1

Introduction

Certain nuclei, as well as electrons, behave much like small spinning magnets and will accordingly interact with an applied magnet field. Oscillating magnetic fields applied at the appropriate frequency can then alter this state, a phenomenon known as nuclear magnetic resonance (NMR), giving rise to detectable signals at frequencies characteristic of each NMR-active nucleus. By examining these signals, information regarding the presence of specific compounds and their chemical environments can be measured using a technique known as magnetic resonance spectroscopy (MRS), and spatially mapped using magnetic resonance imaging (MRI).

In general, spectroscopy is the study of materials via their interactions with electromagnetic (EM) fields, and the energy of these fields determines the associated physics (see Figure 1.1). At typical magnetic field strengths (0.1–10 T), NMR spectroscopy operates in the radiofrequency band. In contrast, electron spin resonance (ESR), which involves electrons rather than nuclei, utilizes frequencies in the microwave region. Dubbed NMR by the physicists and chemists who first discovered and applied the phenomenon, the “nuclear” label was later dropped in the medical field due to unfounded fears of ionizing radiation. For our purposes, we will use the general term magnetic resonance (MR), reserving the labels MRI, MRS, or ESR for when a distinction is being drawn with respect to a specific application or experiment.

A critically important factor to keep in mind is that the MR energies for *in vivo* studies are several orders of magnitude below 37 °C thermal vibrations, leading to fundamentally insensitive measurements. For example, in contrast to other techniques, such as X-ray imaging or computed tomography (CT), where energies are sufficient for the detection of individual photons, MR only effectively observes net signals summed over a very large number of nuclei.

Despite this sensitivity problem and our inability to distinguish individual nuclei, MR-detectable nuclei provide ideal molecular probes. Nuclei are spatially localized, and their magnetic properties are highly sensitive to local magnetic fields. Yet they interact extremely weakly with their physical environment permitting measurements with minimal to no macroscopic effects. Consequently, MR has a rich history with multiple important scientific and medical applications.

1.1 A Brief History of MR

NMR was first detected in 1937. By sending a molecular beam of lithium chloride through an apparatus employing a combination of static and oscillating magnetic fields, I.I. Rabi and colleagues were able to observe resonance peaks of both the lithium and chloride nuclei (Rabi et al. 1938). Often missing from histories of MR but deserving mention is Y.K. Zavoisky, a Soviet scientist whose

Fundamentals of In Vivo Magnetic Resonance: Spin Physics, Relaxation Theory, and Contrast Mechanisms, First Edition.
Daniel M. Spielman and Keshav Datta.

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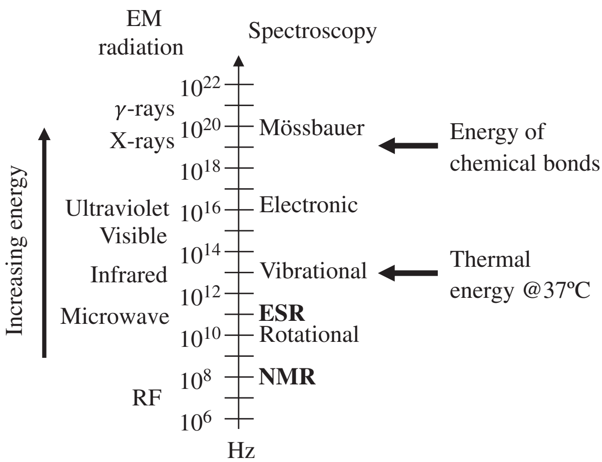


Figure 1.1 Spectroscopy is the study of materials via interactions with electromagnetic (EM) fields. An important feature of NMR is that the associated energy is several orders of magnitude below thermal energy under typical laboratory or *in vivo* conditions.

work was largely overlooked in the West during the Cold War. Since his discovery in 1944 (Zavoisky 1945), Electron spin resonance (ESR), also known as electron paramagnetic resonance (EPR), has been exploited as a highly sensitive method for the investigation of different kinds of paramagnetic species in both solid and liquid states.

