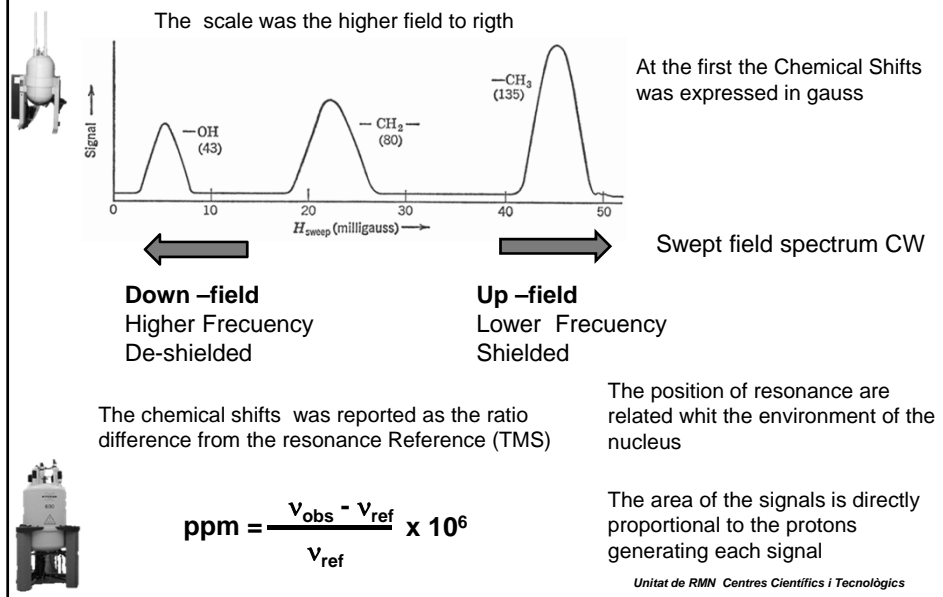


The first commercial NMR spectrometer, the Varian HR-30, was installed at Humble Oil company in Baytown, Texas in September 1952.

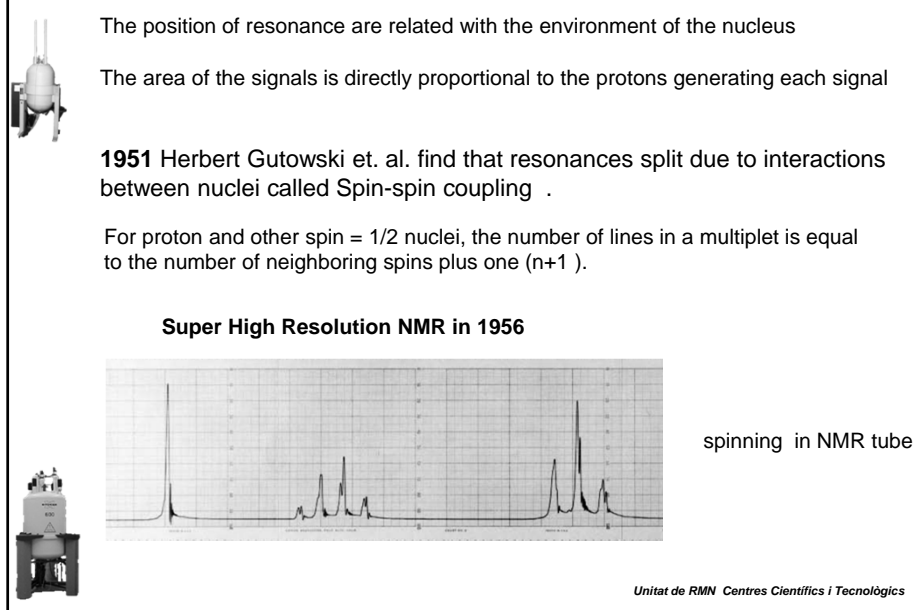


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1951 Chemical Shift, and reference



