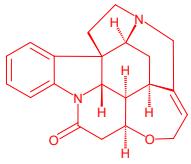


1947 Nobel Prize in Chemistry

Examples of Structure Elucidation


**Strychnine
127 Years!**

Robert Robinson

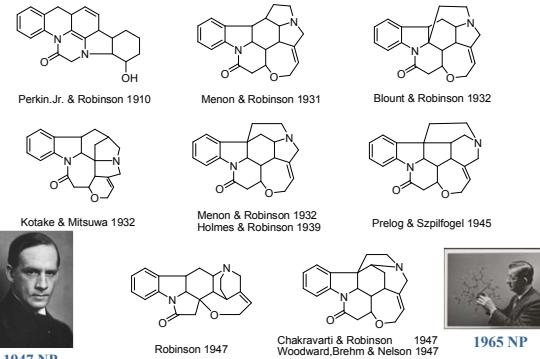
Robert Robinson published 54 paper for structure elucidation And determined it in 1946 and got Nobel Prize in 1947.

Robert B. Woodward Total Syn.in 1954 and 1947 Nobel Prize in Chemistry

90

1947, 1965 Nobel Prize in Chemistry

马钱子碱的结构推断过程



1947 NP

1965 NP

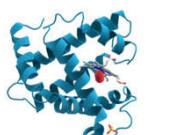
1962 Nobel Prize in Chemistry

X-ray 和生物大分子结构分析

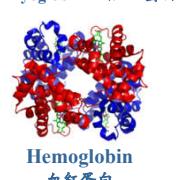


**Sir John C. Kendrew
1917-1997**

**Max F. Perutz
1914-2002**



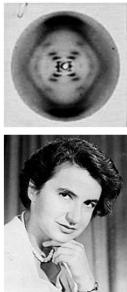
Myoglobin 肌红蛋白



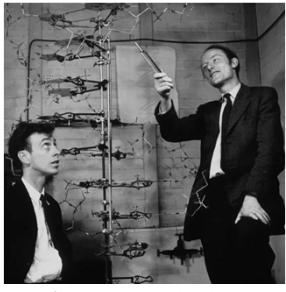
Hemoglobin 血红蛋白

1962年诺贝尔生理学或医学奖

X-ray 和DNA螺旋结构分析-分子生物学的开端



Rosalind Franklin



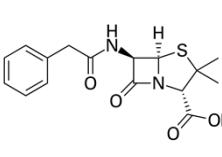
沃森James Watson和克里克Crick

1964 Nobel Prize in Chemistry

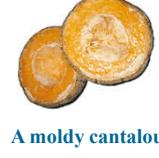
X-ray 和生物小分子结构分析



**晶体王国之花
Dorothy Crowfoot Hodgkin
(1910-1994) 1964 NP**



Penicillin G



A moldy cantaloupe

1945 Nobel Prize in Medicine



Google commemorated Hodgkin's 104th birthday, May 12, 2014



Sir Robert Robinson did not like the β -lactam structure because this would be unstable, unlike penicillin. They were taken aback when a young woman...

John W. Cornforth said "If penicillin turns out to have the β -lactam structure I shall give up chemistry and grow mushrooms." He did not keep his threat but later received a Nobel prize for his enzyme work 30 years later.

1969 Nobel Prize in Chemistry

X-光衍射-“构象分析”-诺贝尔奖

Derek H. R. Barton
1918-1998

Odd Hassel
(1897-1981)

Odd Hassel和Barton利用X-光衍射等方法发现了同一有机物有椅式、船式等不同结构，提出了“构象分析”的原理和方法，获得1969年诺贝尔奖。Hassel是挪威第一个获诺贝尔奖的科学家。

1979年诺贝尔生理学或医学奖

Computer Assisted Tomography (CT)

Godfrey N. Hounsfield
1919-2004

Allan M. Cormack
1924-1998
数学家

计算机辅助X-射线断层成像仪，开创了医学诊断的新时代

1989年诺贝尔物理学奖

Norman Foster Ramsey Jr.

N. F. Ramsey (1915–2011), Who introduced the concept of the *chemical shift* and *J coupling*.

1991年诺贝尔化学奖

R. R. Ernst (1933-)

Richard R. Ernst 提出了利用核磁共振技术来测定物质结构的新方法，将傅立叶变换方法真正引入到了核磁共振技术中，相对于化学界所使用的传统光谱学方法，这一创新数十甚至数百倍的提高了物质结构测定的敏感度（提高了两个数量级），并为二维和多维NMR技术，以及后来的核磁共振成像铺平了道路。

The Nobel Prize in Chemistry in 2002

“发明了对生物大分子进行确认和结构分析的方法”
MS、NMR开始应用到大分子结构分析

John B. Fenn
(1917-2010) USA

Koichi Tanaka
田中耕一
(1959-)

Kurt Wüthrich
(1938-) Swiss

2003年诺贝尔生理学或医学奖

NMR应用到临床-磁共振成像

Paul C. Lauterbur
(1929-2007) USA

Peter Mansfield
(1933-) English

(Nuclear) Magnetic Resonance Imaging (MRI)

2013年诺贝尔化学奖

Karplus Equation: 确定了偶合常数和二面角之间的关系，为确定分子结构找到了重要规律，也为后来蓬勃发展的结构生物学奠定了基础。

$$^3J = J^0 \cos^2\phi - 0.28 \quad (0^\circ \leq \phi \leq 90^\circ) \quad ^3J = J^{180} \cos^2\phi - 0.28 \quad (90^\circ \leq \phi \leq 180^\circ)$$

Martin Karplus (1930-)
J. Chem. Phys., 30, 11-15 (1959).