In 1945, Felix Bloch and Edward Purcell, working independently at Stanford and Harvard University, respectively, first demonstrated the detection of NMR in condensed matter. Bloch's analysis followed the time evolution of the net magnetic moment via nuclear induction processes (Bloch 1946; Bloch et al. 1946), whereas Purcell emphasized the energy absorption lines in corresponding spectra (Purcell et al. 1946).

Starting in the 1960s, Richard Ernst discovered that the sensitivity of NMR techniques could be dramatically increased by replacing the slowing sweeping radiofrequency magnetic fields traditionally used in NMR spectroscopy (known as continuous-wave NMR) with brief, intense pulses (Ernst and Anderson 1966). This discovery, known as pulsed NMR (later, the "pulsed" descriptor was routinely dropped), greatly expanded the utility of this scientific tool. Ernst later extended this method to enable high-resolution studies of larger molecules, resulting in many of the "two-dimensional" NMR methods used today. Building on the two-dimensional pulsed NMR methods introduced by Ernst, Kurt Wüthrich, and coworkers developed novel nuclear MRS method for mapping the three-dimensional structure of large biological molecules (Wuthrich 1995).

From the perspective of medical imaging, the field of MR split in the 1970s and 1980s, from being primarily a chemical analysis tool to also include imaging, with medical applications soon following. The key concept of augmenting the large uniform primary magnetic field with small deliberate spatially varying components (known as gradients), as proposed independently by Paul Lauterbur (1973) and Peter Mansfield and Grannell (1973), allowed the spatial localization of NMR signals, leading directly to MRI. Lacking the harmful side effects of ionizing radiation present in X-ray imaging, computed tomography (CT), and positron emission tomography (PET), and having exquisite soft tissue contrast, MRI rapidly filled an important unmet need in medicine (Figure 1.2).