Spin-Spin Coupling

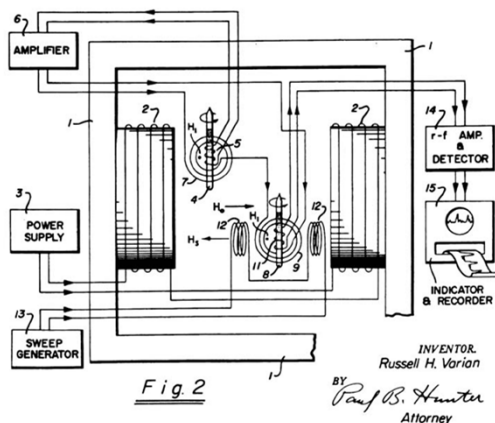


Field/Frequency Lock, 1956



Russell Varian developed the concept of the field/frequency lock utilizing a feedback mechanism.

Oct. 29, 1963 R. H. VARIAN 3,109,138
 GYROMAGNETIC RESONANCE METHODS AND APPARATUS
 Filed Aug. 29, 1956 2 Sheets-Sheet 1



correct for the field drift during data collection

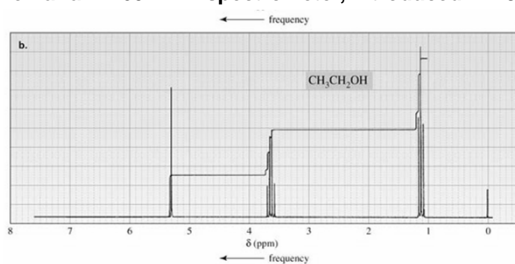
INVENTOR:
 Russell H. Varian
 BY Paul B. Hunter
 Attorney

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60 MHz NMR Spectrometer



The Varian A-60 NMR spectrometer, introduced in 1961



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Starting point



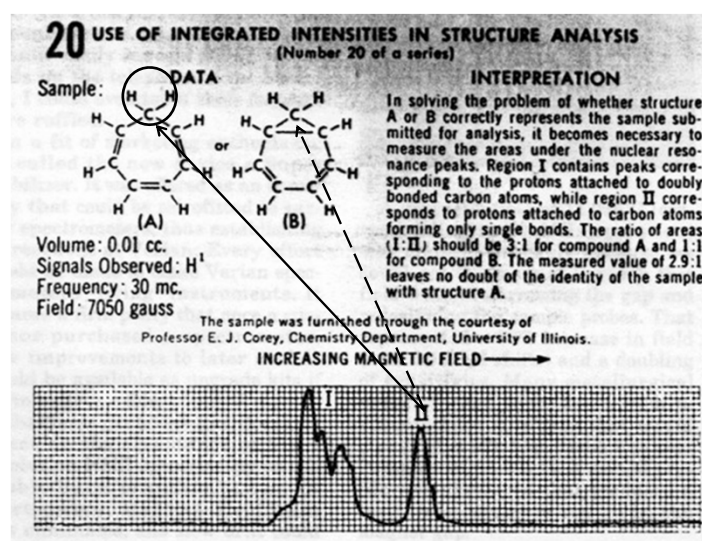
"I put a sample in the instrument, adjusted the resolution, and ran a spectrum on the precalibrated chart. It was perfect. But could the A-60 reproduce a spectrum with the fingerprint quality of the IR instrument? I moved the pen back to the start and restarted the scan. I was momentarily distracted, and when I looked back I saw only one line on the chart. "Why didn't the second scan run properly?" I asked. The answer came back, "It did!" Amazed and almost incredulous, I returned the pen three more times. It laid down five identical spectra with a single trace showing on the paper!