河北医科大学 研究生实验仪器平台课

Introduction of MS, NMR, X-Ray Crystallography

药学院 405, 86261270
<http://202.206.48.213:8091/>

世纪神药-阿司匹林 在分子水平上长什么样？

青霉素、青蒿素、胆固醇、吗啡、马钱子碱…?

Typical Mass Spectrum of Aspirin

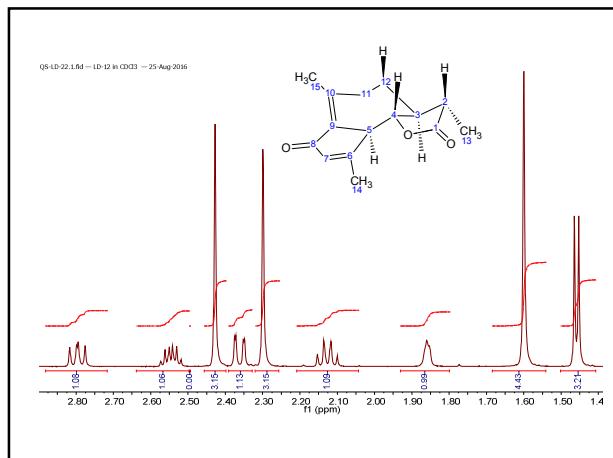
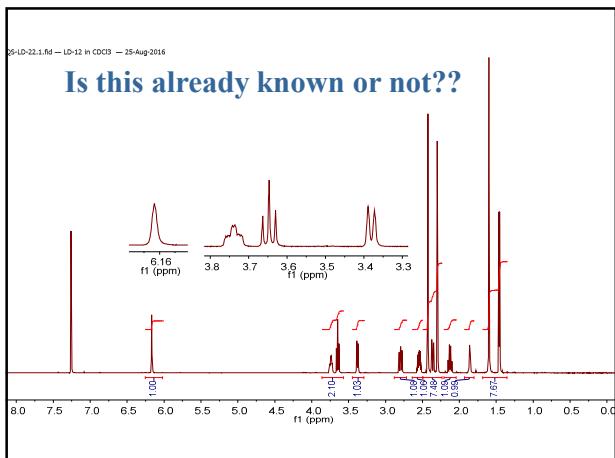
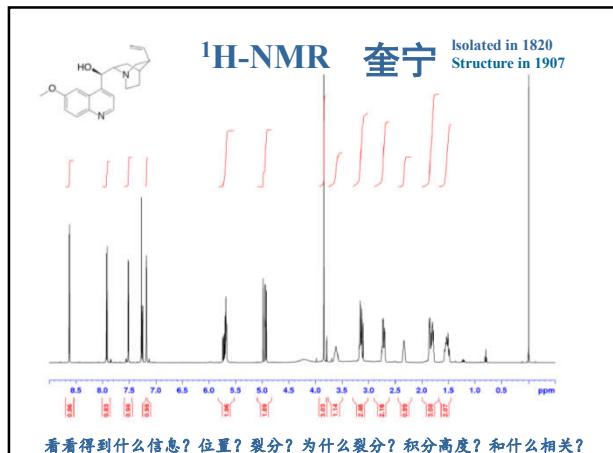
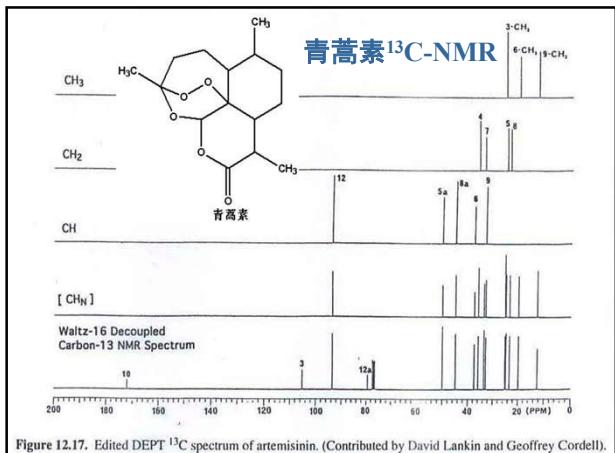
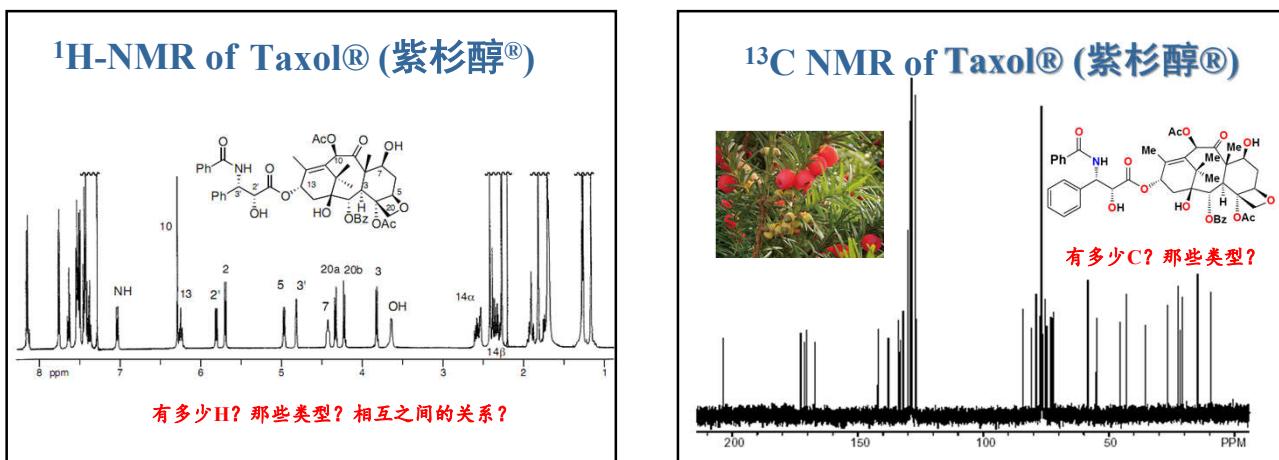
MS-NH-9393
Aspirin
C9H8O4
Exact Mass: 180.04
120 m/z -for singly charged ion this is the mass 105