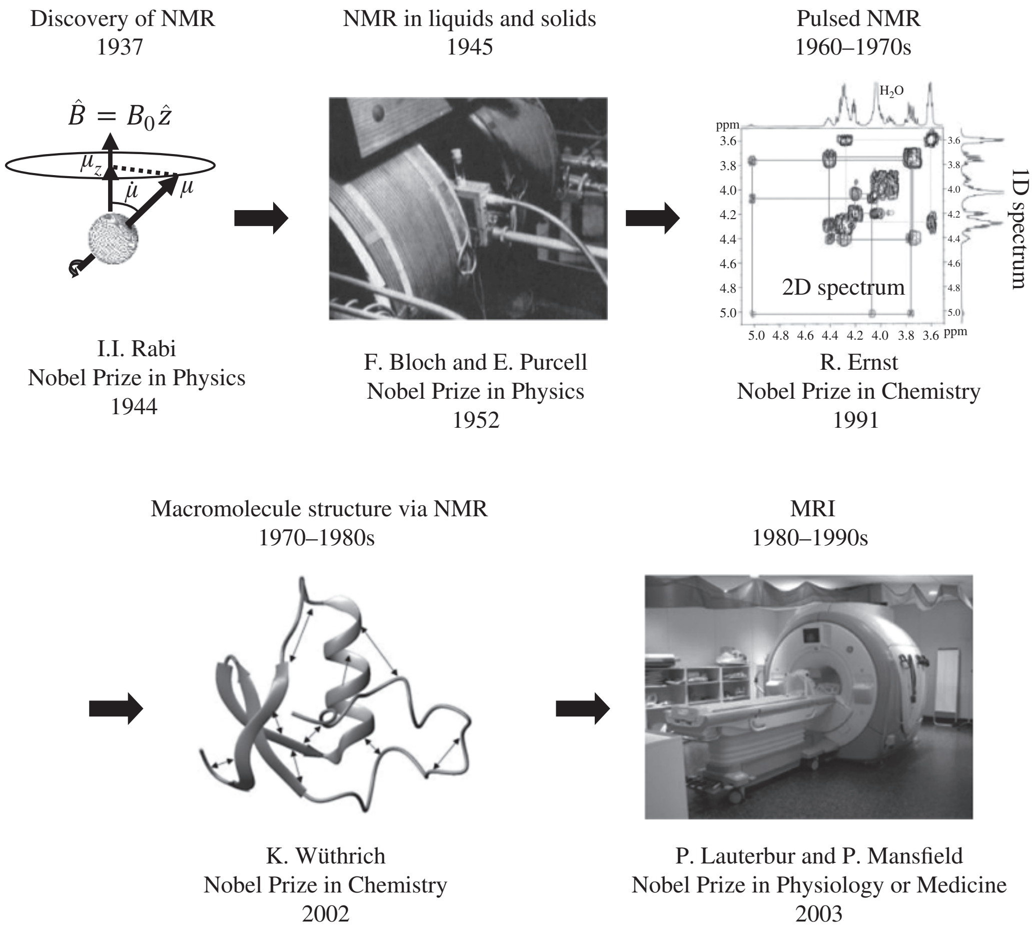


Figure 1.2 A history of Nobel Prizes awarded for development in magnetic resonance. Source: Adapted with permission in part from Bloch (2007) and Foss and Krane (2004).

1.2 NMR versus MRI

The practice of MR in the chemistry laboratory is generally quite different from that employed for *in vivo* imaging applications, and a brief comparison is worthwhile. As a rather broad generalization, typical chemistry experiments involve highly purified samples and ask detailed questions regarding the chemical structure of the materials under study. Further, many laboratories focus on either liquid-state versus solid-state NMR analyses as the performance and associated analysis methods for these two general classes of experiments are typically quite different; rapid molecular tumbling in liquids results in the averaging out of important spin–spin interactions that cannot be ignored in solid or crystalline samples (Figure 1.3).

In contrast, *in vivo* tissues generally contain a complex mixture of materials undergoing multiple physiological processes. Although tissues exhibit both liquid-like and solid-like properties, liquid-state NMR analysis is generally the most appropriate (with some notable exceptions). However, for *in vivo* applications, very different questions are typically asked than those presented in the chemistry laboratory.

Figure 1.3 *In vivo* tissues exhibit both liquid-like and solid-like properties; however, with some notable exceptions, liquid-state NMR analysis is the most appropriate.

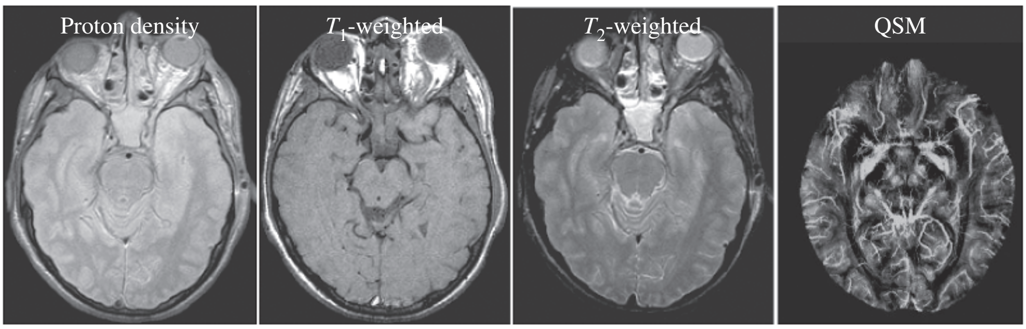
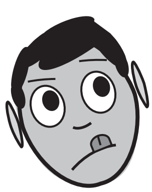


Figure 1.4 Brain MRI. Although all ^1H MRI acquisitions target water (and fat), different imaging techniques yield widely varying contrasts. Images show representative proton density, T_1-weighted, T_2-weighted, and quantitative susceptibility mapping (QSM) axial brain images.