At that instant, I knew the field of organic chemistry would never be the same again. (from *Shoolery*, J.N. "NMR spectroscopy in the beginning." *Anal. Chem.* **1993**, *65*(17), 731A-741A)



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The first problem solved by NMR



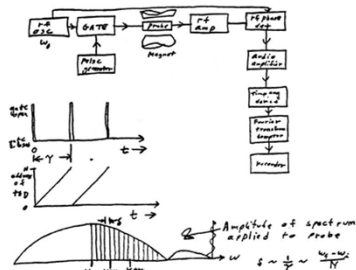
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RF Pulse. 1965

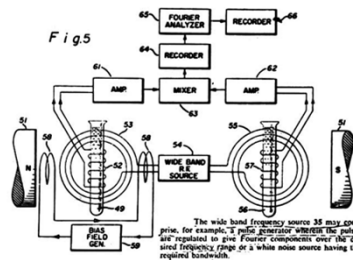


1965-6: Richard Ernst and Weston Anderson (Varian) use pulse excitation to produce the first spectrum.

From Weston Anderson's Engineering Notebook dated June 3, 1964, outlining the idea of pulse-excited high resolution NMR spectroscopy.



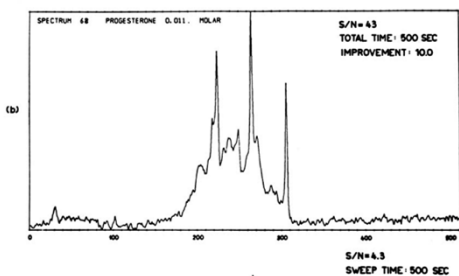
Nov. 22, 1966 R. H. VARIAN 3,287,629
 MAGNETIC RESONANCE METHODS AND APPARATUS
 Original Filed Aug. 29, 1966 3 Sheets-Sheet 3



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Richard Ernst & Wes Anderson, Rev. Sci. Instr. 37, 93 (1966)



Initially it took several hours for the processing of spectra

The computers used punch cards for data entry

Fourier transform (top) and conventional spectra of 0.011 M progesterone showing sensitivity enhancement by a factor ten

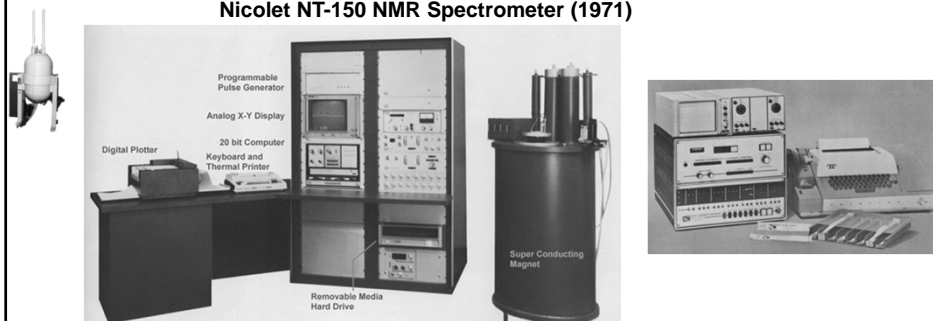


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Commercial FT-NMR 1967..... 2XXX



Nicolet NT-150 NMR Spectrometer (1971)



Advantages of FT over CW

- Faster data collection (Fellgett Advantage or Multiplex advantage).
- Signal averaging allowed better sensitivity (S/N) and the observation of less sensitive and less abundant nuclei.
- Allowed advancements in solid-state NMR.
- Allows the use of multipulse sequences.
- Allowed the development of NMR Imaging.

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Superconducting magnets



Varian HR-220,



1966

Bruker Avance 1000 MHz



Lyon, France in July 2009

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Solid State NMR



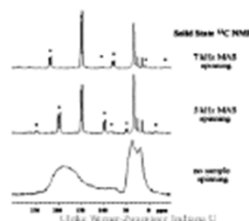
Solid-State NMR:

While advances in NMR through resolution improvements occurred with liquids, solid-state spectra remained broad and featureless.

1958 Andrew and Lowe show that rapid sample spinning narrows solid-state resonances.

1965-1975 Using methods incorporating sample spinning and *FT* pulse techniques, several labs make solid-state NMR as information-rich as liquids spectra (Waugh, Pines, Mansfield and Vaughn).