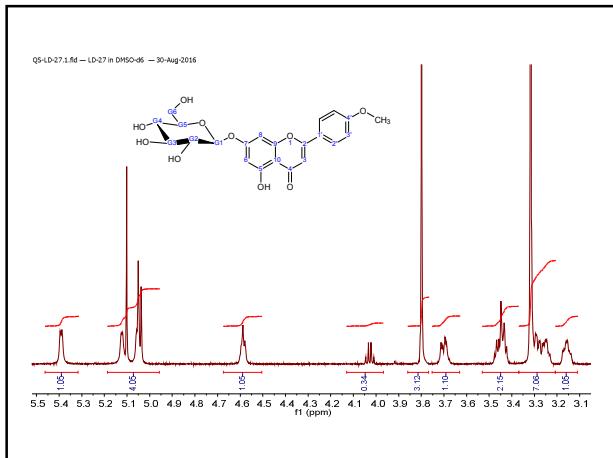
¹H-NMR of Aspirin

www.biosite.dk 160510

¹³C-NMR of Cholesterol

2019/10/31 Thursday





MS, NMR, X-Ray与结构鉴定

化合物的结构鉴定重要吗？

Why?

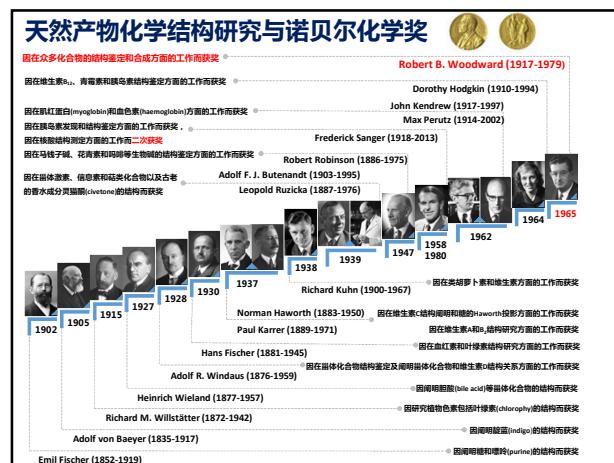
有多少科学家因天然产物的结构研究获得诺贝尔奖？

Before 1950s, structure studies were life-long NP winning activities



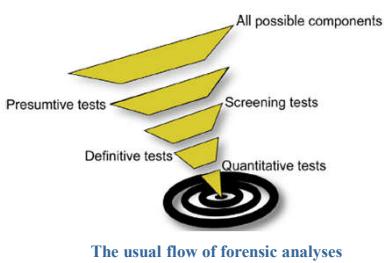
Robert Robinson **James Dewey Watson** **Dorothy Hodgkin** **R. B. Woodward**
咖啡、马钱子碱 DNA 青霉素、维生素B12 河豚毒素、土霉素

天然产物结构研究与诺贝尔奖



Forensic NMR Spectroscopy

Just a beginning of a promising partnership



NMR : highlighting the high reproducibility, the non-destructive and non-selective characteristics, and the ease of sample preparation.

核磁共振波谱法

Nuclear Magnetic Resonance Spectroscopy



核磁共振波谱法

核磁共振 (Nuclear Magnetic Resonance, NMR) :

在外加磁场作用下，某些原子核能产生核自选能级分裂，当用一定频率的射频照射分子时。可引起原子核自旋能级的跃迁，吸收一定频率的射频，即产生核磁共振。

核磁共振波谱 (NMR spectrum) :

以核磁共振信号强度对照射频率 (或磁场强度) 作图，即为核磁共振波谱。

核磁共振波谱法 (NMR spectroscopy) :

利用核磁共振波谱进行结构 (构型和构象) 测定、定性及定量分析的方法。

120

Nuclear Magnetic Resonance

核磁共振(NMR)被誉为有机物的指纹，它使有机物的鉴定和结构测定进入了一个全新的阶段。

核磁就是原子核自旋产生的磁场

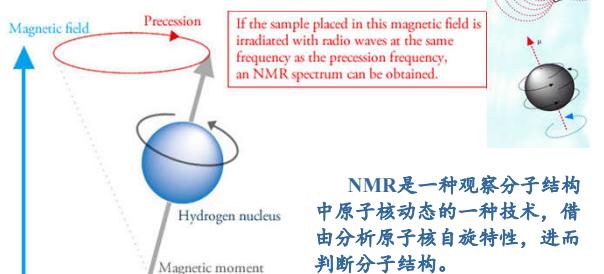
核磁共振谱(Nuclear Magnetic Resonance Spectroscopy, NMR)是指：低能电磁波 (波长约106—109μm)与暴露在磁场中的磁性核相互作用，使其在外磁场中发生能级的共振跃迁而产生吸收信号，称为核磁共振谱。

核自旋实际上已成为科学家探讨物质世界的“探针”。

121

核磁共振波谱法

(Nuclear Magnetic Resonance)



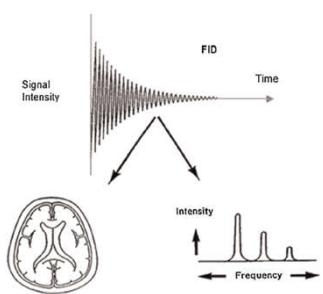
NMR是一种观察分子结构中原子核动态的一种技术，借由分析原子核自旋特性，进而判断分子结构。