Due to a combination of ubiquity and relatively large magnetic moment, hydrogen nuclei (here also referred to as protons) in water molecules are the primary target with inquiries pertaining to location, concentration, and dynamics (e.g., flow or chemical exchange processes). Conventional MRI analysis (to be presented in Chapter 2) is based on assuming the water signal is made up of many independent (*i.e.*, noninteracting) hydrogen nuclei with the addition of phenomenological T_1 and T_2 relaxation times. The combination of a large primary magnetic field, B_0, with smaller linearly varying gradient fields results in a very powerful spatial frequency (*k*-space) signal analysis framework. The result has been the proliferation of many MRI acquisition schemes capable of assessing a wide spectrum of tissue-specific information, as illustrated in Figure 1.4.

However, this figure raises several fundamental questions. Given that clinical MRI primarily images water, why do different tissues exhibit different MRI signal intensities? Are differences solely due to varying water content (typically referred to as "proton density")? If not, why do different tissues have different T_1s and T_2s? What is the effect of magnetic susceptibility or dynamic processes such as molecular tumbling, chemical exchange, and diffusion?



QUESTION: Does it matter that water has two ^1H nuclei? How would MRI be different if water had only one? What about three?

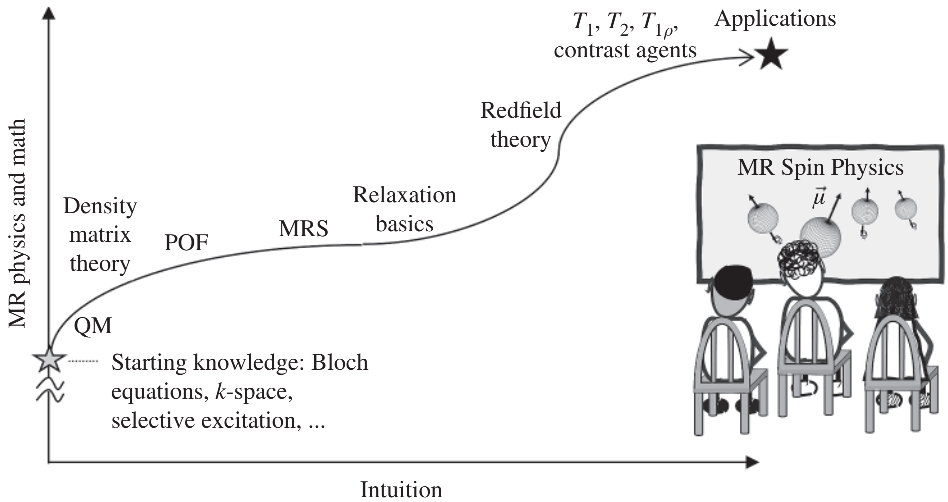


Figure 1.5 An MR roadmap highlighting the balance between physics and mathematical theory, and the development of critical intuitive understanding.

1.3 The Roadmap

This textbook is meant to be a journey. We assume the reader has a basic understanding of classical MRI and the Bloch equations (this material is reviewed briefly in Chapter 2). We next present the quantum mechanical description of MR, with the goal of developing both the analytical tools needed to analyze interactions among nuclear spins and the intuition necessary for putting these principles into practice. J coupling is introduced first, being both fundamental to spectroscopy applications and equally important as the most mathematically tractable spin coupling mechanism. The basic principles of *in vivo* relaxation are then introduced, followed by a deeper mathematical analysis. With these tools in hand, endogenous contrast mechanisms (*e.g.*, T_1, T_2, $T_{1\rho}$, chemical exchange saturation transfer, and magnetization transfer contrast) are discussed in detail, followed by an introduction to the physical principles underlying the most common MRI contrast agents. The last chapter presents a series of representative tissues, dominant contrast mechanisms, and common imaging methods. Figure 1.5 shows the overall roadmap for this textbook. The overall goal is to provide the reader with a deeper understanding of *in vivo* MR than typically provided by a first course in MRI, which will hopefully be useful in the development and evaluation of novel contrast mechanisms with associated imaging methods, basic science studies of physiology, and clinical applications.