1990's- Applications for Bio-molecules become increasingly useful (membrane bound proteins, etc.).



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2D techniques

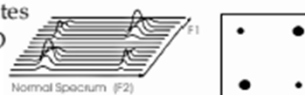


Multi-Dimensional Techniques:

1971 Jean Jeneer conceives the first two dimensional experiment.



1976 Richard Ernst executes and publishes the first 2D experiment (COSY).



1976- Explosions of new techniques and applications.

1985 Kurt Wüthrich publishes first solution-phase protein structure determined by NMR measurements.



1991 Ernst wins the Nobel Prize in Chemistry

2002 Wüthrich wins the Nobel Prize in Chemistry



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R.R. Ernst Nobel Prize 1991

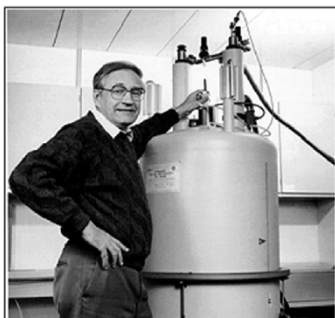


The Nobel Prize in Chemistry 1991

The Royal Swedish Academy of Sciences has awarded this year's Nobel Prize in Chemistry to

Richard R. Ernst
ETH, Zürich, Switzerland

for his contributions to the development of the methodology of high resolution nuclear magnetic resonance (NMR) spectroscopy.



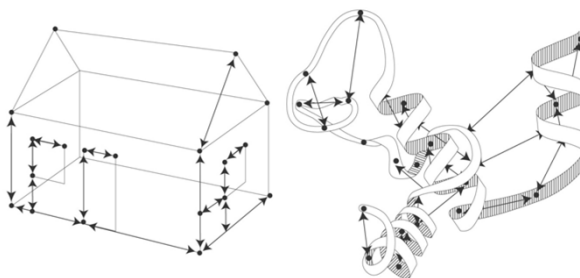
Richard R. Ernst's revolutionary development of the methodology of nuclear magnetic resonance spectroscopy has transformed NMR into maybe the most important instrumental technique within chemistry today. Ernst has contributed more than anybody else to this development by the discoveries of Fourier-transform NMR and two-dimensional (2D) NMR.

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2002 Nobel Prize in Chemistry



Kurt Wüthrich



Showed that NMR was possible for proteins

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More

NMR Imaging (MRI)



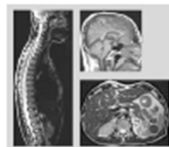
1973 Paul Lauterbur (SUNY, Stony Brook) uses magnetic field gradients in three dimensions and computer axial tomography (CAT)-scan (back-projection) to produce the first NMR images.

1975 Kumar, Welte and Ernst develop a switched time domain gradient method for the basic reconstruction method (which is used in MR imaging today).

1975 Peter Mansfield et. al., develops a phase encoding technique for image collection and publishes first human body part image (finger cross-section).



1983 First commercial imager is introduced.



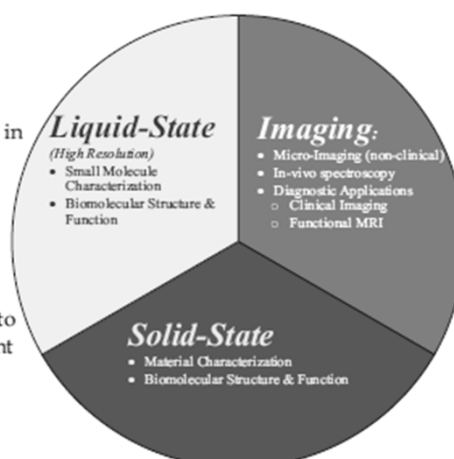
2003 Lauterbur and Mansfield win Nobel Prize in "Medicine or Physiology"

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NMR Overview:

The technique has developed rapidly during its brief history. Advances in instrumentation, especially magnet technology has allowed many different applications. The applications fall into three fairly different groups:



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