Nuclear Magnetic Resonance



桥与风发生共振而倒塌。NMR是核与磁发生共振——如同拉小提琴时琴弓与琴弦的共振一样

Nuclear Magnetic Resonance



The free induction decay (FID) and Fourier transformation to generate MR images or MR spectra

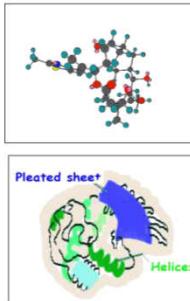
The problem the we want to solve by NMR

分子长什么样？

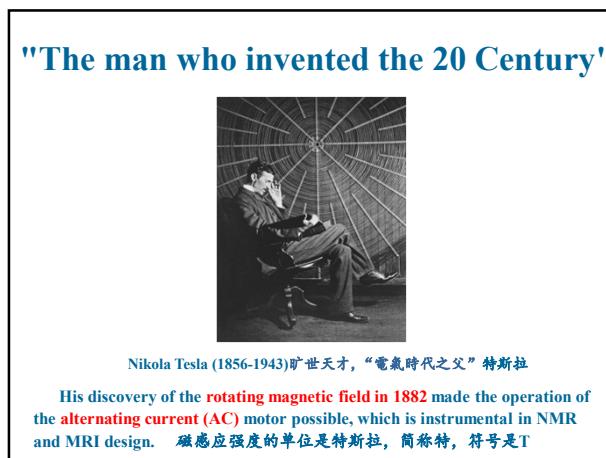
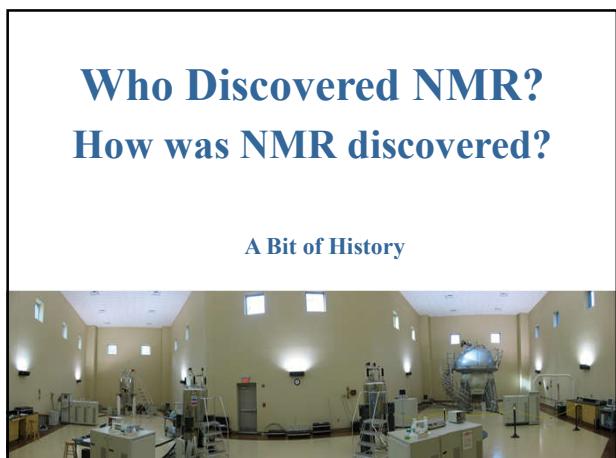
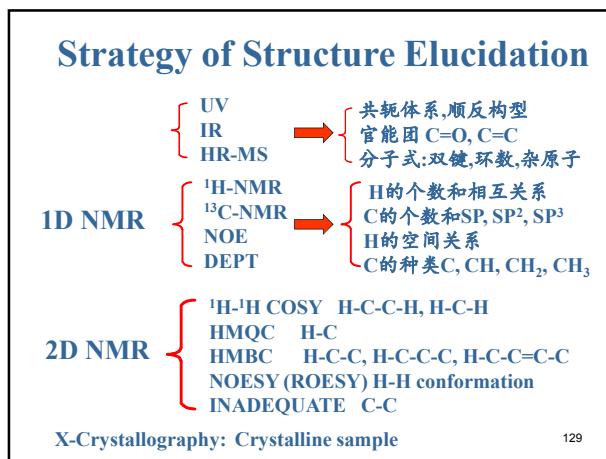
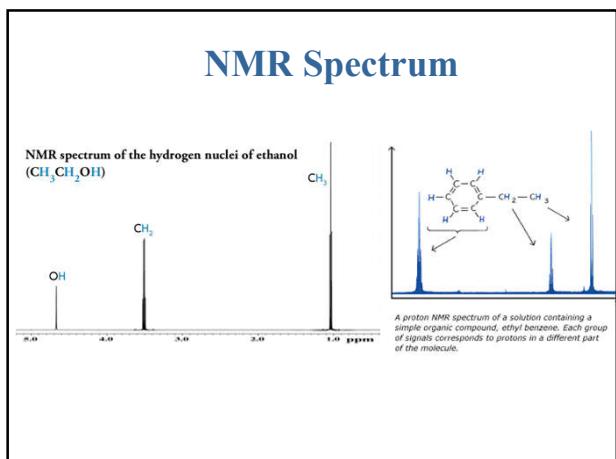
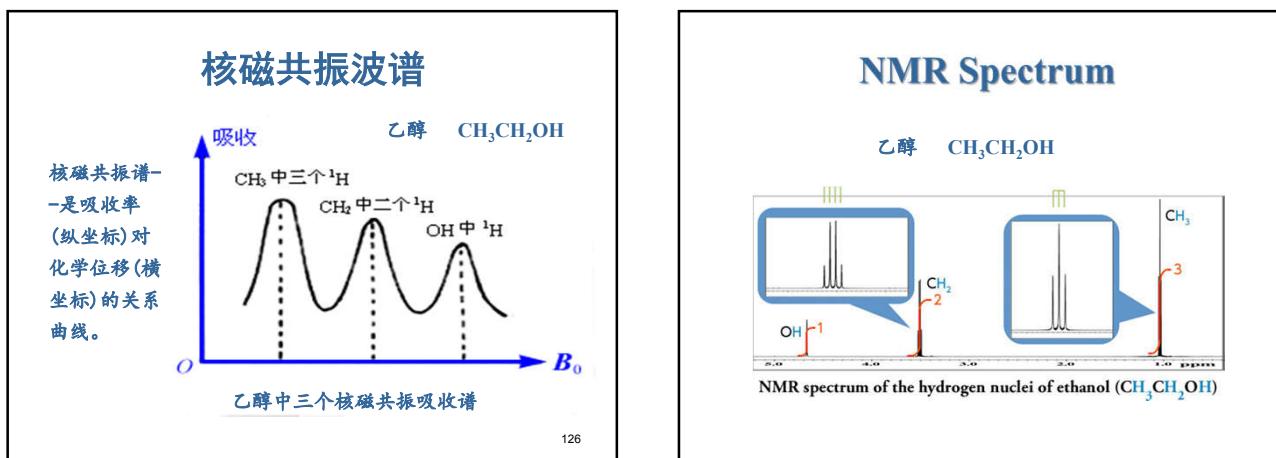
What we “really” see