Historical Notes

Many chapters end with brief biographies of some of the key scientific contributors. While readily acknowledging that marking scientific progress based on Nobel Prizes inevitably leaves out many significant investigators, the ubiquity of Nobel Prizes for MR (in physics, chemistry, and medicine) at least provides a place to start. Other notable contributors are added as appropriate.

Isidor Isaac Rabi, a prominent American physicist born on July 29, 1898, in Rymanów, which was part of Austria–Hungary and is now in Poland, has left a lasting impact on the field of NMR through his groundbreaking contributions. These significant achievements culminated in his receipt of the Nobel Prize in Physics in 1944, recognizing his development of the atomic and molecular beam MR technique.

Rabi's most noteworthy accomplishment involved his work on devising a meticulous and innovative approach to gauge the magnetic properties of atoms, nuclei, and molecules. His research in this field commenced during the 1930s, with a primary focus on measuring nuclear magnetic moments, particularly the spin of protons within an atom's nucleus. This technique enabled him to derive various mechanical and magnetic characteristics, offering insights even into the structural configuration of atomic nuclei. This work paved the way for groundbreaking applications like the atomic clock, maser, and laser, thereby ushering in a new era of scientific and technological advancement.

After relocating to New York City in 1899, Rabi pursued education at Cornell University, achieving a bachelor's degree in chemistry in 1919. However, driven by his passion for physics, he redirected his focus and went on to secure a Ph.D. from Columbia University in 1927. Following this, he became a faculty member at Columbia University in 1929 after completing postgraduate studies in Europe.

In the tumultuous years marked by World War II, Rabi played a pivotal role in leading a distinguished group of scientists at MIT, making substantial contributions to the development of radar technology, which held immense strategic importance during that critical period. Furthermore, he assumed a significant role on the General Advisory Committee of the Atomic Energy Commission from 1946 to 1956, eventually ascending to the position of its chairman from 1952 to 1956. This not only underscores his commitment to advancing scientific progress but also his dedication to responsible governance in the realm of atomic energy.

Beyond his research endeavors, Rabi's visionary outlook extended to the conceptualization of CERN – an international high-energy physics laboratory situated in Geneva, Switzerland – an idea that later materialized into one of the globe's foremost scientific institutions. Furthermore, he played a pivotal role as a founding figure in the Brookhaven National Laboratory located in Upton, New York, further solidifying his indelible mark on the scientific landscape.

(Source: Photo from https://commons.wikimedia.org/wiki/File:II_Rabi.jpg, public domain.)

Yevgeny Konstantinovich Zavoisky, a well-known Soviet physicist, left a notable impact in the field of ESR. Born on September 28, 1907, in Mohyliv-on-Dniester, Ukraine, which was part of the Russian Empire at the time, he made lasting contributions through his groundbreaking discoveries. Despite not being honored with a Nobel Prize, his work in ESR had profound implications across various scientific domains.

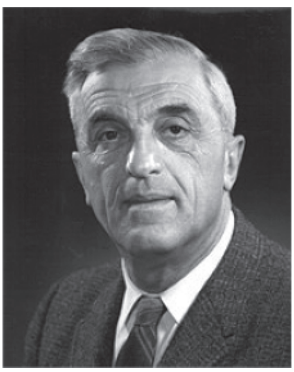
Zavoisky embarked on his academic journey at Kazan State University, completing his studies in 1930. Driven by a deep enthusiasm for physics, he engaged in teaching at the university from 1933 to 1947. During this period, he immersed himself in research related to radio and microwave spectroscopy. In 1944, a pivotal moment came with his breakthrough discovery of EPR, also recognized as ESR. This technique opened avenues for investigating the magnetic properties of paramagnetic materials, revolutionizing research possibilities for scientists in various fields.

Between 1947 and 1971, Zavoisky became a part of Laboratory #2, later renamed the Kurchatov Institute of Atomic Energy, situated in Moscow. During his tenure, he contributed to the development of the Soviet atomic bomb and conducted crucial experimental studies in nuclear physics.

By 1958, Zavoisky had redirected his focus toward nuclear fusion research, particularly concentrating on plasma physics. His notable discovery centered on the phenomenon of turbulent heating. The application of a strong electric field to plasma led to increased resistivity, inducing substantial turbulence. As a result, thermal energy transitioned from macroscale to microscale, consequently raising plasma temperatures to extraordinary levels. This finding held immense importance for the pursuit of controlled nuclear fusion – an area of research with profound implications for both energy production and fundamental physics.

Throughout his illustrious career, Zavoisky's accomplishments garnered recognition from fellow scientists and was the U.S.S.R. Academy of Sciences in 1953. Subsequently, in 1964, he achieved the status of full membership, underscoring the significance of his contributions in the eyes of his peers.

(Source: Photo of Zavoisky's university ID from https://en.wikipedia.org/wiki/Yevgeny_Zavoisky#/media/File:Zavoisky.JPG, public domain)



Felix Bloch, an American physicist originally from Switzerland, was born on October 23, 1905, in Zürich. His impact in the fields of NMR and the quantum theory of solids has led to significant advancements in both physics and medical diagnostics. Bloch's journey in the realm of physics traversed continents, culminating in his recognition as a Nobel laureate and a respected figure within the scientific community.

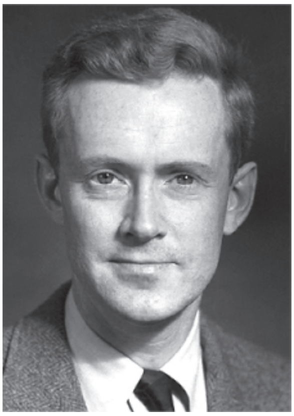
Bloch's academic pursuits commenced with his doctoral research at the University of Leipzig in 1928. During this time, he formulated a quantum theory of solids that offered a foundational understanding of how electrical conduction occurs in materials. This early work laid the groundwork for subsequent explorations in the field of solid-state physics.

In 1933, due to the escalating political situation in Germany, Bloch sought refuge in the United States. He found his academic home at Stanford University in Palo Alto, California, where he joined the faculty in 1934. One of his notable contributions during this period was the proposal of a method to split a beam of neutrons into two components based on their orientations within a magnetic field. Collaborating with Luis Alvarez, Bloch utilized this method in 1939 to measure the magnetic moment of neutrons.

During World War II Bloch conducted atomic energy research at Los Alamos, New Mexico, as well as radar countermeasure work at Harvard University. His role in advancing military technology and nuclear physics was significant. Postwar, he returned to Stanford and collaborated with physicists W.W. Hansen and M.E. Packard to conceptualize the principle of NMR in condensed matter. This groundbreaking idea introduced a precise method for measuring the magnetic field of atomic nuclei, establishing a connection between the magnetic and crystalline properties of materials.

In 1952, Felix Bloch received the Nobel Prize in Physics, an honor shared with Edward M. Purcell. This recognition was based on their independent yet complementary contributions to the development of NMR. This accolade further solidified Bloch's reputation as a pioneering figure in the field of physics.

(Source: Photo from https://commons.wikimedia.org/wiki/File:Felix_Bloch,_Stanford_University.jpg, Licensed under the Creative Commons Attribution 3.0 Unported).



Edward Mills Purcell, was born on August 30, 1912, in Taylorville, Illinois. His groundbreaking advancements in the realm of NMR earned him the Nobel Prize in Physics in 1952, an honor he shared with Felix Bloch.