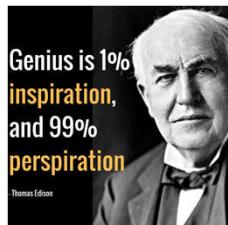
What we want to “see”



NMR provides scientists with an elegant and precise way of determining chemical structure

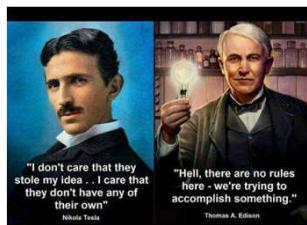


Tesla was a Scientist, Edison was more of a Businessman



Genius is 1% inspiration, and 99% perspiration

Thomas Edison



"I don't care that they stole my idea . . I care that they don't have any of their own"

Nikola Tesla

"Hell, there are no rules here - we're trying to accomplish something."

Thomas A. Edison

"Tesla tried once and figured it out. Edison tried 1000 times and figured it out on the 1001st time."

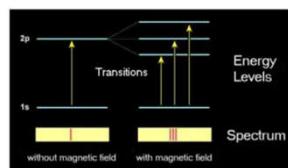
After promising \$50,000 to Tesla if He would improve DC motors, Edison reneged on his word, dismissing the promise as "American humor."

Who Discovered NMR?

Zeeman Splitting in 1896



Pieter Zeeman
1865-1943, 1902 NP



在磁场中单一谱线的钠光谱一下裂变成了三条

自旋数不为零的原子核的能量级在磁场中也会产生分裂，这就是核磁共振的物理基础。

Who Discovered NMR?

Larmor Relationship in 1897

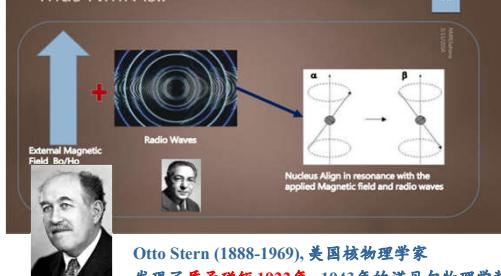


Sir Joseph Larmor
1857-1946

Sir Joseph Larmor developed the equation that the angular frequency of precession of the nuclear spins being proportional to the strength of the magnetic field-Larmor Relationship. Which explain the curious Zeeman Splitting.

Who Discovered NMR?

Thus NMR is..



Otto Stern (1888-1969), 美国核物理学家
发现了质子磁矩 1922年, 1943年的诺贝尔物理学奖

苏黎世联邦理工学院和NMR领航者-Bloch, Ernst, Wüthrich及制造商Bruker

核磁共振研究始于Otto Stern

核磁共振研究是从斯特恩（Otto Stern）的分子束实验开始的

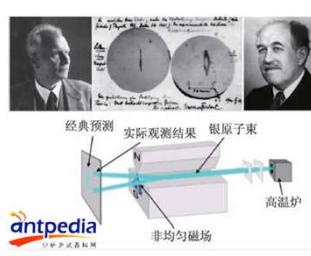


Otto Stern发现了质子磁矩, 获得了1943年的诺贝尔物理学奖

Otto Stern (1888-1969) was a German-American physicist and Nobel laureate in physics. He was the second most nominated person for a Nobel Prize with 82 nominations in the years 1925-1945 (most times nominated is Arnold Sommerfeld 索末菲with 84 nominations), ultimately winning in 1943.

核磁共振研究始于Otto Stern

核磁共振研究是从斯特恩（Otto Stern）的分子束实验开始的



斯特恩-盖拉赫实验
Otto Stern发展了核物理研究中的分子束方法并发现了质子磁矩, 获得了1943年的诺贝尔物理学奖



Otto Stern
1888-1969

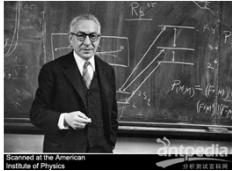
爱因斯坦的助手

Who Discovered NMR?

Rabi refined Stern technique to observe the effect from the nuclear magnetic moment in 1938, 1944 NP



Scanned at the American Institute of Physics



Scanned at the American Institute of Physics



Harold C. Urey
(1893-1981)
1934 Nobel Prize

Isidor Isaac Rabi (1898-1988) was an American physicist who won the Nobel Prize in Physics in 1944 "For his resonance method for recording the magnetic properties of atomic nuclei", which is used in magnetic resonance imaging.

1938年发明了精确测定了一些核磁属性的方法

138

Isidor Isaac Rabi, Man of the Century



The Presidential Science Advisory Committee meets with U.S. President Eisenhower in the mid-50s



The 1927 Solvay Conference brought together the world's leading physicists, including Niels Bohr, Albert Einstein, and Max Planck et al 17 NP laureates.

Bill Moyers presents a profile and interview of I.I. Rabi, winner of the 1944 Nobel Prize in physics and an early developer of radar for use in World War II. Rabi also participated in the Manhattan Project and was present at the detonation of the first atomic bomb — an event which transformed him into an advocate for restraint in the use of nuclear power.

Isidor Isaac Rabi: walking the path of God

从犹太贫民窟中走诺贝尔奖的领奖台



with a new preface



Niels Bohr (1922) with James Franck(1925), Albert Einstein,(1921) and Isidor Isaac Rabi (1944)



RABI
Scientist & Citizen
John S. Rigden

Isidor Isaac Rabi—— A Pioneer In Atomic Physics

把哥伦比亚物理系打造成超一流的物理王国





Brookhaven National Laboratory



Columbia University

Rabi was one of the founders of the Brookhaven National Laboratory also built up the world's finest physics departments at Columbia University

Related Nobel Prize

ALFRED NOBEL
Nobel



1952年诺贝尔物理学奖：布洛赫(Felix Bloch) & 珀塞尔(Edward Purcell)因发展了核磁精密测量的新方法及由此所作的发现——核磁共振。



" Developed of new ways and methods for nuclear magnetic precision measurements"

精确测定物质的核磁属性, 核磁共振开始真正进入实用技术领域

Felix Bloch ETH Zürich
Stanford University
海森堡、Rabi的学生

Edward Purcell
Harvard University

Russell and Sigurd Varian and NMR



Russell Varian
1898-1959



The A-60 was the workhorse NMR instrument for decades as it allowed chemists to determine molecular structures easily and quickly and to follow the progress of chemical reactions.



Sigurd Varian
(1901-1961)

In 1948 two brothers, Russell and Sigurd Varian, armed with \$22,000, founded Varian Associates to manufacture scientific instruments. Varian used its Stanford connection to develop NMR instruments. In 1953 Varian HR-30, 1960 A-60. Varian, Inc., was acquired by Agilent Technologies in 2010.

Varian Co. was established twelve years earlier on April 20, 1948



The first 40 MHz NMR spectrometer (Varian, 1953)



Varian A-60 spectrometer(1961)



The first 90 MHz FTNMR spectrometer
(Bruker, 1967)

Bruker Co. founded in 1960 in Karlsruhe



Prof. Günther Laukien (1923-1997) and his first pulse NMR spectrometer

Why the Name Bruker ?

- Bruker was founded by Prof. Günther Laukien
- Professor for Experimental Physics
- First high-resolution systems for use in analytical chemistry in the US
- Recognized the power of NMR and the need for an impulse spectrometer
- Established BRUKER company in 1960



Prof. Günther Laukien

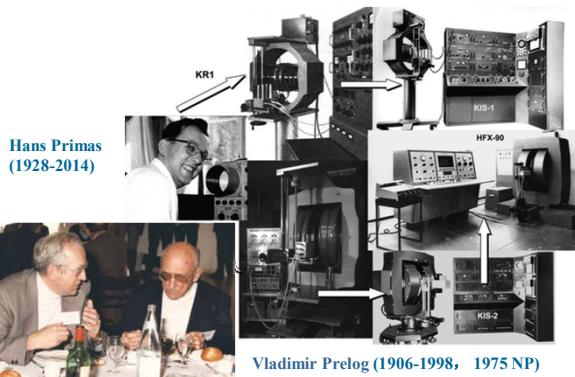
The Founding of Bruker-Physik AG



Frank H. Laukien
(born 1959/1960)
chairman and CEO
of Bruker since 1991.

Bruker Physik AG's first operational facility in Hardtstraße, Karlsruhe, Germany in September 7th, 1960.

Zurich's Contributions to Bruker

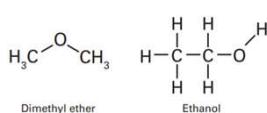


Vladimir Prelog (1906-1998, 1975 NP)

Why Do We Need NMR?

NMR provides scientists with an elegant and precise way of determining chemical structure and properties of materials, and is widely used in physics and chemistry.

NMR also is the basis of magnetic resonance imaging (MRI), one of the most important medical advances of the 20th century.

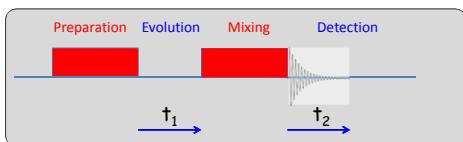


Advantages of NMR

Advantages of NMR include the following:

- (a) The instrument is available in most laboratories;
- (b) An in-depth understanding of the fundamentals of the method is not necessary to apply this method;
- (c) A small amount of sample is needed;
- (d) The sample can be recovered;
- (e) Because the analysis is conducted in solution, it is applicable to both solid and liquid samples.

Two-dimensional NMR



R. R. Ernst



Jean Jeener

Richard R. Ernst 提出了利用核磁共振技术来测定物质结构的新方法，将傅立叶变换方法真正引入到了核磁共振技术中，这一创新数十甚至数百倍的提高了物质结构测定的敏感度，并为二维和多维NMR技术，以及后来的核磁共振成像铺平了道路。

ALFRED NOBEL
Nobel

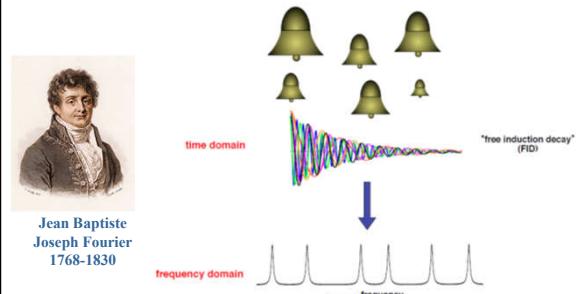
1991年诺贝尔化学奖：R.R. Ernst (1933—) 瑞士物理化学家。
1991年唯一获奖人