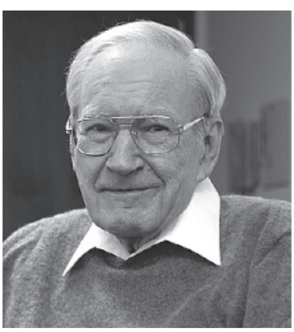
During World War II, Purcell played a vital role in leading a research group focused on radar-related matters at the radiation laboratory situated within the Massachusetts Institute of Technology (MIT). In a notable turn of events in 1946, Purcell independently formulated the NMR technique, applicable to both liquids and solids. This phenomenon involved certain atomic nuclei placed within a magnetic field absorbing and subsequently emitting EM radiation, enabling the examination of molecular structures in both pure substances and mixtures. It swiftly emerged as an indispensable tool in diverse scientific domains, ranging from chemistry and physics to biology and medicine.

Purcell's NMR detection approach demonstrated remarkable precision and represented a significant advancement over the previously introduced atomic-beam method by Isidor I. Rabi. This pivotal contribution marked a turning point in NMR exploration, effectively laying the groundwork for its widespread adoption across a multitude of scientific fields.

By 1949, Purcell had assumed the role of a physics professor at Harvard University. It was during this same year that he achieved another notable feat. By detecting the 21-centimeter-wavelength radiation emitted by neutral atomic hydrogen in interstellar space – an occurrence initially predicted by Dutch astronomer H.C. van de Hulst in 1944 – Purcell made a substantial impact. His study of these radio waves not only aided astronomers in understanding the distribution and placement of hydrogen clouds within galaxies but also facilitated the measurement of the Milky Way's rotation.

Throughout his career, Purcell continued to excel. His work served as a major source of inspiration for students and fellow researchers alike, leaving an enduring impression on the scientific community as a whole. In recognition of his exceptional achievements, Purcell was honored with the National Medal of Science in 1980.

(Source: Photo from https://commons.wikimedia.org/wiki/File:Edward_Mills_Purcell.jpg, public domain)



Richard Robert Ernst, a distinguished Swiss chemist with a passion for education, left an indelible mark on NMR spectroscopy. Born on August 14, 1933, in the picturesque town of Winterthur, Switzerland, Ernst spearheaded transformative breakthroughs in NMR methodologies, culminating in his well-deserved receipt of the 1991 Nobel Prize in Chemistry. This accolade solidified NMR spectroscopy as an indispensable cornerstone across an array of scientific domains.

Ernst earned a Bachelor of Arts degree in chemistry in 1957 and his Ph.D. degree in physical chemistry from the illustrious Federal

Institute of Technology in Zürich in 1962. After graduation, Ernst embarked on an enriching tenure at Varian, nestled in the heart of Palo Alto, California. Serving as a dedicated research chemist until 1968, he contributed significantly to Varian's pioneering scientific endeavors.

A pivotal chapter in Ernst's career unfolded in 1966. Traditionally, NMR techniques grappled with constraints imposed by the slow and incremental sweeping of radio waves, limiting analyses to a select few nuclei. Ernst's ingenious innovation entailed substituting these conventional radio waves with succinct pulses. The key contribution of this idea was a remarkable enhancement in the sensitivity of NMR techniques. Consequently, the analytical scope expanded, encompassing a broader array of nuclei even with minuscule sample sizes. By 1968, Ernst had returned to Switzerland, at his cherished alma mater. Ascending to the rank of full professor in 1976, he became an inspiring beacon for countless students.

Ernst's second significant contribution to NMR spectroscopy was the conceptualization of a groundbreaking technique facilitating high-resolution "two-dimensional" exploration of hitherto elusive larger molecules. This innovation opened doors for scientists to delve into the intricate three-dimensional world of both organic and inorganic compounds. The technique proved invaluable in the study of biological macromolecules, affording insights into their interactions and reaction kinetics.

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