主要成就在于他在发展高分辨核磁共振波谱学方面的杰出贡献。这些贡献包括：

- 一. 一维脉冲傅利叶变换核磁共振谱
- 二. 二维傅利叶变换核磁共振谱
- 三. 傅利叶变换核磁共振成像

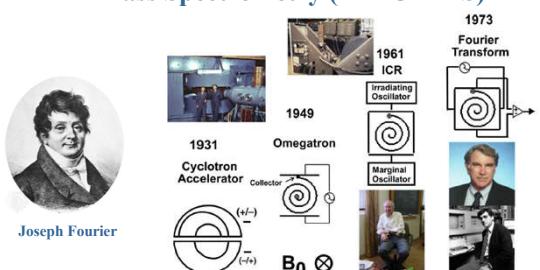
152

Fourier Transformation



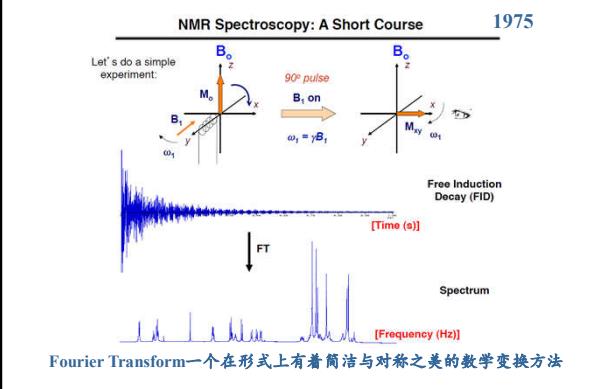
Jean-Baptiste Joseph Fourier (1768-1830) was a French mathematician and physicist
1965-1966: First FT spectrometer by Richard R. Ernst and Anderson (Varian)

Fourier Transform Ion Cyclotron Resonance Mass Spectrometry (FT-ICR MS)



Stages in cyclotron development history. The individuals shown are Lawrence and Livingston (cyclotron accelerator), John Baldeschwiler (marginal oscillator), and Melvin Comisarow/Alan Marshall (Fourier transform). Each stage represents a different experimental configuration/event sequence.

Fourier Transform—Ernst的天才之作



Arts and Sciences. A Personal Perspective of Tibetan Painting

Richard R. Ernst*

Abstract: The relationship between the arts and the sciences is discussed from the standpoint of a scientist and passionate art lover. The two playgrounds of human creativity have much in common and have cross-fertilized each other over centuries. An active involvement in an artistic discipline can stimulate scientific creativity by direct analogy and by emotional and intellectual experience. The excitement of a scientist for the arts is exemplified by the author's adventures in Tibetan painting. The scientific study of Tibetan thangkas is discussed by examples from the author's collection. The analysis of pigments and the dating of the paintings are covered. In addition, some background information on the historical and iconographic context is given.

Keywords: Arts and sciences · Dating of paintings · Pigment analysis · Tibetan Buddhism · Tibetan thangka

1966年，瑞士苏黎世理工学院的恩斯特（Richard Ernst）天才性的发明了用脉冲波来诱发共振的方法和傅利叶变换，给核磁共振带来了革命性的变化。不仅大大提高了实验的效率，也开拓出了多维核磁共振谱这一有着广泛应用的领域—医学成像。

Two-dimensional NMR

The diagram illustrates the 2D NMR process. It shows a 3D surface representing the signal intensity at different points in the F_2 and F_1 dimensions. A vertical axis represents time t , divided into t_1 and t_2 . A red arrow points down the t axis, indicating the progression of time. Labels indicate "Strong signal at the beginning" at the start of t_1 and "Weak signal at the end (thermal noise)" at the end of t_2 . A small portrait of Richard R. Ernst is shown next to the plot.

Richard R. Ernst (1933-)

Raman microscope for Tibetan scroll paintings

Tibetan scroll paintings

Nobel Prize in Chemistry in 1991 Louis Gross Horwitz Prize in 1991 Wolf Prize in Chemistry in 1991

Playing the viola da gamba at Primas' retirement party

A man of many dimensions

One of the first 2D-FT MR images from the research group of Richard Ernst in Zurich, acquired by Anil Kumar in July 1974

Richard Ernst, Primas' second PhD student, developing the first Fourier transform NMR spectrometer in Palo Alto in California, after completing his PhD at ETH.

Who discovered chemical shift and J coupling

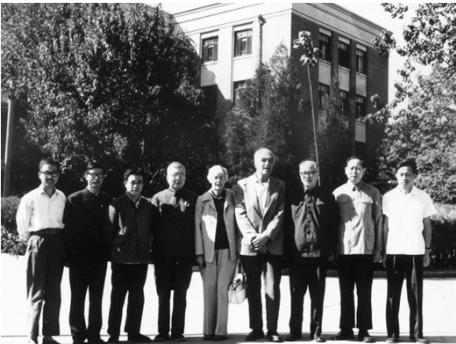
Norman Foster Ramsey Jr.

N.F. Ramsey (1915 –2011), (Nobel Laureate 1989) was Isidor Isaac Rabi's first graduate student and introduced the concept of the **chemical shift and J coupling**.

虞福春 (1914-2003)

Fuchun Yu at Ohio State University

1950年，Bloch (1952 NP)实验室的两名博士后，Warren Proctor和虞福春，发现了化学位移现象，核磁共振开始在分析化学领域大显身手，接力棒由此也传到了化学家手上。¹⁶¹



Yu Fuchun , Mrs. Bloch, Felix Bloch and Wang Ganchang 王淦昌

NMR History



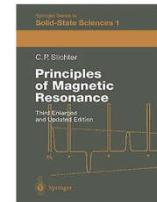
对NMR作过贡献的15位Nobel奖得主

- 1. 1944:** I. Rabi
 - 2. 1952:** F. Bloch
 - 3. 1952:** E. M. Purcell
 - 4. 1955:** W. E. Lamb
 - 5. 1955:** P. Kusch
 - 6. 1964:** C. H. Townes
 - 7. 1966:** A. Kastler
 - 8. 1977:** J. H. Van Vleck
 - 9. 1981:** N. Bloembergen
 - 10. 1983:** H. Taube
 - 11. 1989:** N. F. Ramsey
 - 12. 1991:** R. R. Ernst
 - 13 2002:** Kurt Wüthrich
 - 14. 2003:** Paul Lauterbur and Peter Mansfield
 - 15. 2013:** Martin Karplus



166

Who discovered chemical shift and J coupling



Charles P. Slichter, 1924-2018

In 2017, the American Chemical Society recognized the discovery of J couplings at the University of Illinois with a Chemical Breakthrough Award. "one of the world's top research scientists," Charlie's influential textbook, "**Principles of Magnetic Resonance**" in 1961, till 2010 in press.

Development of NMR



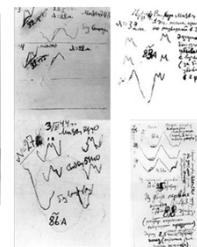
History

- | History | | Jean L. C. Jeener |
|---------|--|---|
| 1946 | Bloch, Purcell first nuclear magnetic resonance | |
| 1955 | Solomon NOE (nuclear Overhauser effect) |  |
| 1966 | Ernst, Anderson Fourier transform NMR | |
| 1975 | Jeener (1971), Ernst 2D NMR | |
| 1985 | Wüthrich first solution structure of a small protein (BPTI) from NOE based distance restraints | |
| | NMR is about 25 years younger than X-ray crystallography | |
| 1987/8 | 3D NMR + ^{13}C , ^{15}N isotope labeling | |
| 1996/7 | new long range structural parameters: | |
| | <ul style="list-style-type: none"> - projection angles from:
residual dipolar couplings (partial alignment)
T_1/T_2 relaxation time ratio (anisotropic diffusion) - projection angles (cross-correlated relaxation) - TROSY (molecular weight > 100 kD) | |

“顺磁化合物的自旋磁共振”1945



Yevgeni K. Zavoisky



1944年鞑靼斯坦共和国喀山大学的物理学家Yevgeni K. Zavoisky (1907-1976) 发现了电子自旋共振。他可能在1941年观察到核磁共振，远在Felix Bloch和Edward Mills Purcell之前，但认为结果不可重复。167

Three Waves of NMR

第一阶段

1945~46年: F. Bloch 和 E. M. Purcell

两个小组几乎同时发现NMR现象

1950年代初: NMR首次应用于有机化学

1960年代初: Varian Associates A60 Spectrometer

问世, NMR开始广泛应用

168

第二阶段

1970年代: Fourier Transform的应用(FT-NMR)灵敏度大幅提高,使得¹³C、¹⁵N等丰度很低元素的NMR的测定成为可能。

¹³C-NMR技术(碳骨架)

(GC, TLC, HPLC技术的发展)

第三阶段

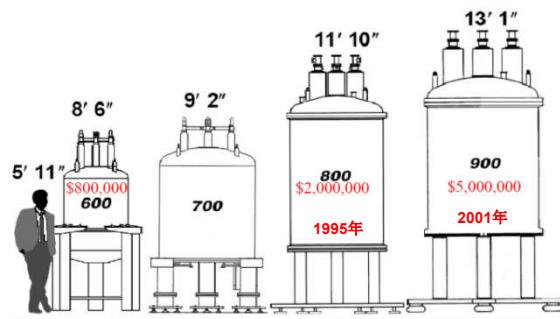
1980年代: Two-dimensional (2D) NMR诞生

(COSY, 碳骨架连接顺序, 非键原子间距离, 生物大分子结构,)

169

NMR Sensitivity

To Increase Magnet Strength is a Major Means



171

Liquid Helium-cooled Magnet



172

Bruker 600 MHz NMR Spectrometer



Bruker 700 MHz Avance III Spectrometer
with carbon-optimized cryoprobe



174

900 & 950 MHz超导核磁共振波谱仪



900 MHz



950 US

175

1000 & 1020 MHz超导核磁共振波谱仪



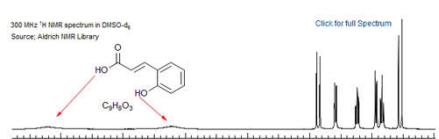
176

Ultra-high field high-resolution NMR

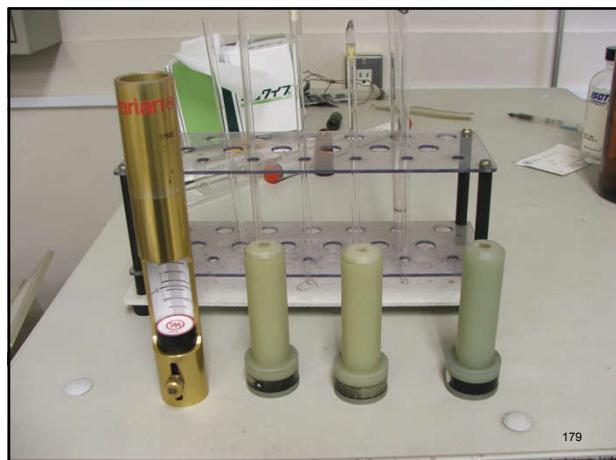
State-of-the-art



April 8, 2019



178



